



# Compendium of Antiviral Medicinal Plants of North East India



**Institute of Bioresources and Sustainable Development  
(IBSD), Imphal, Manipur, India**



**Botanical Survey of India (BSI), Kolkata, India**

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## PREFACE

Healthcare industries are facing tremendous challenges in combating various new ailments including epidemics and pandemics throughout the world. Developments in various fronts have also explored new remedies with the advancements in healthcare, perhaps the traditional knowledge associated with the treatment and control of diseases using herbs for their medicinal properties has once again emerged as the primary source to combat modern diseases. The use of natural resources comprising medicinal plants and associated crude extracts are the sole source for newer drug alternatives.

Use of modern technologies developed through rigorous intervention of Science and Technology has played a major role in the paradigm shift of healthcare. Medicinal plants have been always being a primary source of diverse ailments and have been practiced since ancient times in many countries including China, India, Korea, Japan, Tibet, South America, the Middle East, and Russia.

The importance of medicinal plants in its crude form as well as in consortia with other natural forms is well proven in ancient literature. Traditional Chinese Medicine from China and Ayurveda, Siddha, Unani, and Homeopathy in India is well known for its healthcare practices for humankind worldwide. Herbal medicine is still the mainstay of about 25-30% of the world population in the developing countries for primary health care due to its cultural acceptability and better adaptability with the human body and lesser side effects. More than 90% of the plant species used by the medicine-manufacturers are collected from the wild, out of which 70% involves unorganized harvesting. The North-Eastern region of India is considered to be the gold mine of well-practiced knowledge of traditional medicine, as well as the rich resources of medicinal plants.

The compendium of anti-viral medicinal plants of North Eastern region of India is a compilation of various plants reported for their anti-viral activities and practiced as well as proven for its medicinal properties.

This compendium intends to provide information on the medicinal plants occurred in the biodiversity rich region of the country. This information gives a glimpse on various medicinal plants belonging to diverse geographic locations and habitats of the North Eastern region of India. Information on taxonomic, morphological description, distribution and the parts used along with appropriate photographs provides a blueprint for the botanical researchers as well as to interdisciplinary sciences associated with the plants. The vernacular and common names of medicinal plants could also provide useful information for the local communities for its conservation, cultivation and could also be used for the development of herbal industries in the region.

This book has briefed on the medicinal uses as described in pharmacopoeias and in traditional system of medicine where an extract of information is provided for therapeutics. Uses supported by clinical data, traditional uses and special uses in North East India are also elaborated for the readers. Phytochemical profiles, pharmacological and clinical studies associated with the plants and its toxicological information along with contraindications, precautions and adverse reactions is also being provided for most of the medicinal plants reported from the region. Some marketed formulations derived from the medicinal plants have also been provided in this compendium.



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#### **FOREWORD**

India is one of the world's 25 biodiversity hot spots of the world and the North Eastern Region of the country is considered to be the treasure trove of biodiversity. Exploration of traditional knowledge for sustenance is a part of the cultural tradition of humankind to establish a systematic approach based on traditional practices through use of natural resources. The last century saw the development of vast majority of drugs based on single compound and single target approach. A systemic approach was further developed when cases of viral epidemics and pandemics such as SARS, Bird flu, Swine flu, Zika, Ebola, Nipah, SARS-CoV-2 happened. The exponential growth in the quality and quantity of the research due to such challenges is now setting the scene for further studies in medicinal plants.

I am happy to know about that the Institute of Bioresources and Sustainable Development (IBSD), Imphal has developed a compendium of medicinal plants with special emphasis on therapeutic aspects based on the Bioresources having anti-viral activities.

I am confident that this will be an important document to be a primer for research in various disciplines to combat the viral epidemics and pandemics.

My best wishes for all the activities of IBSD in future.

(Renu Swarup)

# ACKNOWLEDGEMENT

Medicinal plant based traditional medicine is an age old traditionally obliged health care practices plays an important role for the prevention and management of infectious disease by strengthening the immune system. The present global scenario enforces the scientific community to show interest in herbal medicine for the development of the effective alternative medicines to combat infectious diseases.

The North eastern region of India comprises varied climatic and edaphic factors, location, and divergence of physiology and morphology of the species. The region has unique distinction of possessing a wide range of forest types in diverse geographic areas. The region has plants of a wide range of species from the Himalaya to Malaya which is also seen as treasures of biodiversity.

This compilation of around seventy medicinal plants species of NER having anti-viral properties is an attempt to draw the attention of the researchers and academicians to explore the possibilities for the development of efficacious lead/ products/ preparations from natural resources for the management and betterment of the human health at large.

It gives me immense pleasure to express my sincere gratitude to Dr. Renu Swarup, Secretary, Department of Biotechnology, Govt. of India, New Delhi for her encouragement, cooperation and support to make this information available to the scientific fraternity.

I would also like to express my sincere thanks to Dr. Mohd. Aslam, Dr. Anamika Gambhir and Dr. Manoj K Modi of Department of Biotechnology, Govt. of India for their constant support for making this effective compendium.

I am thankful to the Director of Botanical Survey of India, Dr. Ashiho A. Mao who has extensively shown his interest in bringing this compendium to a success by providing his guidance and support from his institution.

My special thanks to Dr. S. Rajan, an eminent ex-scientist from AYUSH who has given his precious time to structure this exercise and provided his valuable inputs in compilation of this compendium.

I would like to express my thanks to all the scientists and staff members of IBSD, especially to Dr. Nanaocha Sharma, Dr. Sunil S. Thorat and Mr. Rajendra K. Labala who has put their efforts in compilation and articulating the exercise in making this compendium.

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# INTRODUCTION: Antiviral Medicinal Plants

The world has experienced a major jolt in the year 2019 with the invasion of a strange organism on the human life on earth in a form of a virus which has its evolutionary resemblance to that of SARS virus, later it was recognized as a Corona virus and named it as Covid-19. The virus spread headed throughout the globe in 218 countries and territories and was declared as a pandemic by World Health Organization.

Researchers throughout the world started knocking their brains to decode the virus to understand its origin and provide measures to combat it in possible ways. Entire world was put on alert to stop the further expansion of the virus, however it still invaded majority of the countries on the globe and was said to be a major pandemic occurred after a century.

Machineries from various sectors including government, industries, academician, and researchers worldwide had made it a priority to counter the covid-19 in all possible ways.

The department of AYUSH, Government of India along with other organizations like ICMR, DST, and DBT has put COVID research on priority. The Institute of Bioresources and Sustainable Development (IBSD), one of the institutes of the Department of Biotechnology, Ministry of Science and Technology, Government of India located at the North Eastern region of the country at Imphal, Manipur was advised to investigate the probable measures to provide inputs to fight against the pandemic caused by the virus.

The North Eastern region of India is well known for its rich biodiversity with various medicinal plants having anti-viral properties. IBSD has taken up the task with the able leadership of the newly joined Director Prof. Pulok K. Mukherjee to explore the antiviral medicinal plants from the region. The team of scientists was given a task to gather the information on plants having anti-viral properties and could identify around seventy medicinal plants from the region.

The Institute has collectively contributed for the preparation of compendium of antiviral plants of North East India. The scientific staff from the IBSD Imphal and from its centre and nodes at Sikkim, Meghalaya and Mizoram was assigned a task to find out the medicinal plants from the region which are reported for anti-viral activities. After receiving the list of around seventy (70) plants from the scientists, details about the enlisted plants based on information pertaining to the taxonomic, therapeutic, phytochemical, and pharmacological information on medicinal plants was categorized accordingly and fields/titles for collecting information was made as under:

1. Scientific classification
2. Vernacular names
3. Synonyms
4. Botanical description of the Plant
5. Photograph of plant
6. Photograph of herbarium
7. Geographical distribution
  - 7.1. Geographical location
8. Plant material of interest: aerial part or entire plant
  - 8.1. General appearance
9. Photograph of the plant part used
10. Medicinal /Therapeutic Uses
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  - 19. References: updated references till April 30, 2020

Based on the data fields, information was gathered for all the enlisted plants from available collections and from the various published literature. The gathered information was studied and referred to experts for their comments. After receiving few suggestions from the experts, it was decided to take a collective view of experts through online meeting and discussions. A meeting was held where discussion on titles listed above was suggested to be restructured by removing the detailed classification, redundant information and renaming of few titles for better understanding. The titles removed and renamed are as under:

- 1. Botanical Name
- 2. Synonym
- 3. Family
- 4. Common names
- 5. Description
- 6. Distribution
- 7. Part used
- 8. Pharmacological studies

The available information was accordingly placed under the suggested titles and each of the plant information was referred to an expert Dr. S. Rajan, former Scientist from AYUSH for his comments and editing. On receiving the comments and suggested changes, the information was restructured and sent to another expert Dr. Ashilo Mao, Director, Botanical Survey of India, Kolkata for his referral and comments along with original photographs of the plants. The instructions suggested by Dr. Mao were implemented and accordingly all the plants information was compiled in a chapter format.

The seventy plants with anti-viral properties are arranged and compiled in a form of compendium of anti-viral plants of North East India.

The compendium of anti-viral plants of NER is prepared with an intention to serve as a reference guide for the researchers and students from the various disciplines of biology including botany, natural product chemistry, pharmacology, and biotechnology. The compendium gives brief and specific information on botanical name, family, common names, or vernacular names of the listed plants along with brief morphological description and plant distribution. Being a compendium on anti-viral plants, the vital information in the form of plant parts used and photograph is specifically provided. Other details on medicinal/therapeutic uses including uses described in pharmacopoeias and in traditional systems of medicine is provided. Information on uses supported by clinical data, traditional/folklore uses described in folk medicine on special uses in north eastern India which is not supported by experimental or clinical data is specified. Information pertaining to dosage forms used in tradition, phytochemical profile, pharmacological studies clinical pharmacology is provided for pharmacological researchers. Other useful information on toxicity and safety, clinical studies, contraindications, precautions, adverse reactions, marketed formulation is extracted from published literatures and provided for the diverse users along with references.

For medicinal purposes, plants were used long before the prehistoric period. Ancient Unani manuscripts identified the use of herbs in Egyptian papyrus and Chinese writings. There is evidence that Unani Hakims, Indian Vaidas, and European and Mediterranean cultures have been using herbs as medicine for over 4000 years. In their healing practices, indigenous cultures such as Rome, Egypt, Iran, Africa, and America used herbs, while western medicine systems such as Unani, Ayurveda and Chinese Medicines were created by others.

Traditional systems of medicine continue to be commonly accepted on many accounts. The increase in population, the insufficient availability of medicinal products, the prohibitive cost of medication, the side effects of several synthetic drugs and the emergence of resistance to commonly used infectious disease drugs have led to increased focus on the use of plant materials as a source of medicinal products for a wide range of human diseases.

India has been recognized by ancient civilizations as a rich repository of medicinal plants. Many medicinal and aromatic plants, which are primarily collected as raw materials for the manufacture of drugs and perfumery products, are the main repository of the forest in India. In INDIA, AYUSH systems have codified approximately 8,000 herbal remedies. The main systems for indigenous medicines are Ayurveda, Unani, Siddha and Folk (tribal) medicines. Ayurveda and Unani Medicine are the most evolved and commonly practiced systems in India.

Recently, 80% of people worldwide rely on herbal medicines for some part of their primary health care needs, calculated by the WHO (World Health Organization). Around 21,000 plant species could be used as medicinal plants, according to the WHO.

About three-quarters of the world's population relies primarily on plants and plant extracts for their health care needs, according to available statistics. About 30 per cent of all plant species have been used for medicinal purposes at one time or another. Plant drugs are estimated to represent as much as 25 percent of the total drugs in developed countries such as the United States, while the contribution is as much as 80 percent in rapidly developing countries such as India and China. The economic value of medicinal plants, therefore, is much greater for countries like India than for the rest of the world. These countries supply two-thirds of the plants used in the western medical system, and the rural population's health care system depends on indigenous medical systems.

Medicinal plant care is considered extremely healthy since there are no side effects or minor side effects. Such therapies are in tune with nature, which is the greatest gain. The golden truth is that every age group and gender is independent of the use of herbal therapies.

The ancient scholars only assumed that herbs were only solutions to treat a variety of problems and diseases related to health. We performed extensive research on the same, experimented to arrive at specific conclusions about the effectiveness of various herbs that have medicinal value. Most of the medications are free from side effects or reactions, hence formulated. Therefore, herbal therapy

is rising in popularity throughout the world. These medicinal-grade herbs provide a reasonable means of treating many internal diseases that are otherwise considered difficult to cure.

We are moving away from nature as our lifestyle is becoming techno-savvy now. Although we are part of nature, we cannot hide from nature. Since herbs are natural products, they are comparatively healthy, eco-friendly, and locally available because they are free from side effects. There are traditionally a lot of herbs used for ailments associated with various seasons. To save human lives, there is a need to encourage them.

In comparison to synthetic medicines, which are regarded as dangerous for human beings and the environment, these herbal products are today the symbol of protection. While herbs have been priced for centuries for their medicinal, flavoring, and aromatic qualities, the synthetic products of the modern age have, for a while, overshadowed their value. The blind dependency on synthetics, however, is over and people return to the natives with the expectation of safety and stability. It is time to internationally encourage them.

Similar to many other pandemics in recent decades, COVID-19 has emerged as a new epidemic, and there is currently no successful treatment for SARS-CoV-2. Because a new drug development program can easily take more than 10 years with a high risk of failure, finding cures for COVID-19 to satisfy urgent needs through this path seems unattainable. Numerous investigational drugs that have recently reached clinical trials for COVID-19 are all repositioned from previously approved molecules or under investigation for other indications. A preliminary clinical trial in France recently showed promising results of chloroquine and hydroxychloroquine in reducing the viral load of SARS-CoV-2 in COVID-19 patients. Interestingly, both chloroquine and hydroxychloroquine are synthetic. Quinine analogs and have previously been replicated for the treatment of HIV, systemic lupus erythematosus and rheumatoid arthritis, in addition to their antimalarial application. Studies of the quinine scaffold have shown that this class of molecules has the peculiar properties of enriching lysosomes that underpin their antimalarial and antiviral activities. Multiple clinical tests using chloroquine and hydroxychloroquine to treat COVID-19 are currently underway.

To completely unleash the medicinal power of plants to treat human diseases globally, a significant amount of interdisciplinary research is required to study the genetics, chemistry, and biochemistry of various medicinal plants, to develop the capacity to produce bioactive natural plant products and their analogs at will through metabolically engineering, and to explain their mechanisms and potential for action.

In the current scenario of lack of any proven cure for COVID-19, possible antiviral, and immune booster herbal medicines, extracts and formulations may be a good treatment that can help to reduce the global mortality rate associated with COVID-19. Ministry of AYUSH, India has already provided guidelines for preventive health measures and enhancement of immunity with special reference to respiratory health using conventional Ayurveda and natural herbs.

1. Botanical Name: *Acorus calamus L.*
2. Synonym: *Acorus calamus var. angustifolius* (Schott) Engl.
3. Family: Acoraceae
4. Common Name
 

Ayurvedic:	Vacha
Bengali:	Bach;
English:	Sweet flag, Sweet cane, Sweet grass, Sweet root, Myrtle grass;
Gujarati:	Gandhilovaj, Godavaj;
Hindi:	Bach, safed Bach, Bajai, Ghorbach;
Kannada:	Athibaje, bajegida
Kashmiri:	Vachi, Vaigandar;
Malayam:	Vaembu, vashampa;
Marathi:	Vekhand;
Nepali:	Bojho;
Sanskrit:	Bhadra, Vacha, Bhutanashini;
Tamil:	Akkitam, Narram, Percollan, Vasambu
Telugu:	Vadaja, Vasa, Wasa;
Tibetan:	Sudag;
Unani:	Bacch, Vaj turki.
Urdu:	Bach, Bachh, Waj-e-turki;
5. Description: A strongly aromatic semi-aquatic perennial herb; rhizomes creeping, jointed, somewhat vertically compressed, 1.3-2.5 cm thick, pale to dark brown and spongy inside. Leaves clustered, narrow, up to 80 cm long, linear to narrowly ensiform, glossy bright green, apex acute, base amplexicaul; petioles sheathing for 20-50 cm. Flowers in spadix, cylindrical, white, or pale green, fragrant, arranged compactly on a sessile, cylindrical, stumpy spadix 5-7 cm long. Fruits (berries) green, angular, 3-celled, fleshy, containing 1-3 oblong seeds.
6. Distribution: Native of Central Asia and Eastern Europe. Species is globally distributed in the North temperate hemisphere and tropical Asia. Within India, it has been recorded throughout in marshes, wild or cultivated, ascending to an altitude of 2200 m in the Himalayas.
7. Part Used: Whole plant.



*Acorus calamus L.*

## 8. Medicinal/Therapeutic Uses



Leaves



Rhizome



Dried Rhizome



Dried Rhizome slice

8.1. Uses described in pharmacopoeias and in traditional systems of medicine: The plant has been used to cure several diseases like asthma, fever, cough, epilepsy, hysteria, skin diseases, depression, haemorrhoids, diarrhoea, insomnia, dysentery, kidney and liver problems, mental retardation, bronchitis, sedative and vascular disorders (Mukherjee *et al.*, 2007). The rhizome paste is used for rheumatism, fever, inflamed joints (Imam *et al.*, 2013). The Rhizome is employed in nervous disorders. It has got prominent action on central nervous system where it improves grasping power, memory, intellect, speech and correct aberrations of emotions, mood and personality of an individual (Dua *et al.*, 2009). The Rhizome contains Aphrodisiac activity so it is used as aphrodisiac agent (Singh *et al.*, 2010).

8.2. Uses supported by clinical data: Anti- viral, Anti- cancer, Antibacterial, Antifungal, Antiulcer, Anti- ischemic Heart disease, Anti- inflammatory, Anti- oxidant, Anti-diabetic, Anti- anxiety, Anti- rheumatitis, Anti- sczizophreni, Antidiarrheal, Bronchodilatory effect, Anticellular and Immunosuppressive activity, Insecticidal activity (Umamaheshwari and Rekha, 2018), (Balakumbahan *et al.*, 2010).

8.3. Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data: It is used in Ayurveda to counter the side effects of

all hallucinogens. It has been used medicinally for a wide variety of ailments and because of its aroma; the essential oil is valued in the perfume industry. The essence from the rhizome is used as a flavour for pipe tobacco. It is eaten in crystallized form which is called "German ginger". In Europe it was often added to wine and the root is also one of the possible ingredients of absinthe. In Lithuania the Sweet flag is added to home baked black bread. In Britain the plant was used as a sweet-smelling floor covering for the packed earth floors of medieval dwellings and churches and stacks of rushes have been used as the centrepiece of rush bearing ceremonies for many hundreds of years. For the Penobscot people this was a very important root. Teton- Dakota warriors chewed the root to a paste and rubbed on their faces, it was thought to prevent excitement and fear when facing an enemy (Kumar *et al.*, 2014). Traditionally it is used as an ingredient of various cocktail preparations and for the management of severe inflammatory disorders in Indian system of medicine (Rajput *et al.*, 2013).

- 8.4. Special uses in North East India: In Sikkim traditionally the Lepcha tribe used for the treatment of skin disease, fever cough. Rhizomes are used by the Apatani tribe of Arunachal Pradesh for cure of cuts, wounds, skin diseases, bone fracture (Pradhan & Badola, 2008).
- 8.5. Dosage forms used in tradition: External application of rhizome pastes cures skin diseases and on the forehead in case of fever. Small piece of dried rhizome is taken curing distressing cough. Dried cut piece is given to child for speech clarity or to stammering child.

## 9. Phytochemical profile

The rhizomes were examined for the content and composition of fatty acids and sugars. Composition of the mixed fatty acids, as indicated by gas chromatography of the corresponding methyl esters were myristic (1.3%), palmitic (18%), palmitoleic (16.4%), stearic (7.3%), oleic (29.1%), linoleic (24.5%) and arachidic (3.2%). In the leaves Beta- Asarone (27.4 – 45.5%) was the major constituent and in the rhizomes, acorenone (20.86%) was dominant (Balakumbahan *et al.*, 2010). The major chemical constituent is volatile oil (1.0%). The leaves are thick which contain the yellow aromatic volatile oils having beta asarone as the main constituent and the rhizomes contain the choline, flavone, acoradin, galangin, acolamone, isocolamone and aerial parts of the plant contains lutcolin-6, 8-c- diglucoside. Other constituents are pinene, cineole, limonene, terpineol, azulene, eugenol, camphene, ethanol, magnesium, zinc, tannins, terpenes, methanol and camphor (Singh *et al.*, 2011).

## 10. Pharmacological Studies

The alcoholic extract is exhibited potent antiviral activity against herpes virus i.e. HSV-1 and HSV-2. The drug in a dose of 1.5- 3gm/day was found effective against ischaemic heart disease, improvement in chest pain, instable angina, dyspnoea reduction of body weight, improving in ECG, decreasing serum

cholesterol, decreasing SLDL and increasing SHDL. The ethanolic extract of root possesses a dose and time dependent anticancer, apoptotic and anti- angiogenic activities on prostate cancer cell culture. Ethanolic extract marks the survival and apoptosis as well as inhibits the angiogenesis (Umamaheshwari & Rekha, 2018). The effect of *rhizome* extract on the cell viability showed a dose response relationship of cell survival. The Poly-(ADP- ribose) polymerase (PARP) cleavage involved in the apoptotic process was found to be at higher expression in rhizome extract treated cells. It was supported by the suppression of mRNA expression of the pro- angiogenic factor VEGF- A in LNCaP cells treated with the extract. The sweet flag and/or its bioactive phytochemical alpha ( $\alpha$ )-and beta ( $\beta$ )-asarone, is a well-known drug in the traditional system of medicine which possesses anti-tumour and chemo-preventive activities as evident from numerous pre-clinical studies both *in-vitro* and *in-vivo* (Das *et al.*, 2019). A polyherbal compound containing rhizome as one of the ingredients has been reported to reduce epilepsy attacks in patients by up to 50% (Amit & Vandana, 2013).

#### 10.1. Clinical pharmacology: Data not available

#### 11. Toxicity and safety

It has been found to contain an alkaloid that may be carcinogenic. (Rammanohar, 2019). In some *in-vivo* and *in-vitro* studies have shown that oil induces malignant tumors due to  $\beta$ -asarone (Amit & Vandana, 2013). It is poisonous under certain conditions causing disturbed digestion, gastroenteritis followed by passage of blood into the feces (Bhatt *et al.*, 2015).

#### 12. Clinical studies: No data available for Clinical studies.

#### 13. Contraindications: Should not be taken in oral doses.

#### 14. Precautions

Usage of sweet flag in any form during pregnancy should be avoided as it demonstrates genotoxic potency and it interferes with pregnancy inter- reactions (Bhatt *et al.*, 2015). It is indeed interesting to see that Ayurvedic texts like the Cakradatta have recommended the purification of calamus root before use (Rammanohar, 2019).

#### 15. Adverse reactions

Feeding studies in rat using the Indian sweet flag oil (high- beta- asarene) have shown death, growth depression, hepatic and heart abnormalities and serious effusion in abdominal and/ or peritoneal cavities. (Gupta & Raina, 1998). The U.S Food and Drug Administration reported that the sweet flag was unsafe, based upon cancerous tumors found in laboratory animals treated with the plant (Bhatt *et. al*, 2015).

16. Marketed formulation, if any:

Formulations	Company
1. Scavon Vet cream	Himalaya Drug Company, Makali, Bangalore, India.
2. Ayurvedic and Herbal Chemicals of <i>Acorus calamus</i>	Jenson Enterprises Private Limited, Chengalpattu, India.
3. Bulk Drugs of <i>Acorus calamus</i>	Hindustan Pharmaceuticals, Amritsar, India.
4. Varch oil	Herbotech Pharmaceuticals, Amritsar, India.
5. Anxi- 6	Kalhan Pharmaceuticals Private Limited, Jalandhar, Punjab, India.
6. Herbal preparations of <i>Acorus calamus</i>	Sydler Remedies Private Limited, Mumbai, India.
7. Ayurvedic Preparations of <i>Acorus calamus</i>	Kebee Pharmachemie Private Limited andheri, Mumbai, India.

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1. Botanical Name:	<b><i>Aegle marmelos</i> (L.) Correa</b>
2. Synonym:	<i>Belou marmelos</i> (L.) Lyons
3. Family:	Rutaceae
4. Common Name	
English:	Bael fruit, Indian bael, Holy fruit, Golden apple, Elephant apple, Bengal quince
Hindi:	Baelputri, Bela, Sirphal, Kooralam
Sanskrit:	Bilva, Shivdurma, Shippala
Manipur:	Heirikhagok, Harikhagok, Heikhagok (Manipuri)
Khasi:	Soh-bel
Nepali:	Bael, Gudu
Bengali:	Bela, Bael
Odissa:	Belo, Bela
Marathi:	Baela
Gujarati:	Bili, Bilivaphal, Bil
Tamil:	Kuvilam, Vilvam
Telugu:	Bilvamu, Meradu
Kannad:	Belapatre, Bilvapatre
Malayalam:	Kuvvalam, Kulakam

5. Description: A medium sized spinous, deciduous, aromatic tree upto 8.0 m height with spines, straight strong and sharp axillary thorns and yellowish brown shallowly furrowed corky bark; Leaves: trifoliate leaves, sometimes pentafoliate, leaflets ovate - lanceolate, lateral subsessile, terminal long – petioled; Flowers: borne in few flowered, greenish white, axillary panicles, sweet scented; Fruits: large, upto 15 cm in diameter, globose, ovoid or pyriform, 8-15 celled, rind grey or grayish – yellow, woody, pulp orange, sweet; Seeds: numerous in aromatic pulp, oblong, compressed, embedded in orange brown sweet gummy pulp, testawooly and mucilaginous (Prajapati et al., 2012; Gupta and Tandon, 2004; Zingare, 2012; Bhutya 2011) .

6. Distribution: *A.marmelos* is a semi tropical plant that flourishes at an approximate altitude of 1200 meter from sea level. It is mainly obtained in hill areas and dry forests. It is found almost in all states of India like Himachal Pradesh, Andhra Pradesh, Bihar, Jammu and Kashmir, Kerela, Karnataka, Madhya Pradesh, Maharashtra, Punjab, Rajasthan, Uttar Pradesh, Tamil Nadu and West Bengal. It is also cultivated in Nepal, Myanmar, Vietnam, Tibet, Ceylon, Laos, Cambodia,

Malaysia, SriLanka, Bangladesh, Thailand, Indonesia, the dried areas of Java, Fiji and some parts of Philippine Islands.

7. Part Used: The whole plant (Leaves, root, bark, flower, fruit, seed) possess high medicinal value and traditionally used for treatments of various diseases. However, the plant parts which are highly in use are leaves and fruits.



*Aegle marmelos*

## 8. Medicinal/Therapeutic Uses

### 8.1. Uses described in pharmacopoeias and in traditional system of medicine

*A.marmelos* has been used as an herbal medicine for the management of diabetes mellitus in Ayurvedic, Unani and Siddha systems of medicine in India. It is traditionally used to treat jaundice, constipation, chronic diarrhoea, dysentery, stomachache, fever, asthma, inflammations, acute bronchitis, snakebite, leprosy, abdominal discomfort, acidity, burning sensation, epilepsy, indigestion, smallpox, ulcers, mental illness, nausea, sores, swelling, thirst, thyroid disorders. It is also used to treat Anaemia, fractures, high blood pressure. (Meena et al, 2011) Sweet drink prepared from the pulp of fruits produce soothing effect on the patients who have just recovered from bacillary dysentery. (Singh et al, 2013)

The roots and the bark of the tree are used in the treatment of fever by making a decoction of them. The leaves are made into a poultice and used in the treatment of ophthalmia (Yogita Choudhary et al, 2017).

### 8.2. Uses supported by clinical data

Extensive experimental and clinical studies prove that *A.marmelos* possesses antidiarrheal, antimicrobial, antiviral, radioprotective, anticancer, chemo preventive,

hepato-protective, antipyretic ulcer healing, antigenotoxic, diuretic, antifertility and anti-inflammatory properties, which help it to play role in prevention and treatment of many diseases.

### 8.3. Traditional/folklore uses described in folk medicine, not supported by experimental or clinical data

The different parts of *A.marmelos* are used for various therapeutic purposes, such as for treatment of Asthma, Anaemia, Fractures, Healing of wounds, swollen joints, high blood pressure, jaundice, diarrhoea, typhoid and troubles during pregnancy. Flowers are used in diarrhoea, excessive thirst, vomiting and eye disorders and it is advisable as diet in eruptive boils.

### 8.4. Special uses in North-east India

Across the North-east region, the fruits of *A.marmelos* have been used in the treatment of various gastric problems. Both the ripe and unripe fruits are used to cure diarrhoea, stomach ulcer, dyspepsia and dysentery. In Assam, Manipur and Meghalaya, the fruit pulp is also used as laxative. In Assam, *A.marmelos* tea is also prepared from the dried fruit which is used for the treatment of heart weakness (Hazarika and Singh 2018; Lalfakzuala et al.2007; Majumdar and Datta 2009; Patiri and Bora 2007; Shankar and Rawat 2008).

### 8.5. Dosage forms used in tradition

- Small unripe fruit is consumed with fennel seeds and ginger in decoction for piles.
- Two tolas of bark juice is given with a cumin in milk to increase the quality of seminal fluid.
- For treatment of asthma, 5 gram of grind *A.marmelos* leaves mixed with one spoon of honey is taken orally in morning and evening.
- In fractures, 10 gram of pulp extract powder mixed with 50 gms of pure ghee and ½ spoonful of turmeric powder with a glass of lukewarm water is taken orally twice a day.
- Equal quantity of rind, roots, leaves, fruit pulp juice extract mixed with 10gm of honey is taken for healing wounds.
- In case of swollen joints, *A.marmelos* pulp mixed with hot mustard oil is applied on the affected area twice a day.
- Extract juice of 100 nos of soft leaves mixed with powder of 10 no's of black pepper and five glasses of sugarcane juice is taken every morning and evening after meals for treatment of Jaundice.
- One spoon of raw fruit pulp if taken twice a day stops frequent vomiting nausea during pregnancy.
- For treatment of Typhoid, 200 leaves boiled in one cup of water till it becomes thick paste with a little honey added to it is taken twice or thrice a day.

## 9. Phytochemical profile

Leaf-Skimmianine, Aeglin, Rutin, Y-sitosterol,  $\beta$ -sitisterol, Flavone, Lupeol, Cineol, Citral, Glycoside, O-isopentenyl, halfordiol, Marmeline, Citronellal, Cuminaldehyde phenylethyl cinnamides, Eugenol, Marmesinin.

Fruit- Marmelosin, Luvangetin, Aurapten, Psoralen, Marmelide, Tannin

Bark – Fagarine, Marmin

Seed-Essential oil: D-limonene, A-D-phellandrene, Cineol, Citronellal, Citral, P-cyrene, Cumin aldehyde

## 10. Pharmacological Studies

**Antibacterial activity:** Antimicrobial activity of different leaf extracts such as Petroleum ether, Dichloromethane, Chloroform, Ethanol and Aqueous extract of *A.marmelos* leaves were tested against Gram positive and Gram-negative bacteria. Results depict that phytochemical extract of *A.marmelos* exhibited significant antibacterial activity (Maheswari *et al*,2009).

**Antiviral activity:** The fruit of *A.marmelos* showed antiviral activity against Ranikhet disease virus (Dhar *et al*,1968).

**Antiulcer activity:** -Antiulcer activity was performed by preparing polyherbal formulation that was investigated by ethanol induced gastric ulcer model in wistar rats. The result shows that the formulation is useful in severe gastric ulcer.

**Anti-histamic activity:** Skimmianine is a quinoline alkaloid isolated from the roots of *A.marmelos*. In the study the effects of skimmianine on the histamine release from rat mast cells are tested.

**Anti-inflammatory, antipyretic and analgesic activity:** The serial extracts of the leaves of *A.marmelos* were investigated for anti-inflammatory property. The analgesic and antipyretic properties were also evaluated.(Arul *et al*,2005)

**Hepatoprotective activity:** The experiments performed on animals indicate that, the *A.marmelos* leaves have excellent hepatoprotective activity (Singanan *et al*, 2007)

**Antidiabetic-activity:** Aqueous extract of *A. Marmelos* leaves was evaluated for hypoglycaemic and anti-oxidant effect by using alloxon induced diabetes in male albino rats (Upadhyay S *et al*, 2004).

**Myocardial infarction:** The effect of *A. marmelos* leaf extract and alpha tocopherol on plasma lipids, lipid peroxide and marker enzymes in rats has been established.

**Testicular activity:** It is predicted that the aqueous extract of leaf of *A.marmelos* has a potent anti-testicular effect at a specific dose.

**Cardiotonic activity:** Fresh fruit juice of *A.marmelos* plant with different dilutions was used for cardiotonic activity. The activity was tested by using isolated frog heart assembly.

**Anxiolytic and Antidepressant activity:** Anxiolytic and Antidepressant activities of methanol extract of *A.marmelos* leaves as well as its interaction with conventional anxiolytic and antidepressant drugs using elevated plus maze and tail suspension test in mice has been proved.

**Wound healing activity:** Effect of topical and intraperitoneal administration of methanolic extracts of *A.marmelos* ointment and injection was studied respectively on two types of wound models i.e. the excision and incision wound models in rats. Both the injection and the ointment of the methanolic extract produced significant response in both of the wound type tested.

**Anticonvulsant activity:** The anticonvulsant effect of ethanolic extract from the leaves of *A.marmelos* concluded that it interferes with gabaergic mechanisms to exert their anticonvulsant effect in addition it reveals the presence of flavonoid attributed to their anti-convulsant action. The activity reported was dose dependent.

**Anti-fertility activity:** The study was carried out to evaluate the effective concentration of aqueous extract of *A.marmelos* leaves on male reproductive system of albino rats. Significant decrease in the weights of testis. A dose related reduction in the testicular sperm count and motility and abnormal sperm count were observed.

#### 10.1. Clinical pharmacology:

→A study was conducted to evaluate the hypoglycaemic effect of *A.marmelos* flower extract in diabetic patient. Daily administration of the extract on the patient significantly reduced the fasting glucose levels and oral glucose tolerance test values with no adverse effects.

→*A.marmelos* leaves were evaluated on non-insulin dependent diabetes mellitus patients. It causes significant changes in postprandial blood glucose level of patients who were receiving *A.marmelos* leaves in comparison to patients who were on their standard oral hypoglycaemic therapy.

→Root extract of *A.marmelos* was administered for the duration of 12 weeks on 46 patients with Irritable bowel syndrome (IBS). The therapy showed statistically significant improvement in all the clinical features of IBS as well as in the IBS severity score.

→*A. Marmelos* has been considered as one of the effective medicines for the treatment of nonspecific diarrhoea. Therefore, its efficacy for the treatment was tested in 25 patients. All the patient was treated with powdered unripe fruit of *A. Marmelos* (5gm thrice daily for 21 days) (Singh et al, 1993).

11. Toxicity and safety: *A.marmelos* has been used for centuries not only for its dietary purposes but also for its various medicinal properties. Hence it is generally considered safe and few studies have been carried out with respect to its toxicity. Total alcoholic, total aqueous and methanolic extracts were collected from leaves of *A.marmelos* and studied in experimental rats for their toxicity. No histopathological changes were found when the extracts were administered intraperitoneally for 14 days successively at the dose of 50mg/kg body weight. The collected data demonstrate that the extracts of the leaves of *A.marmelos* have a high margin of drug safety. Pharmacological studies on animal models involving repeated doses of *A.marmelos* fruit extract over a period of up to 30 days have not reported any adverse effect

12. Clinical studies: No data available

13. Contraindications

- Root is contraindicated in tuberculosis.
- Ripe fruit is contraindicated in irritable bowel disease.
- The leaves are said to cause abortion and sterility in women.
- The bark of the plant is used as a fish poison.
- Excessive bael consumption can lead to stomach upset and constipation
- Marmelosin in large doses cause sleepiness and lowering of respiratory rate.

14. Precautions

Bael fruit is likely safe when consumed as food, however, there are limited human studies on bael's safety, especially in the form of concentrated supplement or extract.

-Taking bael along with diabetes medications might cause blood sugar to drop too low. So, it is generally advised to monitor blood sugar level while taking bael with anti-diabetic drugs. The dose of diabetes medication might need to be changed. Bael can also interact with Thyroid hormones or even anti-thyroid medicines or drugs.

-Pregnant and breastfeeding women should exercise caution with bael products and speak to their doctor about any supplement usage.

15. Adverse reactions: No data available

## 16. Marketed formulations

Sl.No	Marketed formuations	Company name
1	Chyawanprash	Himalaya
2	Aegle marmelos capsule	La-medica(India) Pvt. Limited
3	Leucare capsules	Shrey Nutraceuticals & herbals
4	Entrostat Syrup	Ambika medico
5	Kof-rid Syrup	Ambila medico
6	Pregeight	Sydler Remedies Pvt.Ltd.
7	Ojamin	Tates Remedies
8	Manasamithravatakram	Oushadhi
9	Pushyanugamgulika	Oushadhi
10	Vilwadigulika	Oushadhi
11	Glucomap	Maharishi Ayurveda
12	UlcoBliss Tablets	Bliss Ayurveda
13	Capsule BilvGiri	Ayurvedic Sanjivani
14	R-Qunol syrup	Vatsal Ayurvedic Products Ltd.

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1. Botanical Name: **Allium sativum L.**
2. Synonym: NA
3. Family: Alliaceae
4. Common Names:

Bengali:	Lashan, Lashun, Rasun;
English:	Garlic
Gujarati:	Lasan;
Hindi:	Lahsan, Lasun
Kannada:	Belluli;
Malayalam:	Vellulli, Velutha ulli;
Marathi:	Lasunas;
Sanskrit:	Lashuna, Lasuna, Ugragandha, Bhootaghni, Rasona
Tamil:	Vallai-poondu, Vellai-vengayam;
Telugu:	Velluli, Tella-gadda.
5. Description: *Allium sativum* (Garlic) is a bulbous perennial herb, closely related to the onion. It has a tall, erect flowering stem that reaches 2- 3 feet in height. The plant has pink or purple flowers that bloom in mid to late summer. The part used medicinally is the bulb. The bulb is odoriferous and contains outer layers of thin sheathing leaves surrounding an inner sheath that encloses the clove. Often the bulb contains 10 to 20 cloves that are asymmetric in shape, except for those closest to the center. It is pollinated by bees, butterflies, moths, and other insects.
6. Distribution: *A. sativum* is believed to originate from Kazakhstan, Uzbekistan, and Western China. *A. sativum* was domesticated long ago and is mentioned in ancient Egyptian, Greek, Indian, and Chinese writings. Garlic grows in temperate and tropical regions all over the world, and many cultivars have been developed to suit different climates. Almost 10 million tons of garlic are produced each year with China, Korea, India, USA, Spain, Egypt, and Turkey being the world's largest producers. Garlic is a fundamental component in many or most dishes of various regions, including eastern Asia, South Asia, Southeast Asia, the Middle East, northern Africa, southern Europe, and parts of Latin America. Garlic is essential in Middle Eastern and Arabic cooking, with its presence in many food items. In

Levantine countries such as Jordan, Palestine, and Lebanon, garlic is traditionally crushed together with olive oil, and occasionally salt, to create a Middle Eastern garlic sauce called Toum (meaning "garlic" in Arabic).

7. Part Used: Generally, the bulb, sometimes leaves are also used.



*Allium sativum* (Photo source BSI)

8. Medicinal /Therapeutic Uses:

#### 8.1 Uses described in pharmacopoeias and in traditional systems of medicine:

In India, garlic is used to relieve problems, such as coughs and fevers or applied externally to prevent greying of hair and to improve skin conditions, such as eczema and scabies as well as to treat tetanus and lungs inflammation. In Pakistan, garlic extract is traditionally taken orally to settle the stomach, treat coughs, and reduce fever. In Nepal, East Asia, and the Middle East, it is used to treat several ailments including fevers, diabetes, rheumatism, intestinal worms, colic, flatulence, dysentery, liver disorders, tuberculosis, facial paralysis, high blood pressure, and bronchitis. In Africa, garlic is used as an antibiotic, and it has a reputation for lowering blood pressure and cholesterol, and inhibiting thrombus formation (Kuete, 2017).

*A. sativum* is an extremely important plant species in both ancient and modern ages. Its traditional use has spread in all world cultures, and besides its use in fresh, cooked and dehydrated forms for human consumption, there are many folk medicines based on garlic. Overall, garlic is used for the treatment of many

conditions, including cardiovascular and respiratory ailments. It also is an effective treatment against diabetes and inflammatory diseases (rheumatisms). In middle ages, it was used to cure deafness, earaches, flatulence, scurvy, leprosy, black plaque, dog and snake bites and even clotting disorders in animals (horses) (Mikail, 2010). In Ayurvedic medicine, it is an extremely important plant and is used for a variety of problems: insect bites, intestinal worms, headache and tumours, while folk medicine practitioners in India use it for the management of heart disease, cancer, parasites, fungal infections and diabetes (Rizvi and Mishra, 2013). In Mexico, the bulb epidermis is used to treat stomach-ache and dysentery (Alanís, et.al. 2005). Infusion of garlic is used for the treatment of epilepsy, while 'acetum aromaticum' (garlic boiled with vinegar and sugar) is used as topical antiseptic. Combined with milk, it is used as a vermifuge, while mashed with honey or in a form of extract, it is effective against rheumatisms. Powdered bulb applied locally can treat alopecia (Müberra, et.al. 2006).

#### 8.2. Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data:

Historically, garlic has possessed medicinal and dietary importance in different cultures for more than 4000 years. In addition, there is evidence that proves garlic has been consumed for various purposes over the centuries. For instance, during the Greek Olympics for stamina enhancement in athletes, during the Second World War as an antibacterial agent for prevention of gangrene in soldiers, in India as an antiseptic lotion in order to wash ulcers, and in China as a remedy of headache, fever (Marta. et.al., 2007) dysentery, and cholera. In ancient Greece and Rome, naturalists and physicians such as Dioscorides, Hippocrates and Pliny the Elder mentioned garlic, onion and other alliums as important medicinal plants. Garlic was recommended for a variety of illnesses: skin problems (rashes, birthmarks, leprosy, ulcers, eczema, baldness), eye diseases (cataracts), kidney disorders and for worms, lice, nits, dog and snake bites. In the Middle Ages, herbal physicians such as Paracelsus pointed to significance of garlic against intestinal worms. Later, garlic was used for the treatment of the black plaque and tuberculosis. The use of different alliums, especially garlic and onion, is still employed in folk medicine worldwide (Sharifi-Rad, et.al, 2016)

#### 8.3. Special uses in North East India:

Several species of Allium have been reported from northeast India having ethnobotanical uses and are very popular among the ethnic groups either as spice/vegetables or in folk medicine. Crushed of bulb (about 100g-200g) after frying in mustard oil is applied to chest, throat and back as message to get relief from severe congestion of lungs due to cough (Yumnam et.al., 2012). There is traditional home garden in every *Pangal/Meitei-Panghal* agricultural field from time immemorial used as food additives and medicinal (Ghazanfaret.al., 2020).

#### 8.4. Dosage forms used in traditional medicine:

The following doses are used in traditional forms:

Raw garlic 1–2 cloves (3000–6000 mg)

Garlic oil 2–5 mg

Garlic powder 600–900 mg

Aged garlic extracts 4 ml

1000–7200 mg (as dried form) (Caballero, 2003).

#### 9. Phytochemical profile:

Garlic has a variety of bioactive compounds, including organosulfur compounds, saponins, phenolic compounds, and polysaccharides (Diretto *et.al.*, 2017; Szchowskiet.al., 2018; Bradley *et.al.*, 2016). The major active components of garlic are its organosulfur compounds, such as diallylthiosulfonate (allicin), diallyl sulphide (DAS), diallyl disulphide (DADS), diallyl trisulfide (DATS), E/Z- ajoene, S-allyl-cysteine (SAC), and S-allyl-cysteine sulfoxide (alliin)(Yoo *et.al.*, 2014; Kodera *et.al.*, 2017; Yoo *et.al.*, 2014 and Mansingh *et.al.*, 2018). The total amount of saponin in purple garlic was almost 40 times higher than that in white garlic, and several saponin compounds were only found to exist in purple garlic, such as desgalactogenin-rhamnose, proto-desgalactotigonin, proto-desgalactotigonin-rhamnose, voghieroside D11, sativoside B1- rhamnose, and sativoside R1(Diretto *et.al.*, 2017). Moreover garlic contained more than 20 phenolic compounds with higher contents than many common vegetables (Liu *et.al.*, 2018). The main phenolic compound was beta-resorcyclic acid, followed by pyrogallol, gallic acid, rutin, protocatechuic acid, as well as quercetin (Nagella *et.al.*, 2014). Furthermore, garlic polysaccharides were reported to contain 85% fructose, 14% glucose, and 1% galactose (Shang *et.al.*, 2019).

Bulbs of garlicis reported to contain hundreds of phytochemicals including sulfur-containing compounds such as ajoenes (E-ajoene, Z-ajoene), thiosulfinate (allicin), vinyl dithiins(2-vinyl-(4H)-1,3-dithiin, 3-vinyl-(4H)-1,2-dithiin), sulfides (diallyldisulfide (DADS), diallyl trisulfide(DATS)) and others that accounted 82% of the overall garlic sulphur content (Al-Snafi,2013). Alliin, the main cysteine sulfoxide is transformed to allicin by allinase enzyme after cutting the garlic and breaking down the parenchyma (Zeng *et.al.*, 2017). S-propyl-cysteine-sulfoxide (PCSO), allicin and S-methyl cysteine-sulfoxide (MCSO) are the main odoriferous molecules of freshly milled garlic homogenates (Zeng *et.al.*, 2017). PCSO can produce more than fifty metabolites depend on water content and temperature as well as allinase enzyme that can act on the mixture of MCSO, PCSO, and alliin to produce other molecules, such as allyl methanethiosulfinate, methyl methanethiosulfonate, and further

corresponding thiosulfinates (R-S-S-R0), by which R and R0 are allyl, propyl, and methyls groups (Zeng *et.al.*, 2017). S-alk(en)yl-L-cysteine sulfoxides are the secondary metabolites obtained from cysteine which accumulate in the plants of Allium genus (Souza *et.al.*, 2011). Garlic formulations consist of several organosulfur compounds, N-acetylcysteine (NAC), S-allyl-cysteine (SAC) (Asdaq & Inamdar, 2011), and S-allyl-mercapto cysteine (SAMC), which are derived from alliin (Tran *et.al.*, 2018). Notably, SAC has antioxidant, anti-inflammation, regulated redox, pro energetic, antiapoptotic, and signaling capacities (Souza *et.al.*, 2011), while SAMC shows an anticancer activity through preventing the cancer cells multiplication (Cao *et.al.*, 2017). Allicin (allyl thiosulfinate), is a sulfenic acid thioester and its pharmacological effect is attributed to its antioxidant activity as well as its interaction with thiol-containing proteins (Miron *et.al.*, 2000). In the allicin biosynthesis, cysteine is transformed to alliin that is hydrolyzed by the allinase enzyme (Borlinghaus *et.al.*, 2014). This enzyme composed of pyridoxal phosphate (PLP) which splits alliin and produces ammonium, pyruvate, and allyl sulfenic acid that are highly reactive and unstable at room temperature, where two molecules were combined to form allicin (Miron *et.al.*, 2000 and Shimon *et.al.*, 2007).

## 10. Pharmacological Studies:

### 10.1 Experimentalpharmacology:

Both experimental and clinical studies on different garlic preparations demonstrate these favourable cardiovascular effects. In *in vivo* animal experiments, intravenous administration of garlic extracts produced slight reductions in both systolic and diastolic pressures and oral ingestion of garlic extract in hypertensive animals brought the blood pressure back to the normal level. Although experimental studies demonstrated a clear hypoglycemic effect of garlic, the effect of garlic on human blood glucose is still controversial. Many studies showed that garlic can reduce blood glucose level in diabetic animals. Garlic was effective in reduction of blood glucose in streptozotocin- as well as alloxan-induced diabetes mellitus in rats and mice (Bayan *et.al.*, 2014).

### 10.2 Clinicalpharmacology:

Several clinical studies showed that garlic reduced blood pressure in more than 80% of patients suffering from high blood pressure. In one trial, investigation on 47 hypertensive patients showed that garlic significantly decreased the mean systolic blood pressure by 12 mmHg and the mean supine diastolic blood pressure by 9 mmHg versus placebo. In another study, 200 mg of garlic powder was given three times daily, in addition to hydrochlorothiazide-triamterene baseline therapy, produced a mean reduction of systolic blood pressure by 10-11 mmHg and of diastolic blood pressure by 6-8 mmHg versus placebo. However, these data are insufficient to determine if garlic provides a therapeutic advantage versus placebo in terms of reducing the risk of cardiovascular morbidity in patients diagnosed with

hypertension. Many *in vitro* and *in vivo* studies have suggested possible cancer-preventive effects of garlic preparations and their respective constituents. Garlic has been found to contain a large number of potent bioactive compounds with anticancer properties, largely allylsulfide derivatives. Different garlic derivatives have been reported to modulate an increasing number of molecular mechanisms in carcinogenesis, such as DNA adduct formation, mutagenesis, scavenging of free radicals, cell proliferation and differentiation as well as angiogenesis (Bayan *et.al.*, 2014).

#### 11. Toxicity and safety:

Although the US Food and Drug Administration (FDA) consider garlic safe for humans, it can induce gastric agitation especially if ingested in high doses by sensitive people. To assess the safety of garlic, randomized controlled trials were performed, side effects such as insomnia, vomiting, heartburn, dizziness, diarrhoea, tachycardia, nausea, bloating, flushing, headache, mild orthostatic hypotension, sweating, offensive body odor, and flatulence were observed (Rana *et.al.*, 2011). Allicin is a membrane-permeable compound that can enter cells easily and interact with cellular thiols such as glutathione or cysteine residues in proteins (Miron *et.al.*, 2000; Borlinghaus *et.al.*, 2014 and Shimon *et.al.*, 2007) as well as enzymes containing reactive cysteine and this may be the potential interpretation of allicin's toxicity. The garlic powder or allicin at a concentration of 200 mg/mL can cause significant cell damages in the isolated rat liver (Rana *et.al.*, 2011).

Oxidative hemolysis is the main toxicological mechanism of Allium-derived sulfur compounds and it is distinguished by methemoglobinemia development and Heinz body formation in the RBCs (Salgado *et.al.*, 2011). Allium poisoning symptoms may appear after one day or several days of its ingestion based on the amounts taken (Lee *et.al.*, 2006). Previous reports have reported the cardiovascular effects of garlic including potentially irreversible antiplatelet activity, anticoagulant, fibrinolytic activity, a remarkable decrease in platelet accumulation and mixed activity on fibrinolytic effectiveness (Borrelli *et.al.*, 2007). Chen *et al.*, (2019) revealed that dehydrated raw garlic powder when administered orally resulted in acute injury to the gastric mucosa, whilst Gruhlke *et.al.*, (2016) reported that AGE, the sulfur-free compound, protects the intestinal mucosa of experimental animals. Clinical studies reported that low doses of garlic are safe, whereas therapeutic doses might cause mild gastrointestinal disorders, while high doses have been reported to cause liver damage (Rana *et.al.*, 2011; Dubey *et.al.*, 2017 and Almogren *et.al.*, 2013).

#### 12. Clinical studies:

Short term benefits of garlic on dyslipidaemia in diabetic patients were shown. Garlic significantly reduced serum total cholesterol and LDL cholesterol and moderately raised HDL cholesterol as compared with placebo in diabetic patients. S-allyl cysteine, a bioactive component derived from garlic, restored erectile function in

diabetic rats by preventing reactive oxygen species formation through modulation of NADPH oxidase subunit expression.

Metformin and Garlic treatment in diabetic patients for 12 weeks reduced fasting blood glucose (FBG), but the percentage of change in FBG was more substantial with metformin supplemented with garlic than with metformin alone. Chronic feeding of garlic extracts showed significant decrease in blood glucose level. However, some other studies showed no change of blood glucose level after that in human. Therefore, the role of garlic in diabetic patients needs to be further investigated. The beneficial effect of garlic on diabetes mellitus is mainly attributed to the presence of volatile sulfur compounds, such as alliin, allicin, diallyl disulfide, diallyl trisulfide, diallylsulfide, S-allyl cysteine, ajoene, and allyl mercaptan. Garlic extracts have been reported to be effective in reducing insulin resistance.

In comparison with the antibacterial action of garlic, very little work has been done to investigate its antiviral properties. The few studies have reported that garlic extract showed *in vitro* activity against influenza A and B, cytomegalovirus, rhinovirus, HIV, herpes simplex virus 1, herpes simplex virus 2, viral pneumonia, and rotavirus. Allicin, diallyl trisulfide and ajoene have all been shown to be active (Ankri & Mirelman, 1999).

There are insufficient clinical trials regarding the effects of garlic in preventing or treating the common cold. A single trial suggested that garlic may prevent occurrences of the common cold, but more studies are needed to validate this finding. This trial randomly assigned 146 participants to either a daily garlic supplement (with 180 mg of allicin content) or a placebo for 12 weeks.

The investigation revealed 24 occurrences of the common cold in the garlic group compared with 65 in the placebo group, resulting in fewer days of illness in the garlic group compared with the placebo group. However, claims of effectiveness of garlic on common cold appear to rely largely on poor quality evidence (Lissiman *et.al.*, 2014). Many countries have used garlic extract for clinical treatments, but the untoward actions of garlic following long-term administration should be fully noted. Even though many studies on garlic and its derivatives have been performed, the exact biological mechanism of garlic extract still remains to be elucidated. Compounds derived from garlic have the potential to decrease the expression of proinflammatory cytokines and to reverse the immunological abnormalities to more acceptable levels. It is suggested as a beneficial preventive measure before being infected with SARS-CoV-2 virus (Donma& Donma, 2020). Garlic extracts demonstrated significant virucidal activity against Hepatitis A virus (Odimegw *et.al.*, 2020). *in-vitro* study has shown that *Plumbago indica* and *Allium sativum* extracts can inhibit influenza A (H1N1)pdm09 virus by inhibiting viral nucleoprotein synthesis and polymerase activity (Chavan *et.al.*, 2016).

13. Contraindications: No data available

14. Precautions: No data available

15. Adverse reactions:

Ingestion of raw garlic in high doses on an empty stomach can induce changes in the intestinal flora, flatulence and gastrointestinal upset (Piasek et.al., 2009). Moreover, blisters dermatitis and burns were observed from raw garlic local applications (Piasek et.al., 2009). Garlic does not seem to affect the drug metabolism, although recent reports on healthy participants show inconsistent results regarding the garlic effect in the pharmacokinetics of protease inhibitors, as well as anticoagulants due to its antithrombotic properties (Rahman & Lowe, 2006). Many surgeons recommended stopping garlic administration in high doses up to 7 to 10 days prior to operation due to its effect to prolong the bleeding time that was observed in one patient with epidural spontaneous hematoma (Rahman & Lowe, 2006). Previous *in vivo* experiments revealed that prolonged feeding of raw garlic in high doses led to weight loss and anaemia due to red blood cells (RBCs) lysis, while administration of 5 mL/kg of raw garlic juice resulted in stomach injury that led finally to death (Mathew & Biju, 2008). Additionally, the chronic administration of 50 mg garlic powder per day led to anti-androgenic effects by inhibiting spermatogenesis in rats, leading to decrease sialic acid concentration in the seminal vesicles, testes, and epididymis with reduced Leydig cell function (Mathew & Biju, 2008). Initially, several clinical symptoms were observed including depression, vomiting, loss of appetite, abdominal pain, diarrhoea, as well as anaemia associated with pale mucous membrane, jaundice, rapid heart and respiratory rates, weakness, and hemoglobinuria (Salgado et.al., 2011).

16. Marketed formulation, if any: No data available

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1. Botanical Name: ***Alpinia galanga* (L.) Willd.**

2. Synonym: ***Maranta galanga* L.**

3. Family: **Zingiberaceae**

4. Common names

Bengali:	Barakulanjar, Kulanjan
English:	The greater galangal
Gujarati:	Kulinjan
Hindi:	Barakulanjar, Kulanjan
Kannada:	Dumbarasme
Malayalam:	Arattha, Kol-inji, Peraratta
Marathi:	Kosht-kulinjan
Sanskrit:	Barakulanjar, Kulanjan
Tamil:	Perarattai
Telugu:	Pedda-dumparashtram

5. Description: An erect, aromatic perennial herb with thick root stock. Leaves oblong-lanceolate, base cuneate, apex acute. Inflorescence terminal on the leaf shoot, dense-flowered; peduncle densely pubescent. Flowers shortly pedicellate; bracts membranous. Calyx cylindrical, split on one side, greenish-white. Corolla tube, greenish-white; lobes unequal, spreading, pubescent. Labellum white, with a few oblique, lilac lines on either side of the midrib on the upper surface, base clawed, margins wavy, apex emarginate. Lateral staminodes subulate. Epigynous glands 2. Ovary ellipsoid. Fruit globose, orange-red.

6. Distribution: Afghanistan, Cambodia, China, Bhutan, Laos, Malaya, Myanmar, Nepal, Philippines, Thailand, Vietnam; Peninsular India, North West India, North East India and cultivated commonly.

7. Parts Used: Whole Plant.



*Alpinia galanga*

## 8. Medicinal /Therapeutic Uses

### 8.1. Uses described in pharmacopoeias and traditional systems of medicine

An important medicinal plant in different traditional systems of medicine to treat several diseases, including inflammations, rheumatic pains, and chest pain, and dyspepsia, fever, burning of the liver, kidney disease, tumors, and diabetes. The plant is commonly used as home remedies to treat burns, earache, fevers, hypertension, constipation, seizures, asthma, stomach ache, worms, infertility complications, snake bites, arthritis, diarrhoea and malaria by tribal people of Manipur (Gupta *et al.*, 2010). Herbal medicine is a chemically rich complex mixture containing several.

### 8.2. Traditional/Folklore Uses described in folk medicine, not supported by experimental or clinical data

Traditional uses the rhizome of the plant is used as carminative, digestive tonic, anti-emetic, anti-fungal, antitumor, Anti-helmintic, anti-diuretic, anti-ulcerative, anti-dementia (Shavandi *et al.*, 2012). The extract of rhizome shows anti-tubercular activity, hypothermia, bronchial catarrh, tonic, stomachic, and stimulant. It is also used as pungent, bitter, heating, stomachic, improve appetite, disease of heart, aphrodisiac tonic, expectorant, used in heal, ache, lumbago, rheumatic pains, chest pain, diabetes, burning of the liver, kidney disease, disinfectants. The rhizome is also used as an anti-microbial, anti-bacterial, anti-inflammatory, and flavouring agent (Chouni *et al.*, 2018).

### 8.3. Special uses in North East India

The plant has an active role in the treatment of eczema, bronchitis, otitis internal, gastritis, ulcers, and cholera. The seed is used for emaciation and to clean the

mouth. It stimulates the digestive power, appetite, and acts as a purgative. The rhizome is generally used as a spice (Malik *et al.*, 2016).

## 9. Phytochemical profile

Phenol and flavonoid are considered to be the most important phyto-constituents that are responsible for the pharmacological activities. Total phenol content and total flavonol content were estimated in Table 1. (Srividya *et al.*, 2010).

*Table 1.* Qualitative and quantitative phytochemical analysis of *Alpinia galanga* extracts.

Tests	<i>Alpinia galangae</i>							
	Petroleum ether	Toluene	chloroform	Ethyl acetate	Acetone	Ethanol	Water	
Alkaloids	-	-	-	-	-	+	+	
Carbohydrates	-	-	-	-	-	+	+	
Phytosterols	+	+	+					
Fixed oil and fats	+	+	+	+	+	-	-	
Saponins	-	-	-	-	-	+	+	
Tannins	+	+	+	-	-	-	-	
Protein and amino acids	+	+	-	+	+	+	+	
Glycosides	-	-	-	-	-	+	-	
Flavonoids	+	+	+	-	-	+	-	
Volatile oils	-	-	-	+	+	-	-	
Steroids	-	-	-	+	-	+	-	
Terpinoids	+	+	+		-	+	-	
Total amount of phenols(%) mg/g of Ascorbic acid	137± 0.78	243± 0.38	82± 1.46	227± 1.03	112± 2.01	254± 1.35	220± 0.87	
Total amount of flavonol(%) mg/g) of rutin	119.46± 0.453	157± 1.90	59.86± 0.115	161± 0.45	49.62± 0.342	169.84±0 .145	134± 0.89	

### 9.1. Major chemical constituents

galango flavonoid, 1'S-1'-acetoxychavicol acetate (ACE), phenyl propanoids and hydroxy benzaldehyde (1'S-1'-acetoxychavicol acetate and 1'S-1'-acetoxyeuginol acetate), acetoxy cineoles(trans and cis)-2-and 3-acetoxy- 1, 1, 8-cineoles, 1'-acetoxychavicol acetate(galangal acetate),  $\beta$ -Sitosterol diglucoside(AG-7) and  $\beta$ sitsteryl Arabinoside (AG-8), hydroxy-1,8-cineole glucopyranosides,(1R, 2R, 4S)-and (1S, 2S, 4R)-trans-2-hydroxy-1,8-cineole  $\beta$ -D-glucopyranoside, and (1R, 3S, 4S)-

trans-3-hydroxy-1, 8- $\beta$ -D-glucopyranoside, 4-allylphenyl acetate,  $\alpha$ -farnesene, 2,2-dimethyl-3-methylenenorbornane,  $\alpha$ -curcumene,  $\beta$ -sesquiphellandrene and rosefuran epoxide. Alpha-pinene, 2,2-dimethyl-3-methylenenorbornane,  $\beta$ -pinene,  $\beta$ -mircene, cineole,  $\beta$ -citraal,  $\alpha$ -citraal, bornyl acetate,  $\alpha$ -curcumene,  $\alpha$ -zingiberene,  $\beta$ -sesquiphellandrene, and hexadecanoic acid. (Verma et al., 2011; Shukla et al., 2017; Misawa et al., 2008).

Table 2: Table showing major bio molecules isolated from *Alpinia galanga* and their mechanism of action.

Sl no.	Name of the compound	Type of the compound	Pharmacological activity	References
1	1'S-1'-acetoxychavicol acetate	Phenylpropanoid	Inhibition of the constitutive activation of NF- $\kappa$ B through suppression of IKK $\alpha/\beta$ activation antitumour principles against Sarcoma 180 ascites in mice	LLA et al., 2012; Itokawa et al., 1987.
2	1'-acetoxychavicol acetate	Phenylpropanoid	Induces apoptosis in myeloid leukemic cells. In NB4 cells, ACA-induced apoptosis is in association with the loss of mitochondrial transmembrane potential ( $\Delta\Psi_m$ ) and activation of caspase-9, hence, ACA-induced death signalling is mediated through a mitochondrial oxygen stress pathway. In addition, ACA activated Fas-mediated apoptosis by inducing of casapse-8 activity.	Mitsui et al., 1976
3	1'S-1'-acetoxyeugenol acetate	Phenylpropanoid	In RBL-2H3 cells, participate in the late phase of type I allergic reactions	Matsuda et al., 2003

4	(E)-8β, 17-epoxylabd-12-ene-15, 16-dial	Diterpene	Enhance antifungal activity of quercetin and chalcone against <i>Candida albicans</i>	Haraguchi et al., 1996
5	p-hydroxycinnamaldehyde	Phenylpropanoid	Potential therapeutic agent for treatment of Osteoarthritis as it has an effect on human chondrocytes	Phitak et al., 2009
6	1, 7-bis (4-hydroxyphenyl)-1, 4, 6-heptatrien-3-one (BHPHTO) and bisdemethoxycurcumin (BDMC)	Curcuminoid (natural phenols)	Inhibit proliferation of human melanoma A2058 in the cell viability assay.	Lo et al., 2013.

## 10. Pharmacological Studies

### 10.1. Experimental pharmacology

It is clear that the plant is potentially rich in the antioxidant property. Hence it may be used as a good source of antioxidant. The generation of ROS is also related to cancer development. Again, it has been seen that the plant exhibits good anticancer properties in several cell lines. Apart from antioxidant and anticancer properties, the plant has anti-diabetic, anti-inflammatory, anti-microbial, anti-fungal, anti-ulcer properties. So, it is clear that it possesses rich phytochemical and pharmacological potentials (Chouni et al., 2018).

#### Antimicrobial activity

Rhizome extract has high phenolic and flavonoid contents when compared to leaf extract. Because of elevated phenolic and flavonoid content in rhizome extract there is noticeable antimicrobial as well as radical scavenging potential.

Minimum Inhibitory Concentration (MIC) of essential oils and crude extracts were evaluated by the broth dilution method against bacteria *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhimurium* and *Vibrio cholera*. MIC of crude extract and essential oils of galangal and ginger against all tested microorganisms were relatively high (Cadet et al., 2013).

#### Antacids

*Alpinia* increases stomach acid *Alpinia* might decreases the effectiveness of antacids (Coscia et al., 1975).

#### Diuretics

A slight increase in diuresis was observed in two human studies following the administration. However, there is contradictory pharmacologic evidence suggesting *alpinia*'s anti-diuresis effects as well (Coscia et al., 1975).

### Hypoglycaemics

One animal study reported that alpinia may decrease glucose concentrations. Theoretically, an additive effect with hyperglycemic herbs may occur (Musoke et al., 1975).

### Hypotensives

Small reductions in systolic and diastolic blood pressure have been associated with the use of alpinia in human and animal studies. Theoretically, additive effects may occur (Scherberger et al., 1975).

### Antiallergic

*Alpinia galanga* was found to be effective in the treatment of allergy and the isolated compounds which extract inhibit the release of antigen IgE mediated in passive cutaneous anaphylaxis reactions in mice (Matsuda et al., 2003).

### Anti-diabetic

The investigation was carried out to study hypoglycemic effects of rhizome on blood glucose levels in rabbits. Powdered rhizome and its methanol and aqueous extracts significantly lowered the blood glucose in normal rabbits. (Tabarak et al., 2016). Methanolic extract of aerial parts was effective in controlling blood glucose level and improve lipid profile in euglycemic as well as diabetic rats. (Coscia et al., 1975).

### Anti-HIV

Anti-human immunodeficiency virus type 1 replication by blocking Reverse Transport from 1' S-1'acetoxychavicol acetate isolated from rhizomes extract (Ye et al., 2006).

### Immunomodulator

Study reported Immuno-stimulating activity of the hot water-soluble polysaccharide extracts were tested for their immune-stimulating activity in mice (Bendjeddou et al., 2003).

### Anti-ulcer

They said rhizomes are used widely in Arabian and Unani systems of medicine to treat stomach disorders. The ethanolic extract also significantly reduced gastric secretion and showed marked cytoprotective activity; it is suggested that these properties may be responsible for the antiulcer activity. A study reported treatment on cytological and biochemical changes induced by cyclophosphamide in mice by the effect from the ethanolic extract. The rhizomes are used as a spice and in traditional medicine to treat dyspepsia, gastralgia, sea sickness, and abdominal colic, and as an anti-inflammatory, anti-neoplastic, digestive and tonic (Qureshi et al., 1994).

### Anti-inflammatory

The anti-inflammatory activities of total aqueous extract (TAQ) and total alcoholic extract (TAE) from rhizomes were accessed in acute (carrageenan-induced paw edema; M1) and sub-acute (cotton-pellet-induced granuloma; M2) rat models. It is

reported that the methanolic and phenolic extract of the rhizome exhibit antidiabetic and anti-inflammatory properties (Cadet *et al.*, 2013).

#### Hepatotoxicity

The treatment with the crude extract due to paracetamol hepatotoxicity in rats was reported. This research was conducted to detect the hepatoprotective effect of the crude extract at 200 and 400 mg/kg-1 against paracetamol-induced hepatotoxicity in rats (Trakranrungsie *et al.*, 2008).

#### Anti-oxidant

A study of antioxidative components in extracts and it states 50% ethanol in water was studied for its antioxidant activity and composition in comparison with two other samples based on the essential oil and water extract. The antioxidant activities were resolved by using methods like oxygen radical absorbance capacity (ORAC) and the 2, 2-diphenyl-1-picrylhydrazyl (DPPH). The ethanolic extract produces the highest DPPH free radical scavenging capacity as well as the highest ORAC value when compared to the water extract and the essential oil (Mahae *et al.*, 2009).

#### Antiplatelet

Constituents of *A. galanga* exerted platelet activating factor (PAF) antagonists. In rabbit platelets, methanolic extract showed significant inhibitory effects on PAF with IC<sub>50</sub> value of 5.5ug/ml (Abdelwahab *et al.*, 2009).

#### Antitumor

Compound isolation from the rhizomes of *A. galanga* - 1,7-bis(4-hydroxyphenyl)-1,4,6-heptatrien-3-one(BHPHTO)and bisdemethoxycurcumin (BDMC) were examined for their bio effectiveness on the human melanoma A2058 and inhibited the proliferation of melanoma cells in the cell growth assay significantly. The tests to B16-F10 cell line was also taken in research and showed minor inhibitory results of cellular tyrosinase activities and melanin contents (Lo *et al.*, 2013).

#### Chemoprotection

Two sets of animals were divided into four groups of six animals per group. The first set of animals was normal mice. Treatment was given with chrysanthemic acid and cyclophosphamide as scheduled. The second set was DLA-induced mice and were intraperitoneally transplanted with 1 × 10<sup>6</sup>/ml DLA tumor cells. After 24 h of tumor transplantation, treatment was initiated. The animals were weighed at regular intervals of time and life expectancy was recorded. The blood was collected from the tail vein on day 15 for assessing the liver and kidney function tests. The effects of chrysanthemic acid and cyclophosphamide when treated alone and along with CYP (25 mg/kg bw) was observed on tumor volume regression and percentage of increase in lifespan (% ILS) in DLA bearing mice compared to control mice (Lakshmi *et al.*, 2019).

### 10.2. Clinical pharmacology

Acute (24 h) and chronic (90 d) oral toxicity studies on the ethanolic extracts of rhizomes were carried out in mice. Acute dosages were 0.5, 1.0, and 3 g/kg body weight while the chronic dosage was 100 mg/kg/day as the extract. All external morphological, hematological, and spermatogenic changes, in addition to body weight and vital organ weights, were recorded. No significant mortality as compared to the controls was observed. The weight gain in the treated animals was significant as in the control group. Hematological studies revealed a significant rise in the RBC level of treated animals as compared to the controls. The gain in weights of sexual organs and increased sperm motility and sperm counts were observed groups of extract-treated male mice, however, these changes were highly significant in the *A. galanga*-treated group. Extracts failed to show any spermatotoxic effects (Subash *et al.*, 2013).

#### 11. Toxicity and safety

Ethanolic extract did not show any signs and symptoms of acute toxicity and on this basis the dose of the extract were decided as 200 mg/kg body weight and 400 mg/kg body weight (Srividya *et al.*, 2010).

An acute oral toxicity study was carried out on the methanolic extract residue as per OECD guidelines. The dose of 5000 mg/kg was studied in the present study to know the LD<sub>50</sub> between 2000-5000 mg/kg as the drug is popular and extensively used; this information will help in safeguarding the human health. As there is no mortality even at the highest dose tested the LD<sub>50</sub> was estimated to be more than 5000 mg/kg and accordingly a dose of 500 mg/kg was chosen for the anti-inflammatory study. The present study revealed the presence of complex phytochemical constituents including phenols and flavanoids. The acute toxicity results have classified the test material to fall under the hazard category 2000 mg/kg (Unnisa *et al.*, 2011).

#### 12. Clinical studies

Regulation of blood glucose levels in diabetes can prevent the various complications associated with the disease. The long term maintenance of plasma glucose concentration under a variety of nutritional conditions and energetic demands is one of the most important and closely regulated processes in the mammalian species. Whole-body homeostatic is the product of input from three primary tissues, the liver, skeletal muscle, and  $\beta$ - cells of the pancreas (Alberti *et al.*, 1998). More research and evaluation needs to be done to isolate and identify different chemicals present in the plant which will be used for innumerable applications for human welfare shortly.

#### 13. Contraindications

Particular contradictions have not been identified and also not reported.

#### 14. Precautions: No data available

#### 15. Adverse reactions

The studies based on the animal model established that the major components of *alpinia galangal* are a vital role in the anti-diabetic and anticancer management and modulates the biological process without any adverse reaction.

16. Marketed formulation (if any): No data available

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1. Botanical Name: **Ananas comosus** (L.) Merr.

2. Synonym: *Bromelia comosa* L.

3. Family: Bromeliaceae

4. Common Names

Assam:	Ananas, Matikathal
Bengali:	Anarash;
English:	Pine apple
Gujarati:	Ananas
Hindi:	Anannas
Kannada:	Ananasahannu
Malayalam:	Kaitha chakka, Kazhudhachakka
Marathi:	Ananas
Tamil:	Anashippazham
Telugu:	Anaasachettu, Anaasapandu.

5. Description: An erect, perennial herb. Leaves dense, basal rosettes, linear-lanceolate, rigid, coriaceous, base scarcely enlarged, and green to reddish, margin with ascending spines. Flower colour varies, depending on variety, from lavender, through light purple to red. The ovaries develop into berries, which coalesce into a large, compact, multiple accessory fruit. The fruit of a pineapple is arranged in two interlocking helices, eight in one direction and thirteen in the other. Each of the eyes on the surface is the dried base of a small flower

6. Distribution: Native to Brazil; now the crop is now widely grown throughout the tropics and into the subtropics.



*Ananas comosus*

#### 7. Parts Used: Whole Plant

#### 8. Medicinal /Therapeutic Uses

Pineapple can be used as supplementary nutritional fruit for good personal health. Pineapple fruits are an excellent source of vitamins and minerals. One healthy ripe pineapple fruit can supply about 16.2% of daily requirement for vitamin C(Hemalatha, 2013). Vitamin C is the body's primary water-soluble antioxidant, against free radicals that attack and damage normal cells. A powerful antioxidant, vitamin C supports the formation of collagen in bones, blood vessels, cartilage and muscle, as well as the absorption of iron. Vitamin C also retards the development of urinary tract infections during pregnancy and reduces the risk of certain cancers, including colon, oesophagus and stomach (Debnath et al., 2012). Malic acid makes up 13 % of juice's acidic content. Malic acid is also beneficial for health. It boosts immunity; promotes smooth, firm skin; helps maintain oral health; and reduces the risk of toxic metal poisoning. It is also a good source of vitamin B1, vitamin B6, copper and dietary fibre. Pineapple is a digestive aid and a natural anti-inflammatory fruit. Fresh pineapples are rich in bromelain used for tenderizing meat. Pineapple contains a proteolytic enzyme bromelain, which digests food by breaking down protein. Only modest quantities of bromelain are in the edible parts of the fruit, all commercially available bromelain is derived from the stem. Bromelain supplements are particularly popular among athletes for treating all sorts of physical aches and injuries. Drinking pineapple juice can help hydrate the body and restore the immune

system. It helps to build healthy bones. Pineapples are rich in manganese, a trace mineral that is needed for body to build bone and connective tissues. One cup of pineapple provides 73% of the daily recommended amount of manganese. The benefits of pineapple can affect the growth of bones in young people and the strengthening of bones in older people. Pineapple juice's high manganese content means it is a good choice for boosting fertility through sperm quality(Debnath et al., 2012). Bromelain has demonstrated significant anti-inflammatory effects, reducing swelling in inflammatory conditions such as acute sinusitis, sore throat, arthritis and gout and speeding recovery from injuries and surgery. Pineapple enzymes have been used with success to treat rheumatoid arthritis and to speed tissue repair as a result of injuries, diabetic ulcers and general surgery. Pineapple reduces blood clotting and helps remove plaque from arterial walls. Pineapple enzymes may improve circulation in those with narrowed arteries, such as angina sufferers. Pineapples are used to help cure bronquitis and throat infections. Pineapple is an excellent cerebral toner; it combats loss of memory, sadness, and melancholy. For any kind of morning sickness, motion sickness or nausea, drinking pineapple juice is advised. It works effectively in getting rid of nausea and vomiting sensation. Pineapple is known to be very effective in curing constipation and irregular bowel movement. This is because it is rich in fibre, which makes bowel movements regular and easy. Pineapple is effective in getting rid of intestinal worms and also keeps the intestines and kidneys clean. It helps prevent gum disease and also prevents the formation of plaque, thus keeping the teeth healthy. The flesh of very young (toxic) fruits is deliberately ingested to achieve and as a drastic treatment for venereal diseases. In Africa the dried, powdered root is a remedy for edema. The crushed rind is applied on fractures and the rind decoction with rosemary is applied on hemorrhoids. Indians in Panama use the leaf juice as a purgative, emmenagogue and vermifuge(Debnath et al., 2012). Roasted unripe fruit juice is used by different communities of Gohpur of Sonitpur district, Assam, India for strangury (Saikia, 2006). Pineapple creates low blood pressure, cure inflammation disease, used for weight loss, control the death rate and prevent diabetes & radical damage. It cures the damaged teeth and makes them strong and healthy. Also help to cure sinusitis and throat problem. Cure different diseases like asthma, obesity, swollen in the body, problems of digestion and heart problem. Pineapples are rich of manganese which creates strong bones and muscular body. Atherosclerosis and immune disease can be also cured due to high antioxidant. It does not let damage the cells of body, it is so hot so it is used to ignore cold weather, also used for perfect powerful unbreakable body, prevent cancer, heart attack, nausea and gives the long natural hairs. Use to solve acne, wrinkles, age problem and create strong nails, soft lips and thick hair (<http://worldknowing.com/top-10-pineapple-producingcountries/>). The Garo tribal community of Netrakona district in Bangladesh uses fruit juice for fever and leaf juice for helminthiasis and jaundice (Rahmatullah et al., 2009).*Ananas comosus* leaves have antihyperglycemic and analgesic properties. That can be used as a cheaper and alternative source of medicine for reducing high blood sugar level of diabetic patients(Faisal, et al., 2014). The root and fruit are either eaten or applied

topically as an anti-inflammatory and as a proteolytic agent. It is traditionally used as an anthelmintic agent in Tripura, India. A root decoction is used to treat diarrhoea. It is advised to take advantage of pineapple's myriad healing powers, by drinking 3 ½ ounces of fresh pineapple juice three times daily before meals or by eating a slice of fresh pineapple at each meal(Debnath *et al.*, 2012). Phytochemical screening showed presence of alkaloids, flavonoids, saponins and tannins in the pineapple leave extract, which components can be responsible for the observed blood glucose lowering and analgesic effects (Faisal *et al.*, 2014). One of the best-known properties of pineapple is as a diuretic. This helps to eliminate toxins through the urine, helping patients with ailments of kidneys, bladder and prostate. Due to the fibre content of the pulp, pineapple prevents constipation and regularizes the intestinal flora. Furthermore, there is evidence of appetite reducer, heart protection and aid for fever, sore throat and mouth aches and inflammation. Lightly boiled ground pineapple can be used to clean infected wounds because it eliminates dead tissues, not affecting live tissue, acts as disinfectant (Mundogar, 2004 and Hossain *et al.*,2015).

#### 8.1. Uses described in pharmacopoeias and in traditional systems of medicine

The crude aqueous extract from stem and fruit of Pineapple is known as Bromelain. It is a mixture of different thiol endopeptidases and other components like phosphatases, glucosidase, peroxidases, cellulases, glycoproteins, carbohydrates, and several protease inhibitors. Plant-based enzymes, such as Bromelain from Pineapple, serve as effective digestive aids in the breakdown of proteins (Bhattacharyya, 2008).

#### 8.2. Uses supported by clinical data

All the evidence in one comprehensive review suggests that Bromelain can be used as an effective health supplement to prevent Cancer, Diabetes, and various Cardiovascular diseases. Bromelain is considerably absorbable in the body without losing its proteolytic activity and without producing any major side effects. Bromelain accounts for many therapeutic benefits like the treatment of angina pectoris, bronchitis, sinusitis, surgical trauma, and thrombophlebitis, debridement of wounds, and enhanced absorption of drugs, particularly antibiotics. It also relieves osteoarthritis, diarrhoea, and various cardiovascular disorders. Bromelain also possesses some ant cancerous activities and promotes apoptotic cell death (Bharat Kwatra, 2019).

#### 8.3. Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

Chunks of Pineapple are used in desserts such as fruit salad, as well as in some savoury dishes, including pizza toppings and a grilled ring on a hamburger. Crushed Pineapple is used in yogurt, jam, sweets, and ice cream. The juice is served as a beverage, and it is also the main ingredient in cocktails such as the piña colada.

#### 8.4. Special uses in North East India

Pineapple is one of the most important tropical fruit grown in the north – eastern part of India. India is the fifth largest producer of pineapple with annual output of about

1.2 million. The ministry of commerce and industry has recently sanctioned the Agri-export zone scheme for the entire NER at Tripura. Under this scheme, enhanced international market access would be provided to farmers besides necessary infrastructure, flow of credit, transport assistance and other facilities for promoting agricultural export through pineapple cultivation. In spite of having numerous developments in the field of food processing most of the fruits grown are not getting processed which leads to post harvest losses. Ultimately this leads to less revenue for farmers in turn of their investment. So, there is a need to make cultivators aware of recent developments in the field of pineapple processing and related value-added products. The full potential of pineapple cultivation in the region is yet to be tapped and for this, efforts are being put in various organization and the government both at central and state level, to help the growers in marketing their produce, which is considered to be the key factor for boosting this industry(Shweta *et al.*, 2017).

#### 8.5. Dosage forms used in tradition

Two slices of pineapple contain approximately 100 mg of ascorbic acid (vitamin C). The usual dosage of bromelain is 40 mg taken 3 or 4 times daily. Pineapple products are available commercially in liquid, tablet, and capsule dose forms. Most products contain bromelain 500 mg; manufacturers suggest a dose of 500 to 1,000 mg daily.

### 9. Phytochemical profile

Phytochemical analysis of fruit extracts revealed the presence of 11 phytochemicals (terpenoids, flavonoids, saponins, tannins, alkaloids, anthraquinones, carbohydrate, steroids, phenols, oil, and resins) in ethanol, methanol and chloroform extracts (Vijayanand *et al.*, 2017).

#### 9.1. Major chemical constituents

Therapeutic plants, and the drugs derived from them, are the most important and readily available source of health-care medicines to rural people. Many natural resources are used for obtaining pharmaceuticals that have a high national and international economic value. The plant is reported to contain alkaloids, flavonoids, saponins, tannins, steroids, triterpenoids and phytosterols (Lawal, 2013).

### 10. Pharmacological Studies

The juice contains the following compounds : Acetaldehyde, Acrylic acid, Ethyl ester, Iso butyrate: Ethyl, Iso-butyrat; Ethyl, Iso propyl,- Iso-butyrat; Methyl-Iso butyrate; Ethyl Acetate; Gamma-Eudesmol (a sesquiterpene); Iso-butyl formate; methyl formate, N-butyl-formate; N-propyl formate; Formic acid and Histidine (Howard & Hoffman, 1967). Pineapple contains Acetone, Alanine, 2-3 Dimethyl, Butan -2 ol; Sesquiterpene: adinene; Ethyl caproate; Methyl and Ethyl esters of caproic acid; Methyl Ethyl ester of Beta-Acetoxyacrylic acid and Gamma caprolactone; Decanoic acid and their esters, Ferulic acid phrylpropanoid; and the alkanalalkanone derivatives of hexone (Muller & Willham, 1971). A. comosus leaf contains: Phenylalanine, Allylhexanoate, Arginine, Atpase; Isoleucine; Lysine, Methionine; Tyrosine and Glycine (Yeohet *et al.*, 1986). Indole alkaloid like Haumalol, Haumine,

Haumol, and Hemicellulose in the fruit of *A. Comosus* (Tsuchiya *et al.*, 1999). *A. comosus* stem contains proteolytic enzyme Papain-like enzyme (Vongsinudom, 1977); Bromelain (Shiraishiet *al.*, 1975); Alkaloids (Sofowora, 1978); Phenylpropaniods such as Cinnamic Acid, Coumaric and Ferulic acid (Tawataet *al.*, 1996). Bromelain in the peel of the unripe fruit in Thailand (Khamviwat, 1984). Volatiles lipid compounds such as the Ethyl and Methyl esters of Nonanoic acid, the Methyl and Ethyl Esters of Oct-Cis-4-enoic acid and even the Methyl and Ethyl Esters of Oct-trans-4-enoic acid have been isolated from the fruit of *A. comosus* (Muller & Willham 1971). The plant also contain sulphur compounds like methyl Mercaptan (Muller & Willham 1971); Essential oils such as Butan-1-ol and their derivatives (Flath, 1970); a Triterpene-Annanasic (Takata, 1976); Pentosans (Muller & Willham 1971), Flavonoids from the leaf (Muller & Willham 1971).The ethanolic extract of *A.comosus* peel contains photochemical like alkaloids, flavonoids, saponins, tannins, triterpenoids and phytosterols (Lawal *et al.*, 2011).*A. comosus* leaf extract containstriterpenoids and steroids in the petroleum ether extract; alkaloids and steroids in the chloroform extract; and alkaloids, steroids, saponins, glycosides and carbohydrates in the methanol extract (Sucheta *et al.*, 2011).

#### 10.1. Experimental pharmacology

#### 11. Toxicity and safety

Bromelain is considered to have very low toxicity, with an LD50 greater than 10 g/kg in mice, rats and rabbits. The administrations of 750 mg/kg of bromelain per day have not showed any toxic effect on dogs after 6 months. Administration of 1500 mg/kg per day to rats showed no carcinogenic or teratogenic effects and did not provoke any alteration in food intake, histology of heart, growth, spleen, kidney, or hematological parameters. After giving bromelain (3000 FIP unit/day) to human over a period of ten days found no significant changes inblood coagulation parameters (Livio *et al.*, 1978). In human clinical tests, side effects are generally not observed; however, caution is advised if administering bromelain to individuals with hypertension, since one report indicated individuals with pre-existing hypertension might experience tachycardia following high doses of bromelain. The allergenic potential of proteolytic enzymes should not be underestimated. They can cause IgE-mediated respiratory allergies of both the immediate type and the late-phase of immediate type. Bromelain, due to its use as a meat tenderizer and to clarify beer, is considered a potential hidden dietary allergen.

#### 12. Clinical studies

All the evidence in one comprehensive review suggests that Bromelain can be used as an effective health supplement to prevent Cancer, Diabetes, and various Cardiovascular diseases. Bromelain is considerably absorbable in the body without losing its proteolytic activity and without producing any major side effects. Bromelain accounts for many therapeutic benefits like the treatment of angina pectoris, bronchitis, sinusitis, surgical trauma, and thrombophlebitis, debridement of wounds, and enhanced absorption of drugs, particularly antibiotics. It also relieves

osteoarthritis, diarrhoea, and various cardiovascular disorders. Bromelain also possesses some ant cancerous activities and promotes apoptotic cell death(Rajendra et al., 2012).

#### Digestive Support

Bromelain aids digestion by enhancing the effects of the digestive enzymes' trypsin and pepsin. It can also help to prevent heartburn and ease diarrhoea if either is caused by a deficiency of digestive enzymes.

#### Anti-Inflammatory

Bromelain is of interest to plastic surgeons because of its apparent ability to reduce pain, edema, inflammation, and platelet aggregation. Bromelain has analgesic properties which are thought to be the result of its direct influence on pain mediators such as bradykinin. The earliest reported studies investigating Bromelain were a series of case reports on 28 patients, with moderate or severe rheumatoid or osteoarthritis(Roger, 2007).

#### Anti-Thrombosis

Results suggested that Bromelain could be used for treating acute thrombophlebitis, as it decreases aggregation of blood platelets, have a cardioprotective effect, ameliorates rejection-induced arterial wall re modelling, prevents thrombin-induced human platelet aggregation as well as reduces thrombus formation. Bromelain therapy leads to the formation of platelets with increased resistance to aggregation – the combination of fibrinolytic and antithrombic properties appear to be effective. Two large scale tests on heart patients have shown a practically complete elimination of thrombosis. Bromelain has been effective in the treatment of CVDs as it is an inhibitor of blood platelet aggregation, thus minimizing the risk of arterial thrombosis and embolism(Chit, et al.,2011).

#### Heart Attack Reduced

Bromelain prevents or minimizes the severity of angina pectoris and transient ischemic attack (TIA). It is useful in the prevention and treatment of thrombophlebitis.

#### Cholesterol Reduced

Bromelain may also break down Cholesterol plaques and exerts a potent fibrinolytic activity (Bharat, 2019).

### 13. Contraindications

Hypersensitivity to any of the components in pineapple. Cross-reaction with honeybee venom, olive tree pollen, celery, cypress pollen, bromelain, and papain has been reported. When taken by mouth: Bromelain is possible safe for most people when taken by mouth in appropriate amounts. Bromelain may cause some side effects, such as diarrhoea and stomach and intestinal discomfort. Bromelain may also cause allergic reactions, especially in people who have other allergies. If you have allergies, be sure to check with your healthcare provider before taking bromelain. When applied to the skin: Bromelain is possible safe for most people when applied to the skin in appropriate amounts.

## 14. Precautions

### Pregnancy and breast-feeding

Not enough is known about the use of bromelain during pregnancy and breast-feeding. Stay on the safe side and avoid use.

### Allergies

If you are allergic to pineapple, latex, wheat, celery, papain, carrot, fennel, cypress pollen, or grass pollen, you might have an allergic reaction to bromelain.

### Surgery

Bromelain might increase the risk of bleeding during and after surgery. Stop using bromelain at least 2 weeks before a scheduled surgery.

## 15. Adverse reactions

### Amoxicillin (Amoxil, Trimox) interacts with BROMELAIN

Taking bromelain might increase how much amoxicillin is in the body. Taking bromelain along with amoxicillin might increase effects and side effects of amoxicillin.

### Antibiotics (Tetracycline antibiotics) interact with BROMELAIN

Taking bromelain might increase how much antibiotic the body absorbs. Taking bromelain along with some antibiotics might increase effects and side effects of some antibiotics called tetracyclines. Some tetracyclines include demeclocycline (Declomycin), minocycline (Minocin), and tetracycline (Achromycin).

### Medications that slow blood clotting (Anticoagulant / Antiplatelet drugs) interacts with BROMELAIN

Bromelain might slow blood clotting. Taking bromelain along with medications that also slow clotting might increase the chances of bruising and bleeding. Some medications that slow blood clotting include aspirin, clopidogrel (Plavix), diclofenac (Voltaren, Cataflam, others), ibuprofen (Advil, Motrin, others), naproxen (Anaprox, Naprosyn, others), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, warfarin (Coumadin), and others.

## 16. Marketed formulation, if any:

Pineapple by-product fractions are a promising source of valuable bioactive compounds. Dietary fiber is an interesting target to valorize, but also the insoluble fiber-containing associated polyphenols that exhibit antioxidant activity. These properties together, as well as the neutral color and flavor of pineapple, make it a suitable source of several bioactive and functional ingredients for a wide range of applications, either for the food industry or for cosmetics and nutraceutical industries (Débora et al., 2020).

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1. Botanical Name: ***Anisomeles indica* (L.) Kuntze**

2. Synonym: *Nepeta indica* L.

3. Family: Lamiaceae

4. Common Names

Bengali:	Gobura
English:	Malabar Catmint, Indian Catmint
Gujarathi:	Chodharo, Gopali
Hindi:	Gopoli, Gobara, Kala Bhangra
Kannada:	Mangamari soppu
Khasi:	Nei-liehKhlaw
Malayalam:	Chedayan
Manipuri:	Thoiding Angouba
Marathi:	Gopali
Oriya:	Bhutamari
Tamil:	Chedayan, Erumuttai, Paeimiratti, Vattachadachi
Trade:	Gobura, Gopali

5. Description: Erect, aromatic woody herbs up to 5 feet high, stem 4-angled, grooved on opposite sides, densely pubescent. Leaves broadly ovate to obovate, base turncate, margin coarsely serrate-crenate, apex acute, tomentose on both sides. Flowers in axillary sessile clusters or in terminal interrupted spikes. Calyx campanulate; lobes 5, ovate, ciliate on margin. Corolla pale pink, 2-lipped. Stamens 4, didynamous, exserted; filaments hairy; anthers of upper pair 2-celled, of lower 1-celled. Ovary 4-partite; style slender; stigma 2-fid; disc subentire. Nutlets 4, lenticular, reddish-brown.

6. Distribution: Sri Lanka, India, E Asia and Malaysia; found in India at subtropical regions.

7. Parts Used: Entire parts



*Anisomeles indica* (L.) Kuntze (Photo by S S Dash, BSI)

## 8. Medicinal /Therapeutic Uses

8.1. Uses described in pharmacopoeias and in traditional systems of medicine  
Almost all parts of the plant is being used in traditional medicines of Indian and Chinese to treat various diseases like gastric dysfunction, hypertension, cold, fever, intermittent fever, skin problems, also known to treat viral disease (Baranwale *et al.*, 2012; Ulhe & Narkhede, 2015).

## 8.2. Uses supported by clinical data

It is reported that the leaves consists of diterpenoids, ovatodiolide and its derivatives that are used as HIV inhibitors (Alam *et al.*, 2000; Ushiret *et al.*, 2010).

## 8.3 Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

It is sued in folk medicine as a cure in gastric dysfunction, inflammatory disorder, hypertension and essential oil present in herb issued in uterine infection (Kirtikare *et al.*, 1999; Ulhe & Narkhede, 2015). It is used in folk medicine in the treatment of diverse conditions such as inflammatory skin diseases, liver protection, intestinal infections, abdominal pain and immune system deficiencies. Aerial parts of the plant are valued as stimulant, expectorant, diaphoretic and insecticide. Leaves

are considered useful in chronic rheumatism, psoriasis and other chronic skin eruptions (Ulhe & Narkhede, 2015).

#### 8.4 Special uses in North East India

The nutlets are used as an appetizer in Meghalaya and Manipur. In Arunachal Pradesh, the Tribe Apatani used the shoot for body ache(Kala, 2005).

#### 8.5 Dosage forms used in tradition

For rheumatism: Make decoction and take one tablespoon thrice daily

For stomachic: Two table spoon decoction twice daily.

For toothache: Chew 4-5 leaves in a day

For gastrointestinal disorder: Boil leaves and stem in equal proportion and have one tablespoon after meal.

### 9. Phytochemical Profile

#### 9.1. Major chemical constituents

Whole Plant: Taj *et al.* (2014), had carried out the phytochemical screening of the whole plant collected from Udayagiri Hill Range, Andhra Pradesh, India. The major secondary metabolites are tannins, alkaloids, coumarins, flavonoids, terpenoids and steroids.

Leaves: The phytochemical constituents of the leaves using HPTLC showed that the leaves constitute mainly of alkaloids, tannins, saponins, carotenoids, polyuronids and chemical constituent like Tetracosapentaene,2,6,10,15,19,23-hexamethyl,22-Stigmasten-3-one. FTIR peak spectrum indicated the presence of alcohols, alkanes, alkyl halides, unsaturated hydrocarbons, fatty acids, amines, acid anhydride and carboxylic compounds in the leaves extract (Ulhe & Narkhede, 2015). GC-MS chromatogram of methanolic extract showed the presence of 14 phytocompounds. Out of 14 compound, three compounds have high percentage of Cyclohexane,1-ethynyl-1-methyl-2,4-bis(1-methylethyl)-[1S-(1-alpha,2-beta)-(21.98), Caryophyllene (27.68), Naphthalene,1,2,3,4,4a,5,6,8a-octahydro-4a,8-diemthyl-2-methylethenyl) (25.98) and the low percentage of Bicyclo[7.2.0]undec-4-ene,4,11,11-trimethyl-8-methylene(0.406). The cyclohexasiloxane, dodecamethyl present in the extract of this plant have anti-microbial property (Antil *et al.*, 2019).

Essential oil: The chemical analysis of the essential oil from leaves collected from the Central Himalayan region was performed using GC and GC-MS. The oil was found to be rich in oxygenated diterpenes and diterpene hydrocarbons (54.7%). Total forty-three compounds were identified representing 88.1% of the oil. Abietadiene (20.5%),  $\beta$ -caryophyllene (8.8%), (E,E)- $\alpha$ -farnesene (5.5%), linoleic acid (8.7%), trans-ferruginol (8.1%) and abietol (6.1%) were identified to be the major constituents (Melkani *et al.*, 2016).

## 10. Pharmacological Studies

### 10.1. Experimental pharmacology

**Anti-HIV:** The cytopathic effects of HIV-1 infection were inhibited by ovatodiolide isolated over a modest concentration range with EC<sub>50</sub> of 0.10 µg/mL and IC<sub>50</sub> of 1.20 µg/ml with maximum cellular protection of 80-90%. Ovatodiolide was compared to that of AZT, a known anti-HIV drug which showed an EC<sub>50</sub> of 0.0037 µg/mL (Alam *et al.*, 2000).

**Anti-cancer:** Acute toxicity results in mice suggest that leaf flavonoid fraction (LFF) is non-toxic, as the treated animals survived beyond the 14-day observation period and with no mortality and toxic signs or symptoms. Sub-acute oral toxicity study was carried out for 28 days in Swiss albino mice both sexes. Data revealed no statistically significant dose-related effects on food consumption, body weight gain, clinical signs in LFF treated animals. Cytotoxicity results against human cancer cell lines KB, HepG2, HT-29 and HEK-293 suggests, LFF is cytotoxic to four human cancer cell lines with IC<sub>50</sub> values 36.57, 40.0, 48.6, 68.58 µg/mL respectively (Basappa *et al.*, 2016).

**Anti-inflammatory:** Parmar *et al.*(2015), studied the anti-inflammatory properties of aqueous extract of leaves in rat model using carageenan induced paw edema. Aspirin 100mg/kg was used as standard drug. The leaf extract at 250mg/kg were administered orally in rat models 1 hr before induction of carrageen an and compared with a negative control group given 10ml/kg distilled water. The results showed maximum anti-inflammatory effect and analgesic effect after 4 hr. which indicate that it has potential in phytomedicine.

**Anti-oxidant:** Taj *et al.*, (2014), screened out the anti-oxidant property of 14 plant parts of 10 plant species collected from Udayagiri Hill Range, Andhra Pradesh, India, and that the second strongest antioxidant activity was shown by (flower- Methanol 92.26%; leaves-Methanol 92.08%) using the DPPH method.

**Analgesic and Anti-hyperalgesic:** Water extracts were made from leaves and stems of both pre flowering (E1) and flowering plants (E2). E1 showed a dose-dependent analgesic effect up to 6 h in rats. Further, the analgesic effect of E1 was not accompanied by toxic effects. E1 showed a dose dependent antihyperalgesic activity in rats. In contrast, E2 did not show any analgesic effect even at higher concentration 500 mg/kg. E1 dose dependently retarded the amplitude of the spontaneous contractions of isolated dioestrous rat uterus. Further, E1 induced a dose dependent plasma membrane stabilization effect on rat erythrocytes. The analgesic and antihyperalgesic effects of E1 are mediated from inhibition of COX-1, thus impairing the synthesis of prostaglandins (Dharmasiri *et al.*, 2003).

**Antiepileptic:** The chloroform (4.20% w/w), ethyl acetate (4.23% w/w) and aqueous decoction (12.11% w/w) extracts of the aerial parts of *A. indica* were screened for the

antiepileptic activity against maximal electroshock (MES) model and pentylenetetrazole (PTZ) models at doses of 200, 400 mg/kg, po once. Pretreatment with ethyl acetate extract of *A. indica* for 1 week showed significant antiepileptic activity against pentylenetetrazole induced convulsions in Wistar rats. Isolated flavonoid fraction showed more potent antiepileptic activity as compared to ethyl acetate extract, without any neurotoxic effect (Sundriyal *et al.*, 2013).

10.2. Clinical pharmacology: No documentation

11. Toxicity and safety

Leaf flavonoid fraction (LFF) through *in vivo* and *in vitro* study appears to be safe for oral administration in humans and may be used in traditional medicine (Basappa *et al.*, 2016).

12. Clinical studies: No documentation

13. Contraindications: No documentation

14. Precautions: No documentation

15. Adverse reactions: No documentation

17. Marketed formulation, if any: Not available

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1. Botanical Name: ***Annona reticulata* L.**

2. Synonym: NA

3. Family: Annonaceae

4. Common Names

Bengali:	Luvuni, Nona
English:	Bullock's heart, Custard apple
Gujarati:	Raamaaphal
Hindi:	Anta, Luvuni, Nagnewa, Nona, Raamaaphal
Kannada:	Raamaaphala
Malayalam:	Manilanilam, Parankich-chkka, Raamachchita
Marathi:	Raamaaphal
Oriya:	Barhial, Nena, Raamopholo, Raamositaapholo
Sanskrit:	Krishnabeejam, Livali, Lavani, Raamaaphalam
Tamil:	Aninuna, Manilvatta, Ramachita
Telugu:	Aamaaphalamu, Raamaseethaaphalamu

5. Description: Trees about 5-10 m tall; bark dark brown, fissured and fibrous, branches glabrous. Leaves simple, alternate, lanceolate-elliptic to oblong-lanceolate, 10-20 × 3-6 cm across, base acute or obtuse, margin entire, apex acute or shallow acuminate, subcoriaceous, dark green, subglabrous above, paler glaucous beneath, lateral veins 7-15 on either side of the midrib, almost parallel, impressed above, prominent on the veins and more prominent on the midrib beneath, reticulate veinlets fine and close, petiole pale green, wider near the base, about 1-1.5 cm long. Flowers bisexual, terminal or extra axillary cymes 1-3 together, about 2-2.5 cm across, pedicels slender, glabrous, about 1-2 cm long, bracts basal. Sepals 3, broadly ovate, apex acute, pale green outside and cream white, glabrous inside, about 1.5-3 × 0.3-0.5 cm across. Petals 6, outer ones sub equal, narrow oblong, apex obtuse, somewhat thick triangular or triquetrous, base concave, apex acute, keeled inside, greenish yellow outside, glabrous inside, about 1.5-2 × 0.5 cm across, inner petals minute, reddish at the base. Stamens numerous, about 1 mm long, connectives ovoid at the top. Carpels many linear or ovoid, about 1.5 mm long, style oblong, stigma entire. Ripe carpels, broadly globose or ovoid in fruit, slightly arolate, reticulate, slightly netted, many loculed with white pulp, not very sweet, about 5-10 cm in diameter, puberulous, stalk stout, about 2 cm long, Seeds many, dark brown or blackish, slightly flattened, arillate.

6. Distribution: Native to West Indies; commonly cultivated in all-over the world at subtropical regions for its edible fruits.

7. Part Used: Fruit, leaf, seed and bark



*Annona reticulata* (Photo by S. L. Meena, BSI)

## 8. Medicinal/Therapeutic Uses

### 8.1. Uses described in pharmacopoeias and in traditional systems of medicine

Investigation on the bioactive constituents from the fruit showed that the different bioactive molecules (sesquiterpene, terpenoids fraction, phenolic, polyphenol, flavonoids) possesses antioxidant, anti-inflammatory, anti-allergic and analgesic properties that plays a key role in the health benefits as well as in reducing chronic diseases (Patel *et al.*, 2019).

Leaves are used for antihelminthic, antispasmodic, sudorific, suppurative, stimulant and insecticidal activities (Morton, 1987).

#### Uses supported by clinical data

Analgesic and anti-inflammatory activities: Investigation on the analgesic and anti-inflammatory activities of sesquiterpene fraction (copaene, patchoulane, and 1H-cycloprop(e) azulene) isolated from stem bark showed that sesquiterpene fraction at doses 12.5 and 25 mg kg<sup>-1</sup> exhibited significant central as well as peripheral analgesic and anti-inflammatory activities (Chavan *et al.*, 2012).

Antihelminthic activity: Screening for antihelminthic property from leave extraction of some plants viz., *A. squamosa*, *A. reticulata* *Balanites aegyptiaca* *Caesalpinia*

*bonducella*, *Cleome gynandra* and *Diplocyclos palmatus* showed that these plant species have a strong antihelminthic activity and that had also been found to be used in the Indian traditional medicines for treating the infection (Khyade,2012).

### 8.2. Traditional/Folklore Uses: described in folk medicine

Fruit, leaf, seed and bark: These are used for treating various ailments such as dysentery, boils, vermifuge, scurvy, vomiting, diarrhoea and eye infection (Jain & Srivastava, 2005).

Leaves: It has been reported to be used in treating measles and influenza viral diseases (Pathak & Baishya, 2013).

### 8.3. Special uses in North East India

East Karbi Anglong District, Assam: Fruits and leaves were used for treating diarrhoea, dysentery and helminthiasis by the indigenous Karbi community (Mipun *et al.*,2019).

### 8.4. Dosage forms used in tradition

Leave: The leaf is mixed with salt and given orally to prevent vomiting (Jain & Srivastava, 2005).Leaves are made into a paste and applied to boil to hasten suppuration (Girach *et al.*,1994).

## 9. Phytochemical profile

### 9.1. Major chemical constituents

- Fruit: Investigation on the phytochemical screening of fruit using different solvent extraction revealed that it contain saponins, flavonoids, steroids, terpenoids, alkaloids, glycosides and tannins (Patelet.*al.*, 2019).
- Volatile Oil: A study on the volatile compounds of four *Annona* species was done and the result showed that camphene (0.2–6.6%), α-copaene (2.0–7.3%), β-elemene (5.9–16.6%), β -caryophyllene (8.3–14.9%), β -bisabolene (0.4–10.2%), δ-cadinene (1.7–4.8%) and germacrene D (9.3–22.8%) were the main compounds (Thanget.*al.*,2013).
- Leave: A study on the identification of chemical compounds from hydro-alcoholic leaves extraction using GC-MS analysis revealed the presence of 9,10dimethyltricyclo [4.2.1.1(2,5)] decane-9,10-diol; 4-(1,5-dihydroxy-2,6,6-trimethylcyclohex-2-enyl) but-3-en-2-one, *n*-Hexadecanoic acid, phytol; 3,7-dimethyl-6-nonen-1-ol acetate; 9-octadecenamide, (Z)-,9,10-Secocholesta-5,7,10(19)-triene-3,24,25-triol,(3a,5Z,7E)-Ethyliso-allocholate; glycerine; D-glucose,6-O-α-D-galactopyranosyl-, α-D-Glucopyranoside,O-α-D-glucopyranosyl-(1.fwdarw.3)-α-D-fructofuranosyl;α-D-Glucopyranose,4-O-α-D-galactopyranosyl-, desulphosinigrin and

$\alpha$ -methyl-D-mannopyranoside compounds respectively (Rout & Kar, 2014). Screening of phytochemical constituents from leaf extract showed the presence of coumarins, quinones, steroids, tannins, phenols, alkaloids, betacyanins, cardiac glycosides, saponins, flavonoids and terpenoids compounds respectively (Sangeetha et al., 2014).

- Leaf and Stem bark: Preliminary phytochemical screening from leaf and stem bark extraction showed that they contain terpenoids, flavonoids, amino acids, tannins and phenolic compounds, alkaloids, glycosides, steroids fats and oils, steroids, lignin, and triterpenes constituents (Zaman, 2013).
- Fruit peel: Phytochemical analysis from the fruit peel collected from different locations namely Ooty, Kodaikanal and Kolli Hills revealed the presence of tannins, saponins, quinones, terpenoids, steroids, flavonoids, phenols, alkaloids, glycosides, cardiac glycosides, coumarins and betacyanin (Ethiraj & Sridar, 2018).

## 10. Pharmacological activities

### 10.1. Experimental pharmacology

Anti-HIV: Fruitpeel extraction from *A. reticulata*, *A. squamosa*, *Chrysophyllum cainito*. and *Melicoccus bijugatus* species was studied to investigate their potential as anti-HIV agents. Results showed that *A. reticulata* could consider as an anti-HIV agent as it inhibit more than 70% of the HIV-1 RT enzyme.

Anti-oxidant: Investigation on screening and evaluation of free radical scavenging activity from leaf extract using various solvent system as well as quantification of antioxidant compound using GC-MS in each solvent was done and results revealed that chloroform leave extract possess an effective free radical quenching property with 99.2% (DPPH) and 71.2% (ABTS) at 1000 $\mu$ g/ml respectively. A total of 13 bioactive compounds were also identified from chloroform leave extract as potential antioxidant compounds that would be useful in enhancing human health from the oxidative stress induced diseases.

### 10.2. Clinical pharmacology:

Antihyperglycemic activity: Determination of anti-hyperglycemic study in *Carica carandus* and *Annona reticulata* leaves using methanolic extraction in glucose loaded Swiss albino mice reported that the glucose loaded mice exhibit strong antihyperglycemic activity when administered with methanolic leave extract of *A. reticulata* at doses of 50, 100, 200, 400mg/kg body weight, implying that the plant could be useful in lowering blood sugar level particularly in diabetic patients by (Rahamnet.al., 2011). Evaluation on the efficiency of hydro-alcoholic leaf extract prepared in different fraction to identify the compound responsible for anti-hyperglycemic activity in streptozotocin induced hyperglycemic rats revealed that ethyl acetate fraction could significantly lower the blood glucose level, probably due to the presence of compounds (9-octadecenamide, (Z)-, ethyl isoallocholate and

9,10-secocholesta-5,7,10(19)-triene-3,24,25-triol, (3 $\alpha$ ,5Z,7E)-) in the fraction that attributed the anti-hyperglycemic activity (Rout & Kar, 2014).

11. Toxicity and safety:

Evaluation on safety usage of leaf extract in nutraceutical formulations through the study of acute toxicity in adult nulliparous, non-pregnant female Swiss albino mice report that the leaf powder was non-toxic and non-allergic and that it did not produce any toxicity effect in mice (Shivanna *et al.*,2019).

12. Clinical studies: No data available

13. Contraindications: No data available

14. Precautions: No data available.

15. Adverse reactions: No data available.

16. Marketed formulation, if any: No data available

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1. Botanical Name: ***Artemisia vulgaris L.***

2. Synonym: NA

3. Family: Asteraceae

4. Common Names

English:	Mugwort, Indian wormwood, Fleabane
Hindi:	Nagdona, davana, dauna
Sanskrit:	Damanaka, damana
Manipuri:	Iaibakngou
Bengali:	Nagadana
Tamil:	Macipattiri, makkippu, tirunamacceṭi
Malayalam:	Masipatṛi, makkippuvu
Assamese:	Chiota
Gujarati:	Damro.

5. Description: An erect perennial plant growing up to 2 m tall, with an extensive rhizome system. Leaves are 5–20 cm long, dark green; pinnate and sessile, with dense white tomentose hairs on the underside. The erect stems are grooved and often have a red-purplish tinge. The rather small florets (5 mm long) are radially symmetrical with many yellow or dark red petals. The narrow and numerous capitula (flower heads), all fertile, spread out in racemose panicle. It flowers from mid-summer to early autumn.

6. Distribution: Native temperate Europe, Asia, northern Africa, Alaska and North America; in India growing wild in Himalayas and sometime cultivated.

7. Part Used: Whole Plant.



*Artemisia vulgaris* (Photo source BSI)

## 8. Medicinal /Therapeutic Uses

The essential oils showed antiviral activities against Yellow fever virus (Meneses *et al.*, 2009). It is used to treat dyspepsia, rheumatic pains, fevers, diarrhoea, worm infestations, vomiting, constipation, cramps, colic, hysteria, flatulence, menstrual problems, distention, epilepsy, to promote circulation, and as a sedative (Malik *et al.*, 2019). Mugwort leaves and stem are used medicinally as a bitter digestive tonic, uterine stimulant and antirheumatic. Some reports have revealed that mugwort is a potent immunomodulatory (Grendelmeier *et al.*, 2003), antihypertensive (Tigno *et al.*, 2000), antinflammatory (Shaik *et al.*, 2013), antioxidant (Melguizo *et al.*, 2014 and Pandey *et al.*, 2017) and hepatoprotective agent (Gilani *et al.*, 2005). All parts of the plant are anthelmintic, antiseptic, antispasmodic, carminative, cholagogue, diaphoretic, digestive, emmenagogue, expectorant, nervine, purgative, stimulant, slightly tonic and used in the treatment of women's complaints (Anwar *et al.*, 2015 and koul *et al.*, 2017). The leaves are also said to be appetizer, diuretic, haemostatic and stomachic (Ashok & Upadhyaya, 2013). An infusion of the leaves and flowering tops is used in the treatment of nervous and spasmodic affections, sterility, functional bleeding of the uterus, dysmenorrhoea, asthma and diseases of the brain (Adams, 2012). The compressed dried leaves and stems are used in moxibustion.

### 8.1 Uses described in pharmacopoeias and in traditional systems of medicine

It has been used by several tribes for various ailments such as analgesic properties for women after childbirth by karok tribe. The Kiowa tribe used applied infusion of this plant inside the nostrils to alleviate headache. Most of all the tribes used it as gynaecological aid. Excessive mensuration and after childbirth. Traditionally it is used for treatment in

Cramps labour pain, amenorrhoea and dysmenorrhoea. In addition to its medicinal use, mugwort has been used for smudging, protection, and inducing vivid dreams (when placed underneath a person's pillow). Other nonmedical used includes cleaning solutions, rugs, and beddings.

#### 8.2 Uses supported by clinical data

It is widely used as an alternative medicine for hypertension in the Philippines and has been demonstrated to effectively reverse hypertension in rats (Tigno *et al.*, 2000). AVL has been reported to exert a relaxant effect in tissues such as mesentery, ileum, jejunum and trachea (Natividad *et al.*, 2011). The volatile compounds from this plant possess antifungal and anti-bacterial properties (Oyedemi & Coopooosamy, 2015).

#### 8.3 Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

Traditionally in China, mugwort is used mostly for moxibustion. The dried leaves are also used as a tea for analgesia, excessive bleeding during pregnancy. Mugwort is used to flavour beer long before hops were discovered in Europe. Mugwort has been used in traditional medicine as a food additive, a tonic, a tea, and a bath steep. Moughte means moth or maggot, and mugwort was used traditionally to repel moths. The volatile oils have been used in aromatherapy for their pleasantly aromatic smell. Other traditional uses for mugwort included treating diarrhea, constipation, cramps, and worm infestations. Tonics made from mugwort root were also thought to be beneficial in the treatment of various complaints including anxiety, irritability, and restlessness. Currently, mugwort is occasionally used in Germany for the treatment of intestinal gas, stimulation of digestion, and bloated distension of the stomach.

#### 8.4 Special uses in North East India

The local people in Manipur consume the sprouting leaves as one of the food. Leaf decoction used on cuts and bruises to stop bleeding mostly in nose bleeding and measles and fever (Panda *et al.*, 2010). The crushed leaves with water are used to treat the flu in chicken. It is also used to repel the stored grain pests as well as rodents in and around the granaries in northeast (Bikramjit, 2010).

#### 8.5 Dosage forms used in tradition

The dosage of Mugwort varies according to its parts, age of patient and health conditions. The general therapeutic dosage of Mugwort is as under:

Medicinal Parts	Dosage
Mugwort Roots Powder	125 mg to 1000 mg
Mugwort Leaves Powder	500 mg to 2 grams
Mugwort Flowers powder	500 mg to 2 grams
Mugwort Flowers infusion	25 to 50 ml
Mugwort Leaves decoction	25 to 50 ml
Mugwort Tea	50 to 100 ml.

Mugwort is commonly used in cooking to flavour many foods and beverages, including fish, meat dishes, desserts, pancakes, soups, salads, beer, and more (Polina *et al.*, 2006). The roots of mugwort are used to make a tonic said to boost energy. In ancient cultures, mugwort was smoked to promote vivid dreams. This is because mugwort is said to produce mild psychotropic effects during wakefulness. A psychotropic effect can be induced by a substance that impacts the mental state of a person. A lotion made of mugwort is sometimes applied to the skin for alleviating itching, caused by scars or burns. Research has shown that a lotion made of mugwort and menthol, applied to the skin, relieved itching in burn victims.

#### 9. Phytochemical profile

Phytochemical studies of the Hexane and methanolic extracts showed the presence of carbohydrate, saponins, phytosterol, proteins and amino acid, tannin & phenolic compounds and flavonoids. Volatile oil (thujone, borneol, cineole, pinene), sesquiterpene lactones, flavonoids, coumarins, bitter principle, tannins are present.

#### Major chemical constituents

The major components of the essential oil is monoterpenes (44.49%) and sesquiterpenes (29.98%). The monoterpenes 1,8-cineole, camphor, α - and β-thujones are the main VOCs detected both in hydrodistillation and headspace extraction (Zhigzhitzapo *et al.*, 2015).

#### 10. Pharmacological Studies

The extract of whole plant have been reported to be used in the treatment of diabetes in traditional system of medicine as well as for epilepsy and in combination of psychoneurosis, irritability, depression, anxiety, insomnia & stress, for worm infestation, as sedative, to promote circulation and for irregular or delayed menstruation (Lewis & Lewis, 2003). Stem and leaves have been used as uterine stimulant, anti-rheumatic and digestive tonic (Terra *et al.*, 2007). The leaves and buds have been employed as a flavoring agent to season fat, meat, and fish. Powdered leaves are applied over skin diseases and used as substitute for cinchona to treat fever (Haider *et al.*, 2003).

Mugwort root has been used as a tonic in asthenic states and in conjunction with other remedies including neurasthenia, depression and hypochondria, autonomic neuroses, general irritability psychoneuroses, restlessness (Abiri *et al.*, 2018).

### Experimental pharmacology

Shaik *et al.* (2014) studied the anti-implantation and estrogenic effects of methanolic extract found that extract of this plant species possessed strong dose-dependent estrogenic effect and inhibited the process of implantation depending on the dose. Their study suggested that methanolic extract of the plant has anti-fertility activity. The main sesquiterpene lactones found in this plant is eudesmanolides, group showing high anti-microbial and anti-inflammatory properties. Sharmila & Padma (2014) studied the anti-oxidant potential of methanolic extract of leaves on primary chick embryo fibroblast subjected to oxidative stress and reported the presence of active ingredients that improve the anti-oxidant status in primary cells subjected to oxidative stress. The anti-inflammatory activity from leaves has been assessed by using cotton pellet granuloma method (Shaik *et al.*, 2013). The methanolic extracts of leaves were administered at dose of 200 and 400 mg/Kg body weight to rats after surgical insertion of cotton pellets into groin region of rats. It has been observed that extract at the dose of 400 mg/Kg showed the significant results (55.3% inhibition in weight of wet cotton pellets and 64.0% inhibition in weight of dry cotton pellets) as compared to control. It has been reported that the dose dependent anti-inflammatory property shown by mugwort is associated with the presence of flavonoids. It is used in traditional medicine either alone or in combination with other medicinal plants to treat hypertension at Vietnam and Philippines (Tigno *et. al.*, 2000).

### 10.1. Clinical pharmacology

Clinical studies have not been reported till date.

### 11. Toxicity and safety

High concentrations of certain polyphenolic compounds present in this plant can be a significant factor for obtaining genotoxicity and cytotoxicity and presence of some toxic compounds for fishes at higher doses (Marina *et. al.*, 2020).

### 12. Clinical studies

Clinical studies have not been reported till date.

### 13. Contraindications

In pregnancy & lactation mugwort might cause a miscarriage because it can start menstruation and also cause the uterus to contract. Not enough is known about the safety of taking mugwort if you are breast-feeding.

### 14. Precautions

Mugwort may cause an allergic reaction in individuals who are allergic to the Asteraceae/Compositae plant family (Pastorello *et al.*, 2002). Mugwort might also cause an allergic reaction in people who are allergic to birch, celery, or wild carrot. This has been called the “celery-carrot-mugwort-spice syndrome.” There is also some concern that mugwort might cause allergic reactions in people with allergies to white mustard, honey, royal jelly, hazelnut, olive, latex, peach, kiwi, the Micronesian nut called Nangai, and other plants from the genus *Artemisia*, including sage. Mugwort pollen might cause

reactions in people who are allergic to tobacco.

#### 15. Adverse reactions

Mugwort pollen has also been known to cause allergic reactions in those who have a tobacco allergy. Hives, swelling of the lips, face or eyes, tingling of the mouth, Headaches, Abdominal pain, Nausea and vomiting.

#### 16. Marketed formulation, if any: No data available.

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1. Botanical Name: ***Artemisia parviflora*** Buch.- Ham. ex D. Don

2. Synonym: NA

3. Family: Asteraceae

4. Common Names

English:	Himalayan wormwood
Hindi:	Pati
Khasi:	Ujaiaw
Kumaon Himalayas:	Kunjapati or pati
Manipuri:	Laibakngou
Nagaland:	Ditipati
Sanskrit:	Ganga tulaseeveda

5. Description: An erect perennial, herbs or subshrubs, 40-80 cm tall, yellow or brown pubescent, sometimes glabrescent. Lower stem leaves: petiole 2-3 cm; leaf blade ovate or elliptic-ovate, 2-pinnatipartite or -sect; segments 2 or 3 pairs, elliptic or subspatulate, 2- or 3-partite; lobules lanceolate, or deeply serrate. Middle stem leaves ± sessile; leaf blade obovate-spatulate, flabellate, or cuneate, obliquely 3-5-partite or -sect; lobes linear, linear-lanceolate, or linear-ob lanceolate, apex acuminate. Uppermost leaves 3-partite or entire; leaflike bracts linear or linear-lanceolate. Synflorescence a ± narrow panicle. Capitula many. Involucre ovoid or subglobose. Marginal female florets 2-4. Disk florets 4-10, male. Achenes oblong.

6. Distribution: Distributed in south-east Asia; Myanmar, Pakistan, Nepal, Afghanistan, Bhutan, and Japan in India mainly subtropical regions at an altitude of 900-3500m.

7. Part Used: Aerial parts.



*Artemisia parviflora*

## 8. Medicinal /Therapeutic Uses

### 8.1. Uses described in pharmacopeias and in traditional systems of medicine

The leaf juice is used by the people of Gopeshwar-Tungnath region of Chamoli district of Uttar Pradesh in cut injuries, the decoction of the leaves is used as a vermifuge (Kimothi & Shah, 1989). The plant has been traditionally used as an appetizer, antimalaria, antiviral agent, anti-cancer, wound healer, diuretic, antioxidant, anti-febrile drug and used in the treatment of vaginitis and skin diseases (Yoganarasimhan, 2000)

### 8.2. Uses supported by clinical data

**Anti-Cancer:** The ethanolic extracts were subjected to *in-vitro* and *in-vivo* screening and the anticancer potentials against Ehrlich Ascites Carcinoma were assessed. The drug was standardized both botanically and chemically. The results obtained depicted that the plant extracts were found to be having anticancer activity particularly at the dose levels of 300 mg/kg b.w. and the results were comparable with standard drug, 5-Flurouracil (Parthasarathy, 2011).

**Anti-Malarial:** The methanolic leaf extract against *Anopheles stephensi* larvae and pupae and reported the mortality rate, LC50 and LC90 values. This study revealed that methanolic leaf extract possesses higher toxicity against *Anopheles stephensi* this may be due to the present of caryophyllene, germacrene D, camphor, artemisia ketone, 1,8-Cineole, D-copaene and sabinal acetate in the extract. The LC50 value for first instar larvae is 45.61 ppm and it is increased in the IV instar larvae as 59.60 ppm (Uma et al., 2010).

**Antiviral activity:** The ethanolic extract (50 %) of the entire plant for anti-viral (Ranikhet disease virus and Vaccinia virus) tests on human epidermoid carcinoma of

nasopharynx in tissue culture and P388 lymphocytic leukaemia in mice, observed that the ethanolic extract showed activity against Vaccinia virus. Hence, proving the ethnomedical claim (Dhar *et al.*, 1973).

Skin conditions: US Patent PCT/US 2010/046791 (Florence *et al.*, 2010) applicant patented the invention that the whole plant extracts. The composition was able to inhibit tyrosinase activity, elastase activity, and/ or TNF- $\alpha$  activity in the skin and/ or oxidation of skin.

8.3. Traditional /Folklore Uses: described in folk medicine, not supported by experimental or clinical data

Leaves: Leaves juice used in cut injuries, a decoction is used as a vermifuge, leaves paste applied on the forehead to relieve headache (Kimothi & Shah, 1989, Murugesan *et al.*, 2005).

Shoot: It is used as incense in Northwestern Himalayas (Singh, 2000).

Seeds: It is ground into a powder and take for abdominal pain (Hussain *et al.*, 2007).

Seeds, leaves and fruits: It has antiviral properties, and the ground powder is used to cure stomachache, high blood pressure and diabetes (Ambasta, 1986).

8.4. Special uses in North East India:

- In Arunachal Pradesh, The Nyishi tribe old people used to carry a bunch of leaves on their back for 4-6 hours to get relief in back pain (Srivastava, 2010).
- In Manipur, it is being used as an ingredient in traditional hair care lotion called 'chinghi' and in traditional medicines (Nganthoi & Sanatombi, 2019).

8.5. Dosage forms used in tradition: Not available

9.0. Phytochemical profile:

9.1. Major chemical constituents:

- The main constituents were  $\beta$ -caryophyllene, germacrene D, camphor, artemisia ketone and 1,8-cineole along with  $\alpha$ -copaene, artemisia alcohol, terpinene-4-ol, caryophyllene oxide,  $\alpha$ -pinene, sabinyl acetate and  $\alpha$ -humulene as minor constituents (Rana *et al.*, 2003).
- It contains artemisinin (anti-malarial) in flowers, leaves, roots, and stems. The percentage of artemisinin (dry weight) was 0.8 % in stems of the plant (Mannan *et al.*, 2010, Nganthoi & Sanatombi, 2019).
- The major volatile constituents of the aerial parts were  $\beta$ - eudesmol, spathulenol,  $\beta$ -selinene and citronellol along with  $\gamma$ -cadinene, phytol, guaiol, germacrene D, 10- epi- $\eta$ -eudesmol and  $\alpha$ -cadinol as minor constituents (Sharma *et al.*, 2011).

- It can be utilized as a source of germacrene D,  $\beta$ -caryophyllene and  $\alpha$ -humulene. Minor constituents such as camphene, myrcene, limonene, terpinolene, perillene,  $\alpha$ -terpineol,  $\beta$ - copaene,  $\alpha$ -trans-burgamotene,  $\alpha$ -humulene, bicyclogermacrene, humulene epoxide II, junenol, cubenol<1-epi- $\alpha$ > and  $\alpha$ -cadinol are recorded for the first time in India (Tiwari, 2017).

## 10. Pharmacological Studies

### 10.1. Experimental pharmacology

**Anthelmintic activity:** A study is carried out to evaluate the *in vitro* and *in vivo* effect of *Artemisia parviflora* on *Haemonchus contortus*, a parasitic nematode of small ruminants. Methanolic plant extract was tested against three different developmental stages using an egg hatch assay, infective larvae and adult worm motility assay. A highly significant ability to inhibit the egg hatching (100 %) was recorded. The highest activity for adult motility and larvicidal assay for *A. parviflora* was 89 % and 86.6 % respectively. For *in vivo* trials in sheep, fecal egg counts reduction rate is 73.6 % 50mg/kg body weight. It is concluded that *A. Parviflora* plant extract is effective in reducing worm burden in animals (Irumer et al., 2017).

**Antimicrobial and Antioxidant properties:** An experiment is carried out on antimicrobial and antioxidant properties. They performed antimicrobial susceptibility assay against ten standard reference bacterial strains. Antioxidant activity was analyzed using the ferric thiocyanate and 2, 2-Diphenyl-1-Picrylhydrazyl (DPPH) assays. The n-hexane extract showed high inhibition of the growth of *Pseudomonas aeruginosa*, *Escherichia coli* and *Shigella flexneri*. Methanol extract showed strong radical scavenging and antioxidant activity, other extracts showed moderate antioxidant activity. The major derivatives present in the extracts are of terpenes, steroids, phenols, flavonoids, tannins and volatile oil. The antimicrobial and antioxidant property of the extracts were attributed to the secondary metabolites, terpenes and phenolic compounds present and could be of considerable interest in the development of new drugs (Ahameethunisa & Hopper, 2012). Antifungal property was reported from the essential oil against *Candida albicans*, *Sporotrichum species* and *Cryptococcus* (Mehrotra et al., 1993).

**Gastro-protective potential:** A study was conducted to evaluate the gastroprotective potential from seeds against aspirin-induced ulcers in albino rabbits. Thirty-Six rabbits were randomly divided into 6 equal groups. Group 1 was control; group 2 received aspirin for 14 days; group 3 received omeprazole + aspirin for 14 days; groups 4, 5, and 6 received the seed powder 250, 500, and 750 mg/kg, respectively along with aspirin, for 14 days. Total oxidant status (TOS), total antioxidant capacity (TAC), malondialdehyde (MDA), and catalase (CAT) were determined to check the gastric damage. Ulcer score, gastric volume, gastric pH, and total acid output were also measured to determine gastroprotective potential. The seed powder exhibits gastroprotective potential with significant reduction in the ulcer score, acid output, and gastric volume while the pH of gastric mucosa increases significantly at the dose

of 750 mg/kg when compared to aspirin treated groups. Biochemical analysis showed a significant increase in TAC and CAT activity while it showed significant decrease in the levels of TOS and MDA which indicate reduction in gastric damage. The seed powder proved to be gastroprotective at 250, 500 and 750 mg/kg with gastric protection of 47.5, 58.1, and 73.5%, respectively (Aslam *et al.*, 2017).

10.2. Clinical pharmacology: Not been reported

11. Toxicity and safety: The acute oral toxicity was conducted from the ethanolic extract of aerial parts. Four groups of mice were orally treated with doses of 0.10, 0.50, 1.0 g/kg body weight, parameters like behavioral change, body weight change, and other abnormalities were observed. The result showed that it did not produce any hazardous symptoms or death in acute toxicity study showing a LD<sub>50</sub> higher than 1 g/kg body weight. The administration of this plant material extract did not show any significant changes in the body weight or any type of adverse effect on the body of the animal (Ahuja *et al.*, 2011a).

12. Clinical studies: Not been reported

13. Contraindications: Not available

14. Precautions: Not available

15. Adverse reactions: Some species of *Artemisia* is known to cause nausea, vomiting, kidney failure, insomnia.

16. Marketed formulation, if any: Not available

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***Azadirachta indica***

[Internal Code: IBSDM000]

1. Botanical Name: ***Azadirachta indica*** A. Juss.2. Synonym: *Melia azadirachta* L.

3. Family: Meliaceae

## 4. Common Names

Bengali:	Nim
English:	Indian lilac, Margosa tree, Neem tree
Gujarati:	Limba, Limbado
Hindi:	Nim, Nimb
Kannada:	Bevinamara
Malayalam:	Vepa
Marathi:	Limba
Oriya:	Nimba
Sanskrit:	Arishta, Nimba
Tamil:	Vembu, Veppa
Telugu:	Bebu, Veepachettu, Yapachettu
Urdu:	Nim.

5. Description: An evergreen tree up to 40 feet high with greyish-brown bark. Leaves alternate, imparipinnate, estipulate; slender, swollen at base, glabrous, leaflets 7-15, opposite or subopposite, estipellate; slender, glabrous; lanceolate or falcate, base oblique, apex acuminate, margin serrate, glabrous, coriaceous; pinnate, slender, prominent, intercostae reticulate, faint. Flowers bisexual, white, in axillary panicles; bracteoles scaly; sepals 5, connate at base, ovate, margin ciliate; petals 5, free, white, oblong-ovate, pubescent, spreading, imbricate; staminal tube glabrous, apically 10 lobed; lobes truncate; anthers 10, slightly exserted, apiculate, opposite to lobes, sessile; ovary superior, globose, 3-celled; ovules 2 per cell; style slender, elongate; stigma terete, 3-lobed. Fruit a drupe, oblong-ovoid, greenish-yellow; seed one, surrounded by a sweet pulp.

6. Distribution: Indo-Malaysia; cultivated as well as naturalized tropical to subtropical regions of India.

## 7. Part Used: Whole Plant.



*Azadirachta indica*

## 8. Medicinal /Therapeutic Uses

Traditionally, is used by rural people for its medicinal properties, and it has a long history of use dating back to the Vedic period of India approximately 6000 years BC(Schumacher et al., 2011). In Ayurvedic medicine, the bark and leaves are used for skin diseases, flowers as a tonic and stomachic, and fruits as a purgative and emollient. Various types of organic compounds have been isolated from different parts of the tree. These organic compounds are widely used as medicines and pesticides. Biologically active, volatile organic sulphur compounds are liberated by crushing fresh seeds. As many as 25 volatile compounds have been identified with di-n-propyl-disulfide being the chief constituent. The most active anti feedant in the seed is azadirachtin, found pure as a microcrystalline solid. Stem and root bark have astringent, tonic, antiperiodic and other medicinal properties. The bark, leaves and fruit are used in the treatment of infections and diseases. The bark is bitter, a tonic and an astringent, and has traditionally been used to treat fever, nausea, vomiting and skin diseases. The root bark is more effective in this case than the stem bark and young fruit. The leaves are an old and popular remedy for skin diseases. The fresh juice of the leaves is administered with salt to treat intestinal worms and with honey for skin diseases and jaundice. As an external application for skin diseases, the leaves are used in variety of forms (poultice, ointment, and liniment). A strong decoction of fresh leaves produces an antiseptic which may be used in place of a weak solution of carbolic acid. A hot infusion of the leaves is used for fomenting swollen glands, bruises and sprains, and appears to be an anodyne. The fruits act as a purgative and an emollient, and are useful in the control of intestinal worms,

urinary tract diseases and piles. The dry seeds possess almost the same properties as the oil when brushed and mixed with water or other liquids. The seed oil is the most important medicinal product of this species from a commercial point of view. It is antiseptic and has proved to be useful in treating skin diseases, ulcers, rheumatism, and sprains. The oil saponifies readily and is used in the manufacture of a medicinal soap because of its antiseptic properties. This soap is very effective for washing sores and for general uses like those of carbolic soap. The flowers are useful in some cases of atonic dyspepsia and general debility. There are reports that the toddy (fermented sap) of the tree is useful in the care of some chronic diseases (Schumacher *et al.*, 2011).

### 8.1. Uses described in pharmacopoeias and in traditional systems of medicine

More than 140 compounds have been isolated from different parts of neem. All parts of the neem tree- leaves, flowers, seeds, fruits, roots, and bark have been used traditionally for the treatment of inflammation, infections, fever, skin diseases and dental disorders. Neem leaf and its constituents have been demonstrated to exhibit immunomodulatory, anti-inflammatory, anti-hyperglycaemic, antiulcer, antimalarial, antifungal, antibacterial, antiviral, antioxidant, antimutagenic and anticarcinogenic properties (Saleem *et al.*, 2018).

### 8.2. Uses supported by clinical data

The studies based on animal model established that neem and its chief constituents play pivotal role in anticancer management through the modulation of various molecular pathways including p53, pTEN, NF- $\kappa$ B, PI3K/Akt, Bcl-2, and VEGF. It is considered as safe medicinal plants and modulates the numerous biological processes without any adverse effect. It summarizes the role in the prevention and treatment of diseases via the regulation of various biological and physiological pathways (Mahfuzul *et al.*, 2007).

### 8.3. Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

All parts of neem tree are commonly used in traditional Indian medicine for household remedy against various human diseases. The definition of Siddha medicine is conquest of death: "that which ensures preventive against mortality". This statement is attributed to Tirumular, a revered Siddha whose treatise called Tirumantiram. This system of medicine originated from Tamil Nadu, South India. The system was very popular in ancient India. Believed to be more than 10 000 years old, the Siddha system of medicine is one of the most antiquated traditional medical systems. The Siddha system of medicine is prevalent in the southern states of India, Sri Lanka, Malaysia, and Singapore. The first medicinal plant mentioned in the Siddha medical system is neem (Kumar *et al.*, 2010).

#### 8.4. Special uses in North East India

Neem has been used for centuries in Asia as an insecticide, fungicide, and anticonceptual in popular medicine. Almost every part of the neem tree bark, branches, leaves, roots, seeds, and the trunk has a biological application (Ghonmode *et al.*, 2013).

#### 8.5. Dosage forms used in tradition

There are inadequate clinical trials to support specific therapeutic doses of neem. Based on animal studies, an estimated safe dose of neem oil 0.2 mL/kg has been suggested in adults [Boeke SJ *et al.*, 2004] Deep IM injections of sodium nimbidinate 250 mg daily have been used in a trial in congestive cardiac failure. Intravenous (IV) ethanol extracts of neem leaf caused cardiac arrhythmia in rats and should be avoided (Subapriya *et al.*, 2006).

### 9. Phytochemical profile

It is also rich in various phytochemicals for pharmaceuticals such as alkaloids, steroids, flavonoids, terpenoids, fatty acids, and carbohydrates. The fungicidal potential of the tree is due to the presence of azadirachtin and nimbin (Saleem *et al.*, 2018).

#### 9.1. Major chemical constituents

Neem shows therapeutics role in health management due to rich source of various types of ingredients. The most important active constituent is azadirachtin and the others are nimbolinin, nimbin, nimbidin, nimbidol, sodium nimbinate, gedunin, salannin, and quercetin

Sl. No.	Compound name	Source	Pharmacology activity
1	Nimbidin	Seed oil	Anti-inflammatory, Antiarthritic, Antipyretic, Hypoglycaemic, Antigastric ulcer, Spermicidal, Antifungal, Antibacterial, Diuretic (Anjali <i>et al.</i> , 2013; Ghimeray <i>et al.</i> , 2009; Jabeen <i>et al.</i> , 2013; Mosaddek <i>et al.</i> , 2008; Schumacher <i>et al.</i> , 2011; Udeinya <i>et al.</i> , 2008).
2	Sodium nimbinate		Anti-inflammatory [Mosaddek <i>et al.</i> , 2008; Schumacher <i>et al.</i> , 2011].
3	Azadirachtin	Seeds oil	Antimalarial (Tiwari <i>et al.</i> , 2010).
4	Nimbin	Seed oil	Spermicidal (Ghimeray <i>et al.</i> , 2009).

5	Nimbotide	Seed oil	Antimalarial, Antibacterial (Ghimeray <i>et al.</i> , 2009; Udeinya <i>et al.</i> , 2008).
6	Gedunin	Seed oil	Antimalarial, Antifungal (Anjali <i>et al.</i> , 2013; Udeinya <i>et al.</i> , 2008).
7	Mahmoodin	Seed oil	Antibacterial (Ghimeray <i>et al.</i> , 2009).
8	Gallic acid, (-) epicatechin and catechin	Bark	Anti-inflammatory (Mosaddek <i>et al.</i> , 2008; Schumacher <i>et al.</i> , 2011).
9	Margolone, margolonone and isomargolonone	Bark	Antibacterial (Ghimeray <i>et al.</i> , 2009).
10	Cyclic trisulphide and cyclic tetrasulphide	Leaf	Antifungal (Anjali <i>et al.</i> , 2013; Jabeen <i>et al.</i> , 2013).
11	Polysaccharides		Anti-inflammatory (Mosaddek <i>et al.</i> , 2008; Schumacher <i>et al.</i> , 2011).
12	Polysaccharides G1A, G1B	Bark	Antitumor (Arumugam <i>et al.</i> , 2014; Gunadharini <i>et al.</i> , 2011; Subapriya <i>et al.</i> , 2006).
13	Polysaccharides G2A, G3A	Bark	Anti-inflammatory (Mosaddek <i>et al.</i> , 2008' Schumache <i>et al.</i> , 2011).
14	NB-2 Peptidoglycan	Bark	Immunomodulatory
15	Phytosterols	Fruit	Antiulcer (Bhajoni <i>et al.</i> , 2016).

## 10. Pharmacological Studies

### 10.1. Experimental pharmacology

Several studies have been carried in recent years showing that it possesses diverse pharmacological effects. Some of the important pharmacological actions are as follows:

**Analgesic:** The analgesic effect of an extract of the leaves was assessed in mice using the acetic acid writhing test and the tail flick test. Intragastric administration of 10–100mg/kg body weight of the extract reduced the incidence of writhing and enhanced tail-withdrawal latencies (Kumar *et al.*, 2010).

**Antianxiety/ Anxiolytic:** The freshly prepared leaf extract at low doses (10, 20, 50, 100 and 200mg/kg) produced significant antianxiety effect whereas at high doses (400 and 800mg/ kg) it did not show the activity. Intragastric administration of 10–200 mg/kg body weight (bw) of an aqueous extract of leaf produced anxiolytic effects similar to those of 1 mg/kg bw of diazepam in rats in the elevated-plus-maze and open-field behaviour tests (Jaiswal *et al.*, 1994).

**Anti-atherosclerotic:** The ethanol extract of leaves have been shown to reverse the diabetes-associated increase in circulating immune cells and hence may play a significant role in the control of atherosclerosis and management of diabetic vascular complications in alloxan-induced diabetic rats (Elumalai *et al.*, 2012).

**Anti-bacterial:** The ethanolic extract of stem bark of *A.indica* exhibited antibacterial activity against *Bacillus megaterium* (Ghimeray *et al.*, 2009).

**Anticandidal:** The hexane, methanol, chloroform, water, petroleum ether, dichloromethane, acetone and absolute alcohol extracts of seed kernels were used for evaluating anti candidal effect on *Candida* species using broth dilution method at concentrations from 1 to 0.0625mg/ ml. The hexane extract, ethanol extract of commercial seed oil and ethanol extract of seed kernel showed promising anticandidal activity (Lloyd *et al.*, 2005).

**Anti-fungal:** The ethanolic extract of stem bark exhibited antifungal activity against *A.niger*. The 100% ethanolic extract of neem leaves inhibited the fungus *Pityrosporumovale* causing the dandruff more widely than the lower concentration levels using agar cup method (Anjali *et al.*, 2013; Jabeen *et al.*, 2013).

**Antihepatotoxic:** The effect of an aqueous extract of the leaves was evaluated in paracetamol induced hepatotoxicity in rats. Intragastric administration of 500.0 mg/kg bw of the extract significantly ( $P < 0.01$ ) reduced elevated levels of serum 93 aspartate aminotransferase, alanine aminotransferase and glutamyltranspeptidase (Bhanwra, 2000).

**Anti-inflammatory:** The aqueous extract of leaves exhibited anti-inflammatory activity. Aqueous and petroleum ether extracts of *A.indica* leaves reduced the inflammation caused by *S. typhimurium* and its OMPs as assessed by paw flicking response. Petroleum ether leaf extract was found to be more effective than aqueous extract may be due to presence of steroids and triterpenoids observed in petroleum ether extract. A comparative study of the anti-inflammatory effect of aqueous extract of leaf and dexamethasone was carried by administering 400mg/ kg body weight of extract and 0.75mg dexamethasone intraperitoneally and 1 hour before the formalin injection and once daily for 7 days in rats. The results showed significant reduction in the paw edema of rats (Mohammad *et al.*, 2016; Saleem *et al.*, 2018).

**Antimalarial:** The methanolic extract of the bark containing gedunin showed antimarial activity against *Plasmodium falciparum* (Udeinya *et al.*, 2008).

**Antimicrobial:** The organic extracts of neem (petroleum ether, chloroform, ethanol and aqueous) were screened for its antimicrobial activity against *Streptococcus mutans*, *Streptococcus salivarius* and *Fusobacterium nucleatum* strains causing

dental caries using disc diffusion method and showed that the chloroform extracts of neem has a strong antimicrobial activity (Singh *et al.*, 1997).

**Antipyretic:** The ethanol extract of the leaves showed appreciable antipyretic effect (up to 70%) on rats. This effect might be due to inhibition of the synthesis of prostaglandin E2 which is described as key mediator of fever (Elumalai *et al.*, 2012).

**Antitumor:** The intraperitoneal injection of Leaf Preparation (NLP) in 500 mg/ kg body weight dose for 20 days efficiently suppressed the growth of tumors which was associated with normalization of the LPx levels and augmentation of GSH contents. NLP enhanced the activity of the endogenous antioxidant scavenging enzymes, superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT) and glutathione-S-transferase (GST) in liver and tumor tissue. The effect of NLP was more pronounced when treated as early as day 5 of post-tumor cell inoculation (Arumugam *et al.*, 2014; Gunadharini *et al.*, 2011; Singh *et al.*, 1997).

**Antiulcer:** The aqueous extract of leaves exhibited antiulcer activity (Bhajoni *et al.*, 2016).

**Antiviral:** The aqueous solution of seeds showed antiviral activity against okra mosaic virus (Anonymous, 2004). Oil has been found to slow down the growth of HIV-virus (Badam *et al.*, 1999; Tiwari *et al.*, 2010).

**Hepatoprotective:** The water-soluble portion of alcoholic extract of the leaves was found to possess hepatoprotective activity in rats. The leaf extract was administered in rats with paracetamol induced hepatic damage and significantly enhanced the hepatic level of glutathione dependent enzymes and superoxide dismutase and catalase activity suggesting that the hepatoprotective effect of the extract on paracetamol induced hepatotoxicity may be due to its antioxidant activity (Baligar *et al.*, 2014; Devmurari *et al.*, 2010; Kalaivani *et al.*, 2009).

**Hypoglycemic:** The water-soluble portion of alcoholic extract of the neem leaves was found to possess significant blood sugar lowering effect in glucose fed and adrenalin –induced hyperglycemic rats (Akter *et al.*, 2013; Arika *et al.*, 2016; Dholi *et al.*, 2011; Ebong *et al.*, 2008; Joshi *et al.*, 2011; Patil *et al.*, 2013).

**Hypolipidemic:** The leaf extract exhibited significant hypolipidemic activity. The effect of leaf extract on serum and liver lipid parameters viz. cholesterol, total lipids, phospholipids, and triglycerides was studied in rats fed on anthergenic diet for 4 weeks (Chitta *et al.*, 2014; Jaiswal *et al.*, 1994).

**Larvicidal:** The aqueous extract of leaves shows a slight larvicidal activity. In another study, a major volatile constituent (75.74%) di-n-propyl disulphide from the seed exhibited larvicidal activity against yellow fever mosquito (*Aedes aegypti* L.). The Azadirachtin, the leaf extract exhibited significant larvicidal activity against

*Culexpiiens* mosquito larvae and pupae in east of the Republic of Algeria under laboratory conditions. Mosquito adult fecundity were markedly decreased, and sterility was increased by the Azadirachtin after treatment of the fourth instar and pupal stage. The treatment also prolonged the duration of the larval stage (Baligar et al., 2014; Ghimeray et al., 2009; Kumar et al., 2010; Priyadarsini et al., 2009).

Nimaticidal: The ethanolic extract of the leaves exhibited nematocidal activity against *Cephalobus litoralis*. (Arumugam et al., 2014; Gunadharini et al., 2011; Singh et al., 1997).

Spermicidal: The leaf at a dose of 20mg, 40mg and 60mg/rat/day for 24 days exhibited spermicidal activity. A volatile fraction of the oil is reported to be responsible for spermicidal activity at a dose of 25 mg/ml for human sperm (Ghimeray et al., 2009).

## 10.2. Clinical pharmacology

Various clinical trials-based studies confirmed that herbal products or derivatives from the natural products play vital role in diseases prevention and treatment. A very few studies on active compounds such as nimbiden were made to check the efficacy in the health management. An important study was made based on human subjects to investigate the role of neem bark extract as anti-secretory and antiulcer effects in human subjects. Administration of lyophilised powder of the extract for 10 days at the dose of 30 mg twice daily showed significant decrease (77%) of gastric acid secretion. The bark extract at the dose of 30–60 mg twice daily for 10 weeks almost completely healed the duodenal ulcers and one case of esophageal ulcer and one case of gastric ulcer healed completely when administrated at the dose of 30 mg twice daily for 6 weeks. A double blind clinical drug trial study was performed to check the efficacy of drug made up of aqueous extract of neem leaves in 50 cases of uncomplicated psoriasis taking conventional coal tar regime and results revealed that patients taking drug in addition to coal tar had shown a quicker and better response in comparison to placebo group. A clinical study of six weeks was made to check the efficacy of neem extract dental gel with chlorhexidine gluconate (0.2% w/v) mouthwash as positive control and results of the study showed that the dental gel containing neem extract has significantly reduced the plaque index and bacterial count compared to that of the control group. A study showed that, in ulcer healing tests, nimbiden significantly enhanced the healing process in acetic acid induced chronic gastric lesions in albino rats and dogs (Bhajoni et al., 2016; Ghimeray et al., 2009).

## 11. Toxicity and safety

The seed oil contains low concentrations of aflatoxin that are poisonous in large doses. In a case report of a 35-year-old woman, bilateral vision loss occurred 5 days

after consumption of approximately 150 mL of neem oil. Severe poisoning in infants from neem oil have been reported. A study of the toxicity of nimbidin on frogs showed that the average lethal dose was estimated at 0.25mg/g body wt. Neem oil can cause some forms of toxic encephalopathy and ophthalmopathy if consumed in large quantities (Abdel *et al.*, 2014; Baligar *et al.*, 2014; Deng *et al.*, 2013).

## 12. Clinical studies

Clinical trials were conducted on 9 patients of congestive heart failure with anasarca to study the diuretic effect of sodium nimbidinate. 250mg were administered daily by deep intra-muscular injection in the gluteal region. The injections were repeated for 2-13 days with an average of about 5 injections per patient. Four other patients were also studied as controls on the same lines with bed rest, low sodium diet and adequate digitalization without any diuretic. Eight of the patients showed a definite diuretic response. The control group did not show any diuresis. No toxic reaction was noted except local discomfort or slight pain. Clinical trials were conducted on 12 cases of congestive cardiac failure with sodium nimbidinate for diuretic activity. Encouraging diuretic activity was observed with good response in 4 cases. There was no significant toxicity (Bandyopadhyay *et al.*, 2004).

## 13. Contraindications

Specific contraindications have not been identified. The use of oral neem oil in children cannot be supported due to reported deaths.

## 14. Precautions

These serious side effects include vomiting, diarrhoea, drowsiness, blood disorders, seizures, loss of consciousness, coma, brain disorders, and death. Pregnancy and breast-feeding: Oil and bark are likely unsafe when taken by mouth during pregnancy.

## 15. Adverse reactions

The studies based on animal model established that neem and its chief constituents play pivotal role in anticancer management and is considered as safe medicinal plants and modulates the numerous biological processes without any adverse effect (Mohammad *et al.*, 2016).

## 16. Marketed formulation, if any:

Formulation and Evaluation of Cream of leaf extract on skin renewal rate.

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1. Botanical Name: ***Baccaurea ramiflora* Lour.**

2. Synonym: NA

3. Family: Euphorbiaceae

4. Common Names

Assamese: Leteku

Bengali: Lotqua

English: Baccaurea, Burmese Grape, Lantern Tree, Mafai

Garo: Dojuka

Hindi: Lutka, Latka, Kataphal, Lutco

Khasi: Dieng-Soh-Ramdieng, Dieng-Soh-Myndong

Manipuri: Moktok

Mizo: Pangkai

5. Description: A medium size tree up to 30 feet high; young parts hairy. Bark darkish grey, with vertical lenticels, exfoliating in pieces, thick; blaze brownish; wood cream coloured. Leaves elliptic-oblong or obovate or elliptic-lanceolate, acuminate, membranous, glabrous; lateral nerves 5-10 on either half; base narrowed; petiole thick, geniculate. Flowers dioecious, apetalous, shortly pedicellate, in densely fascicled racemes from old wood or below the leaves. Male bracts longer than the clusters. Female bracts very small. Calyx-segments 4-5, unequal. Stamens 4-8; filaments short, free; anthers small; pistillode pubescent; disc 0. Ovary 2-5-celled, tomentose; stigma small, 2-5; ovules 2 in each cell. Fruit globose, capsular, yellowish-brown, about 1 in. across; endocarp not separable. Seeds orbicular, embeded in rose-coloured pulp.

6. Distribution: India, Bhutan, Bangladesh; Cambodia; China South-Central; East Himalaya; Hainan; Laos; Malaya; Myanmar; Thailand; Vietnam. In India distributed Andaman and Nicobar Islands, Assam, West Bengal, Sikkim, Arunachal Pradesh, Meghalaya, Mizoram, Tripura, Orissa.

7. Part Used: Fruit, Leaves, Bark, Roots and Seeds



*Baccarea ramiflora* L. (Photo by: K. Karthigeyan, BSI)

## 8. Medicinal /Therapeutic Uses:

### 8.1. Uses described in pharmacopoeias and in traditional systems of medicine:

In Chinese medicines, the plant has been used to cure anti-inflammatory and painkiller in treatment of injuries, rheumatoid arthritis, cellulitis, abscesses etc. (Lin et al., 2003).

### 8.2. Uses supported by clinical data:

**Anti-inflammatory:** The anti-inflammatory studies by *in vivo* method of methanolic leaf extract using carrageenan-induced rat paw edema test reported that the extraction reduces the paw edema by 63% when administered at a dose of 200mg/kg (Usha et al., 2014).

### 8.3. Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data:

**Andaman and Nicobar Islands:** The pulp is eaten raw by the tribes of the Onge (Tigga & Sreekumar, 1996).

**Northern Bengal:** The plant is used for the treatment of skin diseases and toothaches (Raj, et al., 2018).

Bangladesh: The community living in Dhaka uses the juice of the fruit for treating cold (Uddin, *et al.*, 2019).

#### 8.4. Special uses in North East India:

Meghalaya: The fruits are either eaten with salt or are made into pickles (Singh, *et al.*, 2012). The flowers of the plant are eaten raw (Kayang, 2007).

Assam: Stem bark is used for the treatment of infected umbilicus in newly born babies and constipation (Buragohian, 2011).The people living in Hollongapar Gibbon Wildlife Sanctuary (HGWLS) use the plant of for treating stomach-ache, toothache and fish-stupefying agent (Sarkar & Devi, 2017).The fruits and the aerial parts are used for treating constipation and stomach problems (Bhuyan & Chetai, 2018).

Mizoram: The stem bark is used for the treatment of uterus problem, dysentery and stomach ulcer (Khiangte & Lalramnghinglova, 2017).The leaves and stem bark of the plant is used for the treatment of stomach-ache, toothache and food allergies (Dutta, *et al.*,2018).

Manipur: The fruits are used for treating digestive problems, while bark for skindiseases (Singh, *et al.*,2014).

#### 8.5. Dosage forms used in tradition:

Bark: The stem bark 500g, 100g of pudina leaf, 5m litter water with 250 grms. of sugar made into a decoction. The filtrate is given 50ml twice a day for stomach problems. Dried bark of 1kg is boiled in 3 liter of water and 1 tablespoon of sugar for 3-4 hours and given twice daily at 50ml for uterus problem (Khiangte & Lalramnghinglova, 2017).Bark decoction is used for treating constipation, while powder made from the bark is applied on infected umbilicus of newly born baby (Buragohian, 2011). Juice from the bark is taken against food allergy (Hazarika, 2012).

Leaves: Leaves (2-3 nos.) are chewed three times a day foe toothache; Infusion from the bark of the plant is used against stomach-ache (Hazarika, 2012).

### 9. Phytochemical profile:

#### 9.1. Major chemical constituents:

Leaf: Phytochemical analysis of the ethanolic extract of leaf the presence of alkaloids, glycosides, tannins, phytosterols, saponins and flavonoids (Saha, *et al.*,2017).

Seed: Phytochemical screening of ethanolic extract of seed revealed that presence of alkaloids, flavonoids, glycosides, phenol, phlobatannin and sterol (Munni, *et al.*,2018).

**Seed, pulp and peel:** Phytochemical analysis of methanolic extract of seed pulp showed the presence of alkaloids, glycosides, phenols, flavonoids, saponin, tannin and terpenoids (Uddin, et al.,2018).

**Fruit:** Methanolic extraction of 26 underutilized ethnomedicinal fruit species showed that *Baccaurea ramiflora* and the other four species namely *Aegle marmelos*, *Emblica officinalis*, *Sapindus mukorossi* and *Artocarpus chama* exhibited a good source of phenolic content (Dutta et al.,2018).

**Peel and seed:** Ethanolic extraction from *Baccaurea ramiflora* peel and seed showed the presence of alkaloids, glycosides, steroids, flavonoids, phenol and saponins constituents (Paul et al.,2020).

## 10. Pharmacological Studies:

### 10.1. Experimental pharmacology:

**Antioxidant:** A notable free radical scavenging activity with an IC<sub>50</sub> value of 4.524µg/ml using DPPH assay was reported from seeds *in vitro* indicating that it has high level of antioxidant property that could be used as an antioxidant agent (Munni et al.,2018).Methanol extract for determining the antioxidant potential in pulp, peel and seed reveal to be high in pulp extract than in peel and seed denoting that the pulp extract have a good antioxidant property that may be beneficial in preventing the progress of different diseases related to free radical mediated oxidative stress (Uddin et al., 2018).Evaluation of antioxidant property by *in vitromethod* of ethanolic extract of fruits using DPPH assay method reported that it showed significant antioxidant activity based on IC<sub>50</sub> value (Paul et al.,2020).

**Antiviral:** This plant fruit have studied antiviral activity against Semliki forest virus (Dhawan, 2012).

### 10.2. Clinical pharmacology:

**Anti-diarrhoeal:** Methanol and ethanol extraction from the pulp and seeds were used for testing the anti-diarrhoeal activity in Swiss albino mice and showed that both the extraction decreases the number of diarrhoeas of the tested animals and the inhibitory % against defecation were 59.7% and 63% compared to the standard drug loperamide that inhibit about 61.34%, indication that the plant has anti-diarrhoeal action (Nesa, et.al.,2018).

## 11. Toxicity and safety:

The ethanolic extracts of leaf did not show any signs of acute toxicity and lack of death at all doses up to 5000mg/kg b.w when administered orally in Wistar rats (Saha, et al.,2017).

12. Clinical studies: Not available

13. Contraindications: Not available

14. Precautions: Not available

15. Adverse reactions: Not available

16. Marketed formulation, if any: Not available:

17. References:

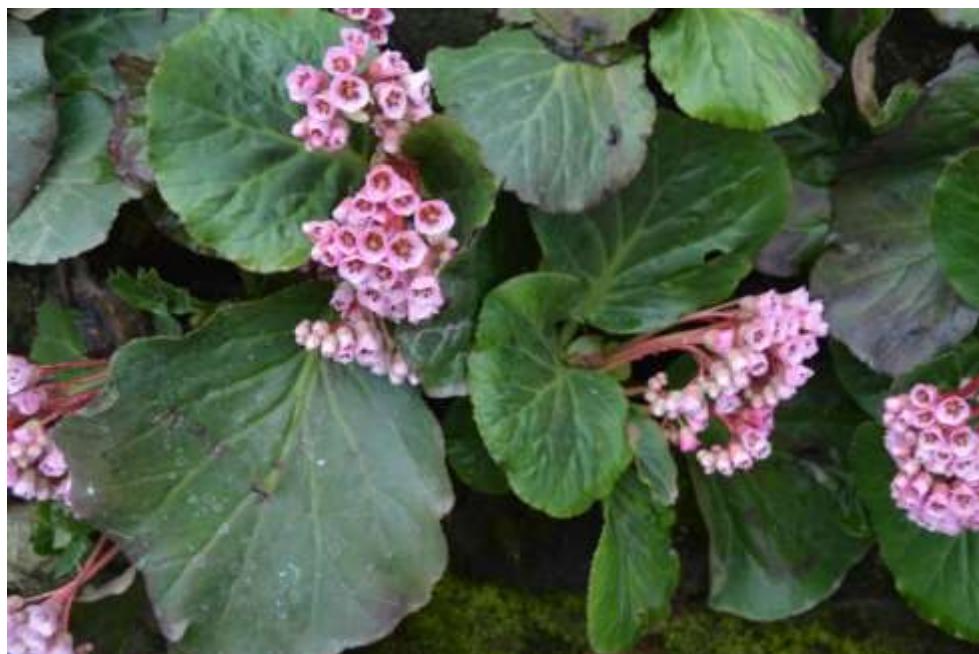
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1. Botanical Name: ***Bergenia ciliata* (Haw.) Sternb.**
2. Synonym: *Megasea ciliata* Haw.
3. Family: Saxifragaceae
4. Common Names
 

Assamese:	Patharkuchi
Bengali:	Patharkuchi, Himasagara, Patrankur
English:	Hairy Bergenia, Stone breaker, Rock foil,
Hind:	Pakhanabherda, Silphara, Patharcua, Sadpottar,
Kannada:	Alepgaya, Pahanbhedi, Hittaga, Pasanaberu, Hittulaka
Kashmiri:	Pashanbhed, Batweyaa
Malayalam:	Kallurvanchi, Kallurvanni, Kallorvanchi
Marathi:	Pashanbheda
Oriya:	Pasanbhedi, Pashanabheda
Punjabi:	Kachalu, Pashanbhed
Sanskrit:	Amabhedak
Tamil:	Sirupilai
Telugu:	Kondapindi
Urdu:Z	ahkm-e-hayat
5. Description: A large scrambling shrubs; young parts brownish, tomentose; branches with short recurved prickles. Leaves simple, alternate, spiral; stipules small, caducous; petioles c. 4-6 cm long; lamina ovate, 3-7-lobed, lobes rounded, cordate at base, broadly acute at apex, crenate-serrate along margins, rugose above, grey velvety tomentose beneath. Flowers terminal or axillary in dense clusters, creamy-yellow or yellowish white; calyx hairy, minutely toothed at apex. Fruits red, globose, stones rugose.
6. Geographical distribution: It is found in Afghanistan, South Tibet, Northern Nepal, Bhutan. Also found in abundance in northern India in Himachal Pradesh in district Shimla. Its commonly known in India as Pathar phor buti.
7. Part Used: Whole Plant.



*Bergenia ciliata*

## 8. Medicinal /Therapeutic Uses:

### 8.1. Uses described in pharmacopoeias and in traditional systems of medicine:

Bastishodhana (cleanses urinary bladder), Asmari (urinary caculi), Meha, Mutrakicchra(dysuria, difficulty to pass urine), Bhedana (Piercing), Vrana (ulcers, wounds), Shoola (abdominal Colic), Pleeha (spleen related disorders, splenomegaly), Prameha (Urinary tract disorders), Hrudruja/Hrudroga (Cardiac disorders), Gulma (abdominal tumor, distension) and Arsha (Hemorrhoids) [The Ayurvedic Pharmacopoeia of India, Volume -1]. In Ayurveda, it is used in the treatment of urinary troubles, cold, hemorrhagic disease, distension of stomach and epilepsy. In Sushruta Samhita, it is used in stones and sugars. In Charak Samhita, it is useful in urinary complaints and stones. In Unani, it is used in dissolving stones. In Chakradatta, it is used in urinary troubles and stones. In Rajnighantu, it is used in treating urinary disease. In Bhavaprakash, it is used as an astringent and purifies the urinary bladder (Ruby, et al.; 2012b).

### 8.2. Uses supported by clinical data:

Anti-viral, Anti-inflammatory, Anti-malarial, Anti-pyretic, anti-tussive, anti-neoplastic, Analgesic, Hepatoprotective, Immunomodulator.

### 8.3. Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data:

Rhizome has been used for curing pulmonary infections, leucorrhea, piles and for dissolving bladder and kidney stones (Chowdhary et al., 2009). In Ayurveda system of medicine, it is commonly used as tonic, astringent, antiscorbutic, laxative, spleen enlargement, dysuria and ulcers (Bagulet al., 2003). Local people of the eastern India use rhizome juice as an anti-tussive for cough and cold (Sinha, et al., 2001b). It is being widely used to treat cough, cold, fever, pulmonary infections, heart diseases,

ophthalmic, hemorrhoids and stomach disorders (Ahmad,*et al.*, 2018). According to some studies (Chauhan,*et al.*, 2012), in the folk medicine of some areas of south East Asia the species is used for the treatment of stomach diseases. The plant is used traditionally as an antipyretic by the local communities in the Himalayan region.

#### 8.4. Special uses in North East India:

In Sikkim traditional practitioners are used for treatment of following ailments those were documented the cross culture ethnopharmacological survey in Sikkim by the team of IBSD-Sikkim Centre, Gangtok in 2016.

##### Bone fracture

1. The rhizome of *Kaempferia rotunda* L. (Bhuichampa), the entire plant of *Viscum articulatum* Burm f. (Harchur) and *Berginia ciliata* Sternb. (Pakhenbed) are ground into paste. Bandage the affected area with it for 20-25 days.
2. *Berginia ciliata* Sternb., *Viscum auriculatum* Burm f., *Kaemferia rotunda* L., *Euphorbia hirta* L., and *Astibleri vularis* Buch-Ham ex D.Don., are harvested on Tuesday, Thursday or Saturday, ground individually and juice extracted. A stone calledDalsaydhungais put into the mixture and boiled for 10 minutes, cooled and bandaged on the fractured area. A powder of *Berginia ciliata* Sternb., *Viscum auriculatum* Burm f., *Euphorbia hirta* L., and *Astiblerivularis* Buch-Ham ex D. Don is made and boiled with water and one glass is taken once a day for 2 months.
3. A powder is prepared from dried whole plant of *Viscum autriculatum*, root of *Rheum accuminatum*, root, and leaf of *Berginia ciliata*, and rhizome of *Kaemferia rotunda*. One spoon of the mixed powder is added in 100ml of boiled water and mixed properly. The mixture solution cooled, mixed with 1 tea spoon of honey, and egg yolk. The formulation is spread on a piece of bandage cloth, a bamboo frame is attached to it and carefully bandage fracture area of the body. After six days luke warm water is put on the bandaged area and the bandage is removed. Again, the same procedure is applied on every seven days. Bandaging should be done on every 7 days especially on Tuesday and Saturday until completed healing. Alcohol and chilly should be avoided during this treatment.
4. 5gm sankhanlahara, root of *Berginia ciliata* Sternb., 2.5 gm whole plant of *Viscum atriculatum* Burm f., 2.5gm of Chausur whole plant half tola raw kachosimnlik i.e. 5gm are dried in the sun and consumed with milk and is consumed two times per day for 1 month after food.25 gms roots bark of Bhuinsey Kawlo, stem and root of Singouta, whole plant of Chausur, roots bark of aurari, whole plant of various types of *Viscum atriculatum* Burm f. like Bhui, Ganthey, Lahare, etc., Root of *Euphorbia hirta* L., Rhizome of *Kaemferia rotunda* L., rhizome of *Berginia ciliata* Sternb., are crushed and boiled in 1 lit of water for 1 hour till it becomes 250 m. With 100gm of the liquid 1 spoon white snail powder and 2 spoon honey and putka honey are added and 100 gms of the mixture is applied on the affected area and bandaged for 9 days. Bandaging is done in every nine days.100 gm of the liquid is consumed for 4 days in empty stomach i.e.1 time per day.

### Sprain

Kaempferia rotunda Linn (Bhuichampa), the entire plant of *Viscum articulatum*Burm f. (Harchur) and *Berginiaciliata*Sternb. (Pakhenbed) are ground into paste, bandage the affected area with it and leave it for 7-8 days.

### Body ache and chest pain

The bark of *Fraxinus floribunda* Wall., stem of *Berginiacilliata*Sternb., and leaves of *Viscum articulatum*Burm f. (Harchur) are ground and are boiled with water for 10-15 mins. One spoon of the solution/decoction mixed in a glass of cow milk and added one spoon honey, the resulting mixture taken before sleeping for one month.

### Piles

Juice is prepared from tuber of *Berginiacilliata*Sternb., *Rubiacordifolia* L. and root of Kalouneu in equal volume and 1 spoon of honey are added into it and is consumed two times a day i.e. 250 ml in empty stomach in the morning and taken after food at night in every alternate day for 1 week. Oily foods should be avoided during the treatment.

### Bodyache and backache-

The rootof *Berginia ciliata* with *Astibleri vularis* Buch-Ham ex D.Don., *Viscum atriculatum* Burm f., and *Lepidium* sp., are dried and powered individually, mixed together and taken one tea spoonful with one glass of milk, honey, egg and mustard oil (optional) every evening for 10 days.

### Gynic problem (Infertility)

50 gms ratosimal root's bark, ratophool leaves, *Costus speciosus* (J. Koenig) Sm. tarul rhizome, satisal roots bark, Ghantiphol flower, Bhairangpatey whole plant, lauhaban whole plant, *Astibleri vularis* Buch-Ham ex D.Don rhizome, *Berginia ciliata* Sternb. Root is boiled in 1500 ml water and 500 ml is prepared. Some mantra is done and taken in empty stomach on every Tuesday and Saturday for four times i.e. 1 time/day. Alcohol, Ajinamoto and warm food products should be avoided during the treatment.

### Weakness

Powder of *Berginia ciliata* root are taken with water for enhancing body Strength.

### Cuts and wounds

The root of *Berginia ciliata* Sternb., and the entire plant of *Aloe Barbadensis* Miller are ground into paste and apply externally on the cuts and wounds for 10-12 days.

In Arunachal Pradesh, the root of *Berginia ciliata* is used in the treatment of fever, diarrhoea and pulmonary diseases (Shankar &Rawat 2013).

## 8.5. Dosage forms used in tradition: Mixture, Powder, Paste, poultice

## 9. Phytochemical Profile:

## Major chemical constituents:

Main categories of active components found in *B. ciliata* are phenol (19%), alcohol (19%), volatile organic compound (VOCs) (16%), terpenoids (14%), fatty acids (8%), sterol (5%), glycosides (5%), carboxylic acids (5%), flavonoids (3%), cinnamic acid (3%) and nitro compounds 3%. Different phenolic compounds like bergenin, tannic acid, gallic acid, catechin, -3-O-galloylcatechin and -3-O-galloylprocatechin are present. Bergenin, catechin, (-)-3-O-galloylcatechin and -3-O-galloylprocatechin were found in rhizome (Ahmad et al., 2018). Roots and leaves contain important phytosterol  $\beta$ -sitosterol. Chemical formula of  $\beta$ -sitosterol is  $C_{29}H_{50}O$ .  $\beta$ -sitosterol is a waxy powder of white color having a characteristic smell and hydrophobic in nature (Dharmenderet al., 2010; Ahmad et al., 2018). Arbutin is the Glycoside present in the rhizome. Its chemical formula is  $C_{12}H_{16}O_7$ . It is also known as Arbutoside hydroquinone  $\beta$ -D-glucopyranoside (Kunwar et al.). Flavonoid present in the rhizome of *B. ciliata* is (+)-Afzelechin, the chemical formula is  $C_{15}H_{14}O_5$ . It is also found in the rhizome of *B. ligulata*. Quercetin 3-o- $\beta$ -D xylopyranoside and quercetin 3-o- $\alpha$ -L-arabinofuranoside are the other flavonoids present in rhizome (Roselliet al., 2012). Decanoic acid and nonanoic acid having chemical formula as  $C_{10}H_{20}O_2$  and  $C_9H_{18}O_2$  respectively are the fatty acids present (Gyawali, 2011). Limonene and linalool with chemical formula  $C_{10}H_{16}$  and  $C_{10}H_{18}O$  respectively are two terpenes present in rhizome.  $\beta$ -caryophyllene, a sesquiterpene was also found in rhizome (Gyawali, 2011). Its chemical formula is  $C_{15}H_{24}$ . A terpenoid  $\alpha$ -Terpineol is also present in oil.

## 10. Pharmacological Studies

### 10.1. Experimental pharmacology

Methanolic extracts also showed high activity with  $IC_{50}$  values from 8 to 10 mg/ml against influenza virus A while  $IC_{50}$  values <6.25 mg/ml was recorded against HSV-1 (Rajbhandari et al., 2009). The methanolic extract of rhizome exhibited significant anti-inflammatory activity (Sinha et al., 2001a). The ethanolic extract of leaf (ELEBC) showed good *in-vitro* and *in-vivo* antiplasmodial activity against *Plasmodium berghei*. Acute toxicity of the extract was observed to be >5 g/kg, which is considered toxicologically safe for oral administration. ELEBC was found to inhibit *P. berghei*/schizont maturation in dose-dependent manner with  $IC_{50}<10 \mu\text{g}/\text{ml}$  (Walter et al., 2013). Maximum inhibition of schizont maturation *in vitro* (100 %) was observed with 100  $\mu\text{g}/\text{ml}$  concentration of extract, which was found to be more than standard drug chloroquine (95.7 %). Local communities of Himalayan Region conventionally use for the treatment of fever, so this result highlights the possible role as antimalarial drug. The antidiabetic potential has been reported by Bhandari et al. (2008). They have isolated two active compounds (-)-3-O-galloylprocatechin and (-)-3-O-galloylprocatechin for the first time. These compounds demonstrated significant dose-dependent enzyme inhibitory activities against rat intestinal  $\alpha$ -glucosidase and porcine pancreatic  $\alpha$ -amylase. Bergenin have been found to have hepatoprotective and immunomodulatory activities.  $\beta$ -sitosterol has been reported to show antioxidant, anti-inflammatory, analgesic and antihelminthic activities. It is also found to be effective in the treatment of benign prostatic hyperplasia (Dharmenderet al. 2010). The methanolic extract of rhizome has been found to possessed anti-tussive activity in mice. It showed potential when it was induced by sulphur dioxide gas in mice in the

form of cough model. In a 90 min, experiment, the extract doses of 100, 200 and 300 mg/kg body wt. caused 28.7, 33.9 and 44.2% inhibition of cough reflex. The rate of antitussive activity depends on the dose (Ahmed *et al.*, 2018). Methanolic extract of rhizome haveshowed anti-neoplastic activities (Ruby *et al.*, 2012a). Root and leaf extracts showed antibacterial activity with of root extract exhibiting much higher activity as compared to the leaves extract (Chauhan *et al.*, 2012; Ruby *et al.*, 2012b).

**10.2. Clinical pharmacology:** Clinical studies have not been reported till date.

**11. Toxicity and safety:**

Root and leaf extracts exhibited systemic and intracutaneous toxicity. In higher doses it also exhibited cardiac toxicity, anti-diuretic and depressant action(Islam *et al.*, 2002; Khan *et al.*, 2016).

**12. Clinical studies:**

Clinical studies have not been reported till date.

**13. Contraindications:**

Asthma, Cardiacdisorder, Hypertension, dépression (Islam *et al.*, 2002; Khan *et al.*, 2016).

**14. Precautions:**

In traditional healthcare practices, consumption of Alcohol, Ajinamoto (Monosodium glutamate) and warm food products are advised to avoid during treatment of infertility, Oily foods are advised to avoid during treatment of Piles and Alcohol and chilly are advised to avoid during this treatment during treatment of Bone fracture.

**15. Adverse reactions:**

The ethanolic, hexane, ethyl acetate and chloroform extracts of rootand ethanolic, hexane, ethyl acetate, butanol and chloroform extracts of leaves have exhibited severe acute toxicity i.e. breathing difficulty on experimental animal (albino rabbit) immediately after intra-cutaneous injection and recovered after 4 hours. The same extracts also exhibited systemic toxicity that caused irritation, erection of hair, idleness and gastrointertinal syndrome (Islam *et al.*, 2002). In higher doses, it is cardio-toxic, anti-diuretic and depressant due to central nervous system action (Khan *et al.*, 2016).

**16. Marketed formulation, if any:**

**Stonhills®(Kidney Support Tablets):** Ayurvedic formulation for kidney health supplement to promote regular kidney functioning manufactured by Herbal Hills Global, Mumbai

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1. Botanical Name: ***Boehmeria nivea* (L.) Gaudich**

2. Synonym: *Urtica nivea* L.

3. Family: Urticaceae

4. Common Names:

Assamese: Remi, Riha

English: Ramie, Rhea Plant, China Grass,

Garo: Kilbra

Khasi: Ustein

5. Description: A perennial, erect herb or small shrub up to 2 mtrs tall, with long rhizome and tuberous roots; stem hollow, green and hairy, turning brownish and woody. Leaves alternate, simple; stipules interpetiolar, connate at base, linear-lanceolate, up to 1.5 cm long; petiole 2.5–12 cm long, pubescent; blade broadly ovate, triangular to suborbicular, 5–20 cm × 3.5–18 cm, base cuneate to subcordate, apex usually abruptly long-acuminate, margin coarsely dentate to dentate-serrate or crenate, upper surface green and scabrid, lower surface glabrous and green or white appressed-pubescent, basal veins 3. Inflorescence: Axillary, racemose, paniculate, 3–8 cm long, each branch bearing several crowded or well-separated flower clusters, mainly female with a few male branches towards base; male clusters small, usually with 3–10 flowers, female clusters larger, usually with 10–30 flowers. Flowers unisexual; male flower shortly pedicelled, perianth 3–5-lobed, stamens as many as lobes and incurved with persistent rudiment of pistillode; female flower sessile, perianth tubular, 2–4-lobed, greenish to pinkish, pistil with 1-celled ovary with 1 ovule, style exerted, slender and hairy on one side, stigma filiform. Fruit subglobose to ovoid achene c. 1 mm in diameter, enclosed by the persistent perianth, hairy, crustaceous, brown-yellow. Seeds ubglobose to ovoid, slightly less than 1 mm in diameter, dark brown.

6. Distribution: E. Asia - China to the Himalayas of Bhutan, Sikkim and Nepal; widely distributed in moist areas of Assam, Western Ghats, Meghalaya and in Khasi Hills.

7. Part Used: Roots and leaves.



*Boehmeria nivea* (Linn.) Gaudich

## 8. Medicinal /Therapeutic Uses:

### 8.1. Uses described in pharmacopeias and in traditional systems of medicine:

It has been used in the traditional system of Medicine in China and Taiwan for diuretic and antipyretic purposes (Lin *et al.*, 1998). The plant extract (BNE) is widely used in southern Taiwan as a folk medicine for hepatoprotection and hepatitis treatment(Chang *et al.*, 2010).

### 8.2. Uses supported by clinical data:

Chang and his colleagues demonstrated that the plant extract (BNE) could reduce the supernatant hepatitis B virus (HBV) DNA in HBV-producing HepG2 2.2.15 cells. They established an animal model of HBV viremia and used it to validate the efficacy of BNE *in vivo*. BNE exhibited potential anti-HBV activity in an animal model of HBV viremia (Chang *et al.*, 2010). The chloroform fraction(CF) and Ethyle acetate fraction (EAF) extracted from leaf (BNL) significantly suppressed HBsAg and HbeAg secretion into the medium and inhibited human HBV DNA replication in HepG2.2.15 cells, without any recorded cytotoxic effects (Jingchen *et al.*, 2014).

### 8.3. Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data:

In China and Taiwan, the native people used for the following purposes (Duke & Ayensu, 1985).

**Leaves:** The leaves are astringent and resolvent. They are used in the treatment of fluxes and wounds.

**Root:** Anti-abortifacient, cooling, demulcent, diuretic, resolving and uterosedative.

The people of Santal community at Malar para village, Bangladesh used the leaves as diuretic and to cure fever (Saha *et al.*, 2018).

#### 8.4. Special uses in North East India:

8.5. Dosage forms used in tradition: The Santal community of Bangladesh used to take 50 ml juice obtained from crushed leaves orally twice daily before meal in the morning and evening for 5 consecutive days to cure from fever (Saha *et al.*, 2018).

#### 9. Phytochemical profile:

##### 9.1. Major chemical constituents:

Roots: The chemical compounds were isolated by Ming *et al.*, (2009), from the roots by repeated column chromatography and preparative liquid chromatography, and their structures were identified as tormentic acid hederagenin, maslinic acid, 2 $\alpha$ -hydroxyursolic acid, trans-p-hydroxycinamic acid, 2,4,4'-trihydroxychalcone, rutin. Three new unsaturated fatty acids, (*Z*)-9,10,11-trihydroxy-12-octadecenoic acid, (*Z*)-7,8,9-trihydroxy-10-hexadecenoic acid and (*Z*)-12-keto-7,8,9-trihydroxy-10-hexadecenoic acid were isolated from the roots. The structures of the new compounds were established by HR ESI-MS,  $^1\text{H}$ ,  $^{13}\text{C}$ , 2D ( $^1\text{H}$ - $^1\text{H}$  COSY, HSQC, HMBC) NMR experiments. The three new compounds showed some antifungal activities by agar assay. Tormentic acid was isolated from the roots (Xu *et al.*, 2011).

Leaves: Liu *et al.*, (2010), study the chemical constituents from the leaves. Their structures were elucidated as kiwiionoside, eugenyl beta-rutinoside, uracil, beta-sitosterol glucoside, 3-hydroxy-4-methoxy-benzoic acid, cholesterol, alpha-amyrin, nonacosanol.

#### 10. Pharmacological Studies:

##### 10.1. Experimental pharmacology:

Antifungal activities: Xu *et al.*, (2011), identified three new unsaturated fatty acids, (*Z*)-9,10,11-trihydroxy-12-octadecenoic acid, (*Z*)-7,8,9-trihydroxy -10-hexadecenoic acid and (*Z*)-12-keto-7,8,9-trihydroxy-10-hexadecenoic acid from the roots. The three new compounds showed antifungal activities by agar assay.

Hepatoprotective and antioxidant activity: The water extracts of whole plant exhibited a hepatoprotective activity against CCl<sub>4</sub>-induced liver injury. It is also showed antioxidant effects in FeCl<sub>2</sub>-ascorbate induced lipid peroxidation in rat liver homogenate. Moreover, the active oxygen species scavenging potencies were evaluated by an electron spin resonance (ESR) spin-trapping technique (Lin *et al.*, 1998).

10.2. Clinical pharmacology: Not been reported.

11. Toxicity and safety: No report.

12. Clinical studies: No report.

13. Contraindications: Not available.

14. Precautions: Not available.

15. Adverse reactions: The pollen of *Boehmeria* sp. is reported to cause asthma (Miura, 1993).
16. Marketed formulation, if any: Not Available.
17. References:
  1. Chang, Kai-Ling Huang, Thomas Ta-Tung Yuan, Yiu-Kay Lai, Le-Mei Hung. 2010. The Anti-hepatitis B Virus Activity of *Boehmeria nivea* extract in HBV-viremia SCID Mice. *eCAM* 7(2): 189–195.
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  9. Xu, Q.M., Liu, Y.L., Li, X.R., Li, X., Yang, S.L. 2011. Three new fatty acids from the roots of *Boehmeria nivea* (L.) Gaudich and their antifungal activities. *Nat. Prod. Res.* 25(6).

1. Botanical Name: ***Bridelia retusa*** (L.) A. Juss.

2. Synonym: Clutia retusa L.

3. Family: Phyllanthaceae

4. Common Names

Assamese:	Kuhir
Bengali:	Geio
English:	Spinous Kino Tree
Gujarati:	Monji
Hindi:	Ekdania, Gondui, Khaja
Kannada:	Goje
Khasi:	Dieng Rishan
Malayalam:	Mukkayini
Marathi:	Asana, Kanta-kauchi, Kutki
Sanskrit:	Asana, Ekadivi
Tamil:	Mullumarathu, Mullu-vengai
Telugu:	Bonthayepi

5. Description: A deciduous trees up to 20 m high, bark greyish-brown, blaze red; young trees armed with sharp thorns; branchlets thinly hairy. Leaves simple, alternate; stipules long, lateral, lanceolate, deciduous; petiole stout, pubescent when young; lamina broadly elliptic, oblong, elliptic-oblong, obovate or obovate-oblong, base round, obtuse, truncate, cordate or acute, apex obtuse retuse or subacute, margin entire or slightly crenulate, bright green and glabrous above(turning pinkish-brown before falling), glaucous and usually finely tomentose beneath, coriaceous; lateral nerves 14-25 pairs, parallel, prominent, dichotomously forked near the margin, intercostae scalariform, prominent. Flowers unisexual; greenish-yellow, sessile or shortly pedicellate, crowded in dense axillary or terminal, sometimes paniculate spikes often exceeding the leaves; bracts scaly; male flowers: 7 mm across, tepals 10, biseriate, valvate; outer tepals 3 mm long, ovate-lanceolate, thick, truncate, shortly connate, acute, inner ones 2 mm, obovate, cuneate, obtuse, fimbriate; stamens 5, monadelphous, born on a gonophore, exserted; filaments 0.7 mm, anthers oblong; pistillode bifurcate; disc annular; female flowers: 6.5 mm across, tepals 10, biseriate, lanceolate, valvate; outer and inner 2.5 and 1.5 mm long, coriaceous, puberulous without, truncate, shortly connate, fimbriate, acute; ovary half inferior, globose, 2 × 1 mm, 2-locular, ovules 2 in each cell; styles 2, forked, 2 mm; stigmatiferous; disc with

an inner, membranous, fimbriate corona enclosing basal part of ovary. Fruit a drupe, purplish-black, seated on the persistent, slightly enlarged calyx, pyrenes 2, epicarp crustaceous; seed one in each pyrene.

6. Distribution: Indo-Malaya origin; found in India, Sri Lanka, Malacca and Burma; in India found in tropical to subtropical regions of all the states.

7. Part Used: Aerial parts.



*Bridelia rutusa* (L.) A. Juss

8. Medicinal /Therapeutic Uses:

8.1. Uses described in pharmacopoeias and in traditional systems of medicine

It is one of the plants sold as a drug name "Pashanabedha" mentioned in the Ayurvedic System of medicine mainly for diuretic, lithotriptic and act as antiurolithiatic (Manjunath, 2010). Pashanabedha is also considered as one of the "Controversial" drugs since more than one Botanical source is made use by physicians in various parts of the country as Pashanabedha of north and Pashanabedha of south (Shantha et al., 2012).

8.2. Uses supported by clinical data:

Makwana et al., (2017) proved the *in vitro* antiurolithiatic potential by using different fraction of methanol extract. Nucleation of calcium oxalate crystals was estimated by the spectrophotometric assay and whereas crystal dissolution was determined by titrimetry/egg shell permeation method, hence the extract fractions exhibited

inhibitory action in both of nucleation and aggregation assays to significant level.

### 8.3. Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data:

The native people of southern India use the bark for treatment of rheumatism and astringent agent (Jayasinghe *et al.*, 2003). An ethno medicinal survey in Rajasthan revealed that bark is given orally to women to develop sterility, as contraceptive, useful in ‘vata’ lumbago, hemiplegia and leaves cure urinary tracts infection (Jain *et al.*, 2004). The stem bark is exhibited antiviral, hypoglycemic and hypotensive properties (Rupali *et al.*, 2016). In Maharashtra and Andhra Pradesh, the plant is used in traditional system of medicine to cure dysentery and diarrhea (Pawar & Patil 2004, Raju & Reddy, 2005). The stem bark has an anti-viral property against ranikhet disease virus, interferon induction, semliki forest virus through the screening of Central Drug Research Institute Lucknow (CDRI) (Dhawan, 2012). In coastal areas of Karnataka, the native people used the bark to cure Herpes.

### 8.4. Special uses in North East India:

In Meghalaya the bark and fruit juice is used for treatment of wound and earache (Lakshman, 2016)

8.5. Dosage forms used in tradition: One or two drops of fruit extract poured in ear to cure earache and ripen fruits are eaten (Jain *et al.*, 2005).

## 9. Phytochemical profile:

### 9.2. Major chemical constituents:

Bark: The variety of phytochemicals is reported in stem bark of this plant which are biologically active belongs to different classes like steroids, triterpenoids, tannins, phenols, fats, and minerals. Minerals like Calcium, Copper, Iron, Manganese, Magnesium, Phosphorus and Zinc are reported in plant. Triterpene Ketone [4 - desmethyleupha 7, 24 - diene - 3 - one], stigmasterol and dehydrositosterol was isolated and reported. A literature survey showed presence of Benzoic acid derivatives like 4-[R-6-methyl-4- oxohept - 5en - 2yl] benzoic acid, (-) isochamminic acid, (+) - sesamin, 5-allyl - 1, 2, 3 trimethoxy benzene and 4-[(R)-6-methyl - 4 - oxoheptan-2-yl] benzoic acid, gallic acid and ellagic acid are also isolated and having therapeutic value (Ngueyem *et al.*, 2009, Alekya *et al.*, 2011).

Leaves: Isoflavone was isolated from leaves its structure characterized by IR and NMR spectroscopy which shows antibacterial activity. Chitosan flavonoids are isolated from the leaves which exhibiting analgesic and anti-inflammatory properties (Alekya *et al.*, 2011)

Fruits and Seeds: The chemical components found in fruit pulp and seeds are sitosterol, ellagic acid and gallic acid. These compounds showed antibacterial, antifungal activities. The ellagic acid and gallic acid exhibited antioxidant properties (Pawar & Patil, 2004, Jain *et al.*, 2005).

## 10. Pharmacological Studies:

### 10.1. Experimental pharmacology:

**Analgesic and Anti-Inflammatory:** The ethanolic extract of leaves showed Chitosan flavonoid. Chitosan flavonoid screened for anti-inflammatory and analgesic activity in experimental animal models. The anti-inflammatory activity was determined by formalin tail flick method and hot plate latency method by using external standard indomethacin and chitosan. Chitosan significantly exhibited anti-inflammatory and analgesic activity at a dose 250 mg/ Kg (Alekya *et al.*, 2011). The stem bark of this plant extracted in petroleum ether, chloroform, methanol and water by soxhlet extractor. The literature study revealed that petroleum ether extract in the acute inflammation model was carrageenan- induced rat paw edema and chronic model showed potent anti-inflammatory activity (Tatiya *et al.*, 2011).

**Anti-microbial activity:** Antifungal activity of solvent extracts of the stem bark against *Cladosporium cladosporioides*, furnished new bisabolane sesquiterpenes, (E)-4-(1,5-dimethyl-3-oxo-1-hexenyl)benzoic acid, (E)-4-(1,5-dimethyl-3-oxo-1,4-hexadienyl) benzoic acid, (R)-4-(1,5-dimethyl-3-oxo-4-hexenyl)benzoic acid and isochamminic acid, together with the known (R)-4-(1,5-dimethyl-3-oxohexyl)benzoic acid (artodomatui acid), 5-allyl-1,2,3-trimethoxybenzene (elemicin), (+)-sesamin and 4-isopropylbenzoic acid (cumatic acid). All these compounds showed fungicidal activity on TLC bioautography method at very low concentrations except elemicin (Jayasinghe *et al.*, 2003). Phytochemical analysis of fruits revealed the presence of secondary metabolites like alkaloid that have antimicrobial activities against seven human pathogens (Kumar & Naidu, 2016).

**Hypoglycemic activity:** The stem bark extract studied for hypoglycemic activity. Methanol extract fractionated in petroleum ether and n-butanol did not show any hypoglycemic effect in normal glycemic rats on fasting condition on other hand, the hypoglycemic effect of the extracts in the glucose fed rat by an intestinal glucose absorption and the stimulation of the glucagon like peptide. The literature survey revealed that extracts produced hypoglycemic effect due to polysterols and triterpenoids (Tatiya *et al.*, 2011).

**Anti-oxidant Activity:** The stem bark extracted in acetone: water (70:30) to get tannins rich fraction of bark. Tannin rich fraction has strong antioxidant activity by inhibiting DPPH, ALP reducing power, hydroxyl radical and hydrogen peroxide and nitric oxide scavenging when compared with standard (Banerjee & Bande, 2011).

**Immunomodulatory Activity:** The leaves extracted in methanolic extract presence of alkaloids, glycosides flavonoids, tannins, phenolic substances and saponin. It is significantly potentiated the cellular immunity by facilitating the foot pad thickness responses to the sheep RBC's in sensitized rats. The study stated that it shows a significant stimulation of the cell mediated immunity and no effect on normal immunity (Chakraborty, 2011)

**10.2. Clinical pharmacology:** Not yet reported.

**11. Toxicity and safety:** NA

12. Clinical studies: Clinical studies have not been reported.
13. Contraindications: NA
14. Precautions: *Bridelia retusa* should not be taken during pregnancy, decrease blood pressure, bleeding disorder.
15. Adverse reactions: NA
16. Marketed formulation, if any: Pashanbhed Powder - 1-3 gm twice a day or as directed by a physician.
17. References
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15. Shantha, T. R., Yoganarasimhan, S. N., Shiddamallayya, N., Venkateswarlu, G., 2012. Comparative pharmacognostical studies on the different botanical sources of Pashanabedha. *J. Econ. Tax. Bot.* 36(3): 464-485.
16. Tatiya, A.U., Ujwaldip, V.D., Pankaj, G., Jain Surana S. J., 2011. Hypoglycemic potential of *Bridelia retusa* bark in albino rats, *Asian J. Bio. Sci.* 4(1): 84-89.

1. Botanical Name: ***Calotropis gigantea* (L.) W. T. Aiton**
2. Synonym: ***Asclepiapias gigantea* L.,**
3. Family: **Asclepiadaceae**
4. Vernacular Name
  - Bengali: Akanda, Gurtakand, Swetakand;
  - English: Bowstring hemp, swallow-wort, Madar, Milk weed;
  - Gujarati: Akado;
  - Hindi: Ag, Ak, Akand, Ark, Madar;
  - Kannada: Arka-gida, Lekkedagide;
  - Malayalam: Erikku, Vellerukku;
  - Marathi: Akand, Lal akra, Lal madar, Rui;
  - Oriya: Akondo, Kotuki;
  - Rajasthan: Moto-aak;
  - Sanskrit: Aditya, Arka, Mandara;
  - Tamil: Erukam, Erukku;
  - Telugu: Jilledu, Jilleedudoodi, Mandaramu, Nallajilleedu.
5. Description: A woody shrubs, stem rounded. Leaves smaller in branchlets, elliptic-ovate to obovate, apex acute or obtuse, base cordate; lateral nerves 5-7 pairs, adpressed pubescent when young, becoming glabrous on maturity. Flowers pale purple or greenish-white, 3 cm across; pedicels to 3 cm long, stout; calyx lobes to 3 mm long; corolla campanulate, tube short, lobes ovate to oblong, recurved; staminal corona of 5 vertical lobes, 1 cm long. Fruit saccate, ovoid; seeds many.
6. Distribution: Native to Sri Lanka, India, SE Asia, Malaysia and found almost all over the world. It established well in Peninsular India and some part of northern India.
7. Part Used: Leaf, bark, flower, seed, and latex.



*Calotropis gigantea* (L.) R. Br.

## 8. Medicinal / Therapeutic uses

It is used as appetizer, cure tooth ache, joint pains, sedative, anthelmintic, ring worn infection, anti-insecticide, rheumatic pains, skin diseases, diarrhoea, ulcers, malarial infection, stomach ache, asthma etc (Mushir et al., 2016, Kumar et al., 2011).

### 8.1. Uses described in pharmacopoeias and in traditional system of medicine

All parts of the plant are used in traditional system of medicines and pharmacopeia in different forms and decoction for the treatment of several diseases. Roots are used for the management of lupus, tuberculosis, leprosy, and ulceration due to syphilis. Leaf juice is used for external swellings (Mushir et al., 2016). A combination of roots and leaves made in the form of powders, balms, enemas and clarified butters are used for the treatment of abdominal tumors. Root powers is mixed with milk and given for recovery from ear troubles and boils (Asolkar et al., 2005). The combination of root bark and milk in small doses is given for the treatment of skin infections, leprosy and secondary syphilis. Paste of root bark in vinegar is given for the treatment of elephantiasis (Chatterjee & Pakrashi, 2003). The root bark is also used for the recovery of pain from scorpion bite, body ache, mumps, headache, joint pains, swellings, tooth ache, ring worm and cuts (Mushir et al., 2016). Roots are powdered and soak it in its own milk and dried, made in the form of bougies and fumes of it is given for inhalation to cure from cough (Daymock et al., 2005). The flowers are used for analgesic properties, antimicrobials; wound healing, antioxidant, antitumor, antiviral etc (Mushir et al., 2016; Khan et al., 2014).

### 8.2. Uses supported by clinical data: Not data available.

### 8.3. Traditional /folklore uses described in folk medicine

The extracts prepared from this plant are much healing properties and it used in folk medicine for curing many diseases and infections. The milky sap or latex of the plant is used for making different drugs for ailments mainly for the treatment of boils, infected wound, and rushed skin (Upadhyay, 2014). The whole plant is dried; boiled and filtered extract is consumed as a good health tonic, anthelmintic and expectorant. Root powder is orally given to recover asthma, bronchitis, eczema, leprosy and elephantiasis. The latex from the bark is used to treat vertigo, baldness, hair fall, wound and tooth ache (Boomibalagan *et al.*, 2013). The leafy slimy latex extract is topically applied to relax the uterine muscles or to increase uterine contraction during childbirth. It is also given to induce abortion (Upadhyay, 2014).

#### 8.4. Special uses in North East India

Powdered flower is used for the treatment of asthma and cough, and cough. Fresh leaves are applied for swellings. Dried barks of the roots are used for the treatment of dysentery. The plants are used for tooth ache, fracture and dog bites(Sankar *et al.*, 2017).During rheumatism, the leaf warm used for massage. The latex is given to the person suffering from snake bite; it is considered bitter as long as poison is present in the body but the taste of latex turn sweet when the poison is removed (Debbarma *et al.*, 2017). The leaf and flower paste are used for the treatment of diabetic's problems (Chakravarty & Kalita, 2012).

#### 8.5. Dosage forms used in tradition

Root bark power 0.5-1g, Flower powder 1-2 g.

#### 9. Photochemical profile

This plant possesses alkaloids, cyanogenic glycosides, phenolics, tannins, cardenolides, flavonoids terpenes, sterols, proteinases, nonprotein amino acids. But this plant leaf, root, areal part, and latex possess different phytochemicals. The cardenolides such as 19-Nor- and 18, 20-Epoxy-cardenolides, 15-beta-hydroxy cardenolides and 16-alpha-hydroxycalactinic acid methyl ester found in leaves. Flavanol such asisorhamnetin-3-O-rutinoside, isorhamnetin-3-O-Glucopyranoside and taraxasteryl acetate detected from the areal part. Proteinases such as Calotropain-F1, Calotropain-FII, Calotropins DI, and Calotropins DI1. Triterpene esters like 3'-methylbutanoates of  $\alpha$ -amyrin and  $\psi$ -taraxasterol detected from the latex of the plant. Triterpenoids of Di-(2-ethylhexyl) Phthalate and Anhydrosophoradiol-3-acetate present in flowers. Cardiac glycoside of Calotropone, terpene of Calotropisesjuiterpenol, Calotropisesterterpenol, aromatic compounds of Calotropbenzofuranone, cardenolides of Coroglaucigenin, and Frugoside found in roots. Stigmasterol,  $\beta$ -sitosterol, Giganticine (non protein amino acids) found in root bark (Kadiyala *et al.*, 2013; Kumar *et al.*, 2011).

## 9.1. Major chemical constituents

The major chemical constituents are alkaloids, cyanogenic glycosides, phenolics, tannins, cardenolides, flavonoids, terpenes, sterols, proteinases, nonprotein amino acids.

## 10. Pharmacological Studies

### 10.1. Antiviral activities

Compound isolated from the latex were screened for A/PR/8/34 (H1N1) inhibition activity through cytopathic effect (CPF) inhibition assay on MDCK cells. The study showed that pinoresinol 4-O-[6-O vanillyl] b-D-glucopyranoside compounds has inhibitory activity against H1N1. This compound was further evaluated for the *invitro* study against human and avian influenza activity by CPE inhibition assay. Result showed that the compound has inhibitory effect against human influenza virus subtype A and B. The time course study showed that this compound has antiviral activity at the early stage of viral replications (Parhira *et al.*, 2014).

### 10.2. Antimicrobial activity

The whole plant extract showed activity against many gram positive and negative bacteria. The aqueous extract from the leaf was studied in vitro by well diffusion methods in MH agar. Results showed that extract has maximum zone of inhibition against *E.coli*. Maximum relative percentage inhibition obtained from *B.cereus*. The extract showed 50, 25, 6.25, 3.1, 1.5, and 12.5 mg/L minimum inhibitory concentrations (MIC) value for *S. aureus*, *K. pneumoniae*, *B. subtilis*, *P. aeruginosa*, *M. luteus* and *E. coli*, respectively (Kumar *et al.*, 2010). Leaf extract from different solvent are tested against *B. cereus*, *B. subtilis*, *E. coli*, *K. pneumoniae*, *S. aureus*, *S. typhi* and *M. luteus* for antibacterial activity. Ethyl acetate fraction was found to be most effective with MIC value ranging from 0.25 to 1.0 mg/ml. whereas aqueous leaves extract showed weak activity among tested strains (Seniya *et al.*, 2011). The extract from the latex is tested for its potential antibacterial activity against six bacteria and two fungal species. The results highlighted that *S aureus*, *B. Cereus* and *E. Coli* are the most susceptible organism, while *C. Krusei* moderate susceptible, no effect was observed for *m. Luteus*, *K. Pneumonia*, *P. Aeruginosa* and *A. Niger*.

### 10.3. Anticancer properties

The cardenolides has anticancer activity (Hoops *et al.*, 2017). The Leaf extract displayed strong positive anti-proliferation activity (APF). Dichloromethane (DCM) extract of the plant showed activity against tested six human cancer cell lines. In the MCF-7 and MDA-MB-231 cell line showed stronger activity than standard drug of curcumin, tamoxifen, and xanthorrhizol. Hence, leaf extract showed great promise as a potential candidate for anticancer drug (Wong *et al.*, 2011).

Antioxidant activity: The *in vitro* antioxidant activity of root extract of the plant was studies by 2,2-diphenyl-1-picrylhydrazyl and fluorescent recovery after photo

bleaching method. In both methods extract showed high antioxidant activity compared with standard (ascorbic acids) (Elakkiya & Prasanna, 2011).

**Anti-inflammatory activity:** Anti-inflammatory activity of the plant was tested by albumin denaturation technique. The percentage inhibition of denaturation produced by tested drug was comparable with that produced by ibuprofen (85.71%) which showed that tested drug posses' significant anti-inflammatory property (Jagtap *et al.*, 2010).

#### 10.4. Wound healing activity

It is used in some part of India in combination with other plants for wound healing (Deshmukh *et al.*, 2009). Latex of the plant was evaluated for potential for wound healing activity of excision wound. Topical application of ointment prepared from latex of the plant for 14 days significantly improved contraction of wound compared with control (Saratha *et al.*, 2010).

#### 10.5. Experimental pharmacology

Ethyl acetate fraction of root was used for the identification of active compounds calotroposide A (glycoside terpenoid). The compound was tested for induction of apoptosis colon cancer cells. The study highlighted that calotroposide A is capable of inhibiting the growth of WiDr colon cancer cells in IC<sub>50</sub>: 17.23 µg/ml through apoptosis induction and increased the expression of caspase-8 (Mutiah, 2018). Anticancer compound isolated from the flowers of the plant was tested for reduction in viable tumor cells, body weight, altered biochemical and hematological parameters to normal levels. Hence enhancing the life span of Ehrlich's ascites carcinoma (EAC) bearing mice. The study concluded that the compound anhydrosophoradiol- 3-acetate was effective for inhibiting growth of EAC and improving the cancer induced complications (Habib *et al.*, 2013). The ethanolic extract tested for its anticancer activity in lung cancer cell lines. Results showed that plant extract induced apoptosis through the stimulation of intrinsic and extrinsic signaling pathways in A549 and NCL-H1299 lung cancer cells. Cell cycle arrest was induced by the extract in both cell lines. The reactive oxygen species which can induce cell death was also produced in the treated cell lines. The study confirmed that extract caused apoptosis through via activation of intrinsic and extrinsic pathways, cell cycle arrest, and ROS regeneration in lung cancer cell lines (Lee *et al.*, 2019). Thus extract of this plant can be used as potential agent for cancer therapy. Study conducted for antiasthmatic activity of methanolic extract of the plant on ovalbumin induced asthma and arachidonic acid induced paw edema in rats' models. Different concentrations of extract were tested for changes in inflammatory cell count, level of nitric oxide total protein in bronchial lavage (BAL) fluid, lung antioxidant enzymes (LPO, GSH, SOD, Catalase) and histopathological were detected. Change in paw edema volume was measured in arachidonic acid induced paw edema model. Different concentrations of the extract showed significant inhibition of haematological cell count in bronchial lavage (BAL) fluid. In BAL fluid, extract significantly reduced the nitric oxide and total protein levels. The plant

extract significantly restored the levels of GSH, SOD and LPO in lungs. These results suggest that CG may prove to be potential therapeutic drug for treating asthma owing to its anti-inflammatory, anti-lipoxygenase and antioxidant activities (Bulani *et al.*, 2011). The anti-diarrheal properties of hydrolacoholic extract of the plant was studies against castor oil induced diarrhoea rat models. The results showed that like atropine significant reduction in fecal output and frequency of droppings was observed when when plant extract of 200 and 400mg/kg doses administered intraperitoneally compared with control (Chitme *et al.*, 2004). Hypoglycaemic properties of chloroform extract from leaves and flower part of the plant was evaluated at a concentration of 10, 20, and 50mg/kg in streptozotocin induced diabetic rates which was further compared with glibenclamide. The administration of leaf and flower extract to streptozotocin induced diabetic rats showed significant reduction in serum glucose level (Rathod *et al.*, 2011).

Antivenom activity was evaluated for its efficacy to neutralize various effect of snake venom (*Vipera russelli*) like haemorrhagic activity, edema, necrotizing activity and lethality. Oral administration of different concentrations of extract effectively neutralized the leather effect of 2LD50 and 3 LD50 of venom in mice. Effective inhibition of induction of haemorrhage and necrosis was also observed. Different dose levels of plant extract at different time intervals showed significant anti-inflammatory activity which was comparable with the standard antivenom (Chaco *et al.*, 2012).

Anthelmintic activities of alcoholic extract is tested in earth worms for paralysis and death time analysis. During study this plant showed significant anthelmintic activity at aconc. of 100 mg/dl and analyzed by time taken for paralyse / death of the earth worms. The result of different conc. of methanolic extracts of plants can compared with the rules of standard drug, such as Albendazole and Carboxy Methyl Cellulose (CMC) as control (De *et al.*, 2019).

10.6. Clinical pharmacology: Not yet done.

#### 11. Toxicity and safety

Ethanol extract from flower was evaluated for the acute and sub-acute toxicity studies *in-vivo* in rat models. A dose of 2000 mg/kg was tested for acute toxicity whereas 250, 500 and 1000mg was used for sub acute toxicity studies. Haematobiochemical parameters, total body and organ weight was checked after 30 days of administration. Results acute and sub-acute toxicity studies did not show any signs mortality in a time dependent evaluation and there were no abnormal changes in the haematological and biochemical parameters. The crude ethanolic root extract was tested for acute oral toxicity study with single dose of 2000mg/kg in diarrhoeal study and the doses were determined as 100, 200, 400mg/kg. There is no toxicity effect is observed (Rahman *et al.*, 2012).

12. Clinical studies: Not yet reported.

### 13. Contraindications

Taking calotropis along with digoxin can increase the effects of digoxin and increase the risk of side effects. Stimulant laxatives interact with *C.gigantea*.

### 14. Precautions

If it is consuming orally above the therapeutic doses causes vomiting, diarrhoea, and nausea. Prolonged higher doses cause headache, burning micturition and intestine weakness. In pregnant woman it will affect heart and liver or even it may lead to abortions (Mushir *et al.* 2016).

### 15. Adverse reactions

Overdose may cause vomiting and diarrhoea and it is not safe to take during pregnancy and lactations.

### 16. Marketed formulation

Ayurveda: it is marketed as Loharasayanam, in Unnani marketed formulation is Jauhar-e-kafoor, Siddha marketed formulations are Moolathirkkupugai Muzangalvathathirkku- Poochu, Sannnikku Pottanam, and Thirilogacenturam (Kadiyala *et al.*, 2013).

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1. Botanical Name: ***Camellia sinensis* (L.) Kuntze**

2. Synonym: *Thea sinensis* L.

3. Family: Theaceae

4. Common Names

Assamese:	Chah-pat
English:	Tea plant, Tea
Gujarati:	Cha
Hindi:	Chai, chha
Kannada:	Cha , chaha , theyale
Malyalam:	Chaya, theyila
Marathi:	Chaha
Oriya:	Cha
Sanskrit:	Syamaparni, Chaha
Tamil:	Thayilai
Telugu:	Tiyaku, Nallateyaku, Teyaaku
Urdu:	Chai

5. Description: shrubs or small tree up to 20 feet high. Leaves 8-10 × 3-4 cm, elliptic-oblong, apex acuminate, base acute, serrate; petiole to 5 mm. Flowers axillary, solitary to 3 cm across, white; pedicel to 1.5 cm; bracts 2 or 3, small; sepals 5, 5 mm across, orbicular; petals 5, 2 × 1.5 cm, obovate, connate with outer whorl of stamen; stamens numerous, biserrate; ovary 3-celled, villous, style 3. Capsule to 2 cm across, woody, subglobose.

6. Distribution: Indigenous to China, Java and Ceylon; cultivated in large states at higher altitudes of the States like; West Bengal, Assam and Southern India.

7. Part Used: Leaves



*Camellia sinensis*

#### 8. Medicinal /Therapeutic Uses

8.1. Uses described in pharmacopoeias and in traditional systems of medicine

8.2. Uses supported by clinical data

Anticancer activity, Lipid lowering activity, Anti carcinogenic activity, Neuro muscular blocking action, Immunomodulatory effect, Anti-viral activity, Anti-viral activity, Anti spasmodic activity, Anti cataract activity, Anti-oxidant activity, Anti diabetic activity, Anti genotoxic activity, Hepatoprotective activity, Chemo protective activity, Anti-inflammatory activity, Chemoprotective activity, effect on oxidative stress, DNA Effect (Bhatt et al., 2010).

8.3. Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

Green tea can help in the treatment of headaches, body aches, pains, constipation, and depressions. Green tea can enhance the blood flow throughout the body, as it comprises of caffeine. Even it stimulates the heart and makes the blood to flow freely in the blood vessels. It stimulates the flow of the blood freely in through the blood vessels. It also stimulates mental clarity, detoxifies the body. It keeps the body free from diseases. As it contains antioxidants, it can enhance the immunity, preserve young looking skin and brighten the eyes. It is helpful in digestion and banishes fatigue. Even it enhances lifespan. (Agarwal et al.; 2017)

8.4. Special uses in North East India: NA

8.5. Dosage forms used in tradition

3-5 cups/day (1200MI) of green tea provides 250 mg of catechins. The green tea extract should not be consumed on an empty stomach due to the potential for hepatotoxicity from excessive leaves of epigallocatechin gallate. (Agarwal et al.,2017).

#### 9. Phytochemical profile (as per available literature)

##### Major chemical constituents

Gallocatechin gallate (GCG), Gallocatechin (GC), Catechin gallate (CG), Catechin (C), and flavonoids such as kaempferol, quercetin and myricetin. Other important components include theanine, derived from amino acid, the xanthine alkaloid caffeine, theophylline, theobromine, saponins, and tannins. epigallocatechin gallate (EGCG), epicatechin gallate (ECG), epigallocatechin (EGC), epicatechin (EC) (Sanchez et al.,2012).

#### 10. Pharmacological Studies

The anticancer activity of the green tea is already reported and it is because of the presence of the polyphenol compounds. The cytotoxic and apoptogenic effect of root extract of tea and two of its steroidal saponins is TS1 and TS2, on human cell lines and on cells of leukemia patients. TRE, TS1 and TS2 decreases the cell count and TRE causes apoptosis.

Tea supplements with Vitamin E, when administered to male Syrian hamsters, reduced plasma low density lipoprotein cholesterol concentrations, LDL Oxidation and early atherosclerosis compared to the consumption of tea alone by hamsters.

Extracts of green tea in human umbilical vein endothelial cells, reduces the cell proliferation dose dependently and produced a dose depended accumulation of cells in the gastro intestinal phase.

The arabin fraction of black tea was tested for neuromuscular blocking action of botulinum neurotoxin. To find the effect of tea on transplant related immune function *invitro* lymphocytes culture assay, IL-2 and IL-10 from mixed lymphocyte proliferation were performed. Tea has an immunosuppressive effect. This effect was mediated through a reduction in the production of IL-2.

IL-2 and IL-10 production from mixed lymphocyte proliferation were performed to find the effect of tea on transplant-related immune function in lymphocyte proliferation tests with the use of phytohemagglutinin mixed lymphocyte proliferation. Tea had immunosuppressive effect.

Extract of green tea in cell culture at a dosage of 10mg/L corresponding to 15 mmol/L EGCG for 24 hours, did not protect Jurkat cells against H<sub>2</sub>O<sub>2</sub> induced DNA damage. The DNA damage, evaluated by the Comet assay, was dose dependent. But it reached plateau at 75 mmol/L of H<sub>2</sub>O<sub>2</sub>, without any protective effect exerted by the extract.

Epigallocatechin 3 gallate, when administered to Hep2 cells in culture, provided a therapeutic index of 22 and an IC<sub>50</sub> of 25 PM. The agent is most effective when they were added to the cells during the transition from early to the late phase of viral infection.

Alcohol extract of black tea when assayed on *Salmonella typhi* and *Salmonella paratyphi A*, was active on all strains of *Salmonella paratyphi A* and only 42.19% of *Salmonella typhi* strains were inhibited by the extract.

Hot water extract and tannin fraction of the entire dried plant were active on the rabbit and rat intestines versus pilocarpine induced spasms and barium induced contractions.

Tea, when administered in culture to enucleate rat lens, reduced the incidence of selenite cataract *in-vivo*.

Black tea leaves when administered to human red blood cells, is efficient against damage by oxidative stress induced by various inducers like phenylhydrazine, Cu<sup>2+</sup> - ascorbic acid and xanthine/xanthine oxidase system.

The aqueous green leaf extract shows a strong glucose lowering effect after oral administration of green leaf extract in rats.

Tea is a rich source of effective antioxidants. Epidemiology observations and laboratory studies show that the polyphenols act as anti-oxidants *invitro* by scavenging reactive oxygen and nitrogen species and chelating redox active transition metal ions.

It was observed that the administration of tea significantly lowers the serum ( $p<0.05$ ), the serum and tissues levels of malondialdehyde as well as AST and ALT activities in a dose dependent manner.

The whole plant extract as food supplement in livestock nutrition has been suggested for the prevention of livestock intestinal diseases.

The whole plant extracts can reduce the number of potential pathogenic bacteria in the gut of piglet and thus improve the health of the animal.

The methanol water extract of dried tea root extract possess anti-inflammatory, analgesic and antipyretic activities at 1/10<sup>th</sup> of its LD<sub>50</sub> dose of 100 mg/kg.

The protective action of aqueous black tea extract against ovariectomy induced oxidative stress of mononuclear cells and bone loss was found out in the study.

Various types of herbal teas comprises of bioactive compounds that are associated with less risks of chronic diseases such as cancer.

#### 10.1. Clinical pharmacology

#### 11. Toxicity and safety

Green tea does not have any toxicity after consuming by both humans as well as animals meant for experiment. Humans can easily tolerate green tea solids upto 4.5 g/day (Agarwal *et al.*, 2017).

12. Clinical studies: NA

13. Contraindications

The large amount of Fluoride in the leaves is a potential source of high fluoride ingestion and recommendations should be made for the patients who have a risk of dental fluorosis (Potawale *et al.*, 2008).

14. Precautions

15. Adverse reactions:

The side effects of green tea can range from mild to serious which includes headache, nervousness, sleep problem, vomiting, diarrhoea, irritability, irregular heartbeat, tremor, heart burn, dizziness, ringing in the ears, convulsions and confusion. It seems to reduce the absorption of iron from food (Agarwal *et al.*, 2017).

16. Marketed formulation, if any

17. Reference

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1. Botanical Name: ***Capparis multiflora*** Hook.f. & Thomson

2. Synonym: NA

3. Family: Capparaceae

4. Common Names

English: Capper shrub

5. Description: An erect shrubs or trees, up to 8 feet high. Branches sparingly branched, branchlets glabrous; stipular thorns c. 1 mm long, weak, straight, often absent; cataphyllus subulate, c. 2-3 mm wide at base. Leaves simple, alternate; petioles 1 cm long; lamina 12-30 × 4-10 cm, elliptic-oblong, lanceolate or oblanceolate, broadest above the middle, attenuate or cuneate at base, abruptly acuminate with 5-15 mm long tip at apex, entire, membranous, glabrous, dull greenish when dry; secondary nerves 8-10 pairs, forming intra-marginal loop, reticulations distinct. Inflorescences supra axillary vertical rows; flowers 6-10; c. 4-6 mm across, white or greenish-white, fragrant; pedicels filiform, 6-23 mm long, slightly thickened while fruiting; Sepals c. 3-4.5 × 1.5-2.5 mm, deflexed, imbricate, subequal, sparsely appressed hairy to glabrate; outer pair boat-shaped, ovate-obtuse; inner pair obovate, rounded at apex; petals 5.5-6.5 × 3-4 mm, white, broadly elliptic or suborbicular; stamens 8-12; filaments 6-9 mm; anthers 0.8 mm; gynophore 5-12 mm long, Ovary 1.2-1.5 × 1 mm, ovoid, glabrous or minutely pubescent; placentae 2, ovuled. Fruit globose, 10 mm across, 1-3 in a row, reddish-purple, glabrous, turning blackish; stipe slender, 2.5 × 0.5 mm. Seeds 1-3.

6. Distribution: Northeast India (Assam), China South-Central, East Himalaya, Myanmar, Tibet, Vietnam

7. Part Used: Whole Plant



*Capparis multiflora* (Photo by S. S Dash)

8. Medicinal /Therapeutic Uses: No Data available

9. Phytochemical profile: No Data available

#### 10. Pharmacological Studies

Experimental pharmacology: Dhawan (2012) have summarized the anti-viral potential of the medicinal plants (plant without roots) was tested to be effective against Ranikhet disease virus as reported (Bhakuni *et al.*, 1988).

10.1. Clinical pharmacology: No Data available

11. Toxicity and safety: No Data available

12. Clinical studies: No Data available

13. Contraindications: No Data available

14. Precautions: No Data available

15. Adverse reactions: No Data available

16. Marketed formulation, if any: No Data available

## 17. References

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1. Botanical Name: **Castanea sativa** Mill.
2. Synonym: *Fagus castanea* L.
3. Family: Fagaceae
4. Common Names
  - English: European chestnut, Spanish chestnut, Sweet chestnut.
  - Hindi: Mitha khanor, Poo
  - Tamil: Kaskottai
  - Khasi: Soh-ot-phareng.

5. Description: A large, deciduous tree up to 40 feet high. Leaves alternate, oblong lanceolate, acute to acuminate, narrowed or rounded at base, coarsely serrate, with spreading teeth, tomentose beneath when young. Flowers greenish. Fruit a large rounded, brown nut with prickly.
6. Distribution: Nature of Europe, N. Africa, W. Asia; introduced and cultivated in Himalayas and in Tamil Nadu Dindigul and Nilgiris.
7. Part Used: Bark, Seeds, Nuts, Leaves



*Castanea sativa*- Tree and fruiting branch

## 8. Medicinal /Therapeutic Uses

### 8.1. Uses described in pharmacopoeias and in traditional systems of medicine: Siddha, Homeopathy

### 8.2. Uses supported by clinical data

### 8.3. Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

Sweet chestnut leaves and bark are a good source of tannins and these have an astringent action which is useful in the treatment of bleeding, diarrhoea etc. The leaves bark and twigs, flowering catkins, and spiny cases of the nuts are used as anti-inflammatory, astringent, expectorant and tonic. They are also used to control bleeding, aid in healing wounds, and against diarrhea. They are harvested in June or July and can be used fresh or dried. An infusion has been used in the treatment of fevers and treating convulsive coughs such as whooping cough and in other irritable conditions of the respiratory system. The leaves can also be used in the treatment of rheumatism, to ease lower back pains and to relieve stiff muscles and joints. A decoction is a useful gargle for treating sore throats. The nuts are also reported in folk remedies for the treatment of fever, hematochezia, infections, sores, inflammation, wounds, sclerosis, kidney ailments, myalgia, nausea, and stomach ailments (Caballero *et al.*, 2003).

### 8.4. Special uses in North East India: Seed are eaten raw or cooked. Tree is used as firewood, timber

### 8.5. Dosage forms used in tradition

Chestnut wood is particularly used for extraction of natural tannin. It is also used as timber, fire wood, charcoal, poles and wood for small products like barrels, shingles, sleepers, etc. Fruits are edible and can be consumed in different ways: roasted, candied, boiled, dried, or transformed to flour. The meal of the seed has been used as a source of starch and also for whitening linen cloth. A hair shampoo is made from the leaves and the skins of the fruits. It imparts a golden gleam to the hair. Flowers are rich in pollen and nectar and therefore really appreciated for honey production by bee keepers (Conedera *et al.*, 2016).

## 9. Phytochemical Profile

The aerial parts have been reported to contain a wide diversity of compounds. Of all the compounds isolated, phenolic compounds such as flavonoids and tannins are the most abundant. The flavonoids identified were castalin, castalagin, vescalagin, kurigalin, 5-O-galloylhamamelase, (3, 5 dimethoxy-4-hydroxyphenol)-1-O- $\beta$ -D-(6-O-galloyl) glucose, chestanin acutissimin A (Lamprie *et al.*, 1998), rutin, hesperidin, quercetin, apigenin, morin, naringin, galangin and kaempferol (Basile *et al.*, 2000). Regarding tannins, both hydrolysable and condensed tannins were found (Živkovic *et al.*, 2009a; Carocho *et al.*, 2014a; Pandey *et al.*, 2018).

## 9.1. Major chemical constituents

Chestnoside A and chestnoside B, together with two known oleanen-type analogs have been isolated by Perez *et al.*, (2017). HPLC-UV-HRMS profiling of aqueous extracts contain several hydrolyzable tannins, mainly ellagitannins, and glycoside flavonols Ellagic acid (EA) and chestanin are predominant components as reported by Esposito *et al.* (2019). Phenolic and tannic composition has been extracted from heartwood using HPLC-DAD and HPLC-DAD/ESI-MS, and some low molecular weight phenolic compounds and hydrolyzable tannins were found. The low molecular weight phenolic compounds were lignin constituents such as the acids gallic, protocatechuic, vanillic, syringic, ferulic, and ellagic, the aldehydes protocatechuic, vanillic, syringic, coniferylic, and sinapic, and coumarin scopoletin. Vescalagin and castalagin were the main ellagitannins, and acutissimin. Some gallotannins were also identified including different isomers of di, tri, tetra, and pentagalloyl glucopyranose, and di and trigalloyl-hexahydroxydiphenoyl glucopyranose, comprising of 20 different compounds, as well as some ellagic derivatives such as ellagic acid deoxyhexose, ellagic acid dimer dehydrated, and valoneic acid dilactone (Sanz *et al.*, 2010).

Eight phenolic compounds were isolated from chestnut bark and these includes castalin, castalagin, vescalagin, kurigalin, 5-O-galloylhamamelose, (3', 5'-dimethoxy-4'-hydroxyphenol)-1-O- $\beta$ -D-(6-O-galloyl) glucose, chestanin, and acutissimin A (Lampire *et al.*, 1998).

## 10. Pharmacological Studies

Chestnut leaves contain phenolic compounds and aqueous, methanol, and ethyl acetate of leaf extracts had a good antioxidant potential (Calliste *et al.*, 2005). Other authors showed the high capacity of chestnut extracts scavenge DPPH radical (Barreira *et al.*, 2008; Živkovic *et al.*, 2009b; Barreira *et al.*, 2010; Carocho *et al.*, 2014b); and the capacity to protect cellular membranes from oxidative stress damage. This was performed by protecting liposomes from lipid peroxidation (10), or by reducing it when induced by high n-3 PUFA intake in young pigs (Frankic & Salobir, 2011). Different extracts have been demonstrated to show antimicrobial activity. An ethyl acetate-soluble fraction of the aqueous extract of leaves showed activity against *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, *Staphylococcus aureus*, *Proteus vulgaris*, *Pseudomonas aeruginosa* and *Enterobacter cloacae* (Basile *et al.*, 2000). These authors refer to quercetin and rutin as the most active compounds against the bacteria. The different extracts had the highest antibacterial activity against *M. pyrogenes* var. *albus*, *S. aureus*, and *S. typhimurium* (Živkovic *et al.*, 2010). According to Carocho *et al.*, 2014b, antifungal activity of the extracts showed that infusions of chestnut leaves are effective against several strains of *Aspergillus fumigatus*, *Aspergillus ochraceus*, *Aspergillus versicolor*, *Aspergillus niger*, *Trichoderma viride*, *Penicillium funiculosum*, *Penicillium ochrochloron* and *Penicillium verrucosum* var. *cyclopium*.

## Experimental pharmacology

According to Mujic *et al.* (2011) leaf extracts showed antidiabetic activity. After the treatment of rat pancreatic Beta--cells with STZ (a diabetogenic agent) together with chestnut extract the authors verified an increase of cells viability and an inhibition of lipid peroxidation. These results indicate an antioxidant capacity of the chestnut extract which is linked to the increase of GSH concentration and the decrease of GSH oxidation.

The effects of sweet chestnut bark extracts have also been tested in cultured heart cells and in overweight rats on a high fat diet. The results obtained showed that these extracts have a great potential in the prevention of cardiovascular diseases (Chiarini *et al.*, 2013).

The leaf extracts of Sweet chestnut was reported to have antispasmodic activity and it was also verified that the antispasmodic activity of the chestnut extracts does not only depend on an anticholinergic action but also on alpha-adrenergic action, mainly alpha-1-adrenergic (Neves & Cunha, 2019). De Vasconcelos *et al.*, (2010) have reviewed fresh chestnut fruits and their home-processed and industrial products in terms of their nutritional values, antioxidant property and useful bioactive. Vella *et al.*, (2018) have assessed the potential antioxidant activity of chestnut leaves, shells and burs. Boiling water was the best extraction solvent referring to polyphenols, whereas the most efficient for leaves resulted 60% ethanol at room temperature. Greatest polyphenol contents were 90.35, 60.01 and 17.68 mg gallic acid equivalents g<sup>-1</sup> in leaves, burs and shells, respectively. Almeida *et al.* (2008) performed test for antioxidant activity of leaves by 1,1-diphenyl-2-picryl hydrazyl (DPPH) free radical scavenging test and polyphenols extraction (measured by the Folin Ciocalteu assay). Iron-chelating activity and the phenolic composition (high performance liquid chromatography/diode array detection) were evaluated for the extract obtained under optimized conditions. The IC<sub>50</sub> found for the iron chelation and DPPH scavenging assays were 132.94 ± 9.72 and 12.58 ± 0.54 microg/ml (mean ± S.E.M.), respectively. The total phenolic content was found to be 283.8 ± 8.74 mg GAE/g extract (mean ± S.E.M.). Five phenolic compounds were identified in the extract, namely, chlorogenic acid, ellagic acid, rutin, isoquercitrin and hyperoside. Silva *et al.* (2020) performed antibacterial test of the ethanolic extracts of chestnut shell, inner shell, bur, and leaves against *Staphylococcus epidermidis*, *Escherichia coli* and *Salmonella enteritidis*. *S. epidermidis* showed susceptibility to all extracts while none of the extracts was able to suppress the growth of *E. coli* and *S. enteritidis*. Piazza *et al.* (2019) investigated the biological effect of tannins-containing extracts by using *in vitro* models of gastric inflammation. Gastric epithelial cells (AGS and GES-1) were stimulated with TNFα (10 ng/mL) or co-cultured with different bacterial strains from clinical samples. IL-8 and IL-6 release after 6 h was found cagA independent. Based on their previous work on TNFα-challenged cells and chestnut fruits, they tested the effect of the extracts in AGS co-cultured with *H. pylori* cag<sup>+</sup> (ATCC strain). Extracts from fruit episperm and pericarp, both rich in condensed tannins, inhibited *H. pylori*-induced IL-8 release at 25 µg/mL, compared to 5 µg/mL during previous TNFα treatments. The effect of an extract from chestnut leaves were

also investigated, in addition to castalagin, vescalagin and ellagitannins which occur in bark and leaves. Leaves extract inhibited TNF $\alpha$  and *H. pylori*-induced IL-8 secretion at 10  $\mu$ g/mL and 50  $\mu$ g/mL, respectively. Both ellagitannins strongly inhibited TNF $\alpha$ -induced IL-8 with the same IC<sub>50</sub> (0.04  $\mu$ M), whereas *H. pylori*-induced IL-8 was impaired at 50  $\mu$ M. Although the extracts exhibited a lower inhibitory potency in co-culture model with respect to TNF $\alpha$  induced gastric epithelial cells, the higher concentrations of extracts tested (25-50  $\mu$ g/mL) may be easily achieved *in vivo* after oral consumption. Jovanovic *et al.*, (2017) showed the administration of chestnut and mushroom extracts, either individually or together, activates a coordinated cytoprotective response against diabetes-induced hepatorenal injury not only through recovery of the antioxidant defense system of the cell, but also through a marked antiglycation activity. Chestnut wood extracts containing tannins and currently used in the animal feed industry, were tested for *in vitro* antiviral activity against avian reovirus (ARV) and avian metapneumovirus (AMPV) by Lupini *et al.*, (2009). The MTT assay was used to evaluate the 50% cytotoxic compounds concentration (CC<sub>50</sub>) on Vero cells. The antiviral properties were tested before and after the adsorption of the viruses to Vero cells. Antiviral activities were expressed as IC<sub>50</sub> (concentration required to inhibit 50% of viral cytopathic effect). CC<sub>50s</sub> of tested compounds were >200  $\mu$ g/ml. All compounds had an extracellular antiviral effect against both ARV and AMPV with IC<sub>50</sub> values ranging from 25 to 66  $\mu$ g/ml. Quebracho extract had also evident intracellular anti-ARV activity (IC<sub>50</sub> 24  $\mu$ g/ml). These preliminary results suggest that the examined extracts might be good candidates in the control of some avian virus infections.

### 10.1. Clinical pharmacology

The cytotoxicity of chestnoside A and chestnoside B, together with two known oleanen type analogs were tested against two cancer cell lines (PC3 and MCF-7), and normal lymphocytes by Perez *et al.*, (2017). Breast cancer cells (MCF-7) were more affected by tested compounds than prostate cancer cells (PC3). Chestnoside B exhibited the strongest cytotoxicity with an IC<sub>50</sub> of 12.3  $\mu$ M against MCF-7 cells, lower than those of positive controls, while it was moderately active against normal lymphocytes (IC<sub>50</sub> = 67.2  $\mu$ M). These results highlight the occurrence of triterpenoid saponins in sweet chestnut heartwood and their potential for the chemoprevention of breast cancer (Pérez *et al.*, 2017). Moreover, Lenzi *et al.*, (2017) showed that bark extract induced apoptosis in Jurkat cells in a dose- and time- dependent manner activating the extrinsic pathways as evidenced by the increase of activated caspase-8 positive cells. The value of IC<sub>50</sub> calculated after 24 h treatment resulted 304 and 128  $\mu$ g $\text{mL}^{-1}$  in PBL and Jurkat cells respectively. The natural extract of chestnut increasing gallbladder contraction and inducing the relaxation of the sphincter of Oddi can be of benefit in pathological conditions associated with increased transit time at risk of gallstones (Micucci *et al.*, 2014). Cacciola *et al.*, (2019) assessed the possible potential anticancer effect of chestnut shell dry extract (CSDE) on six human cancer cell lines (DU 145, PC-3, LNCaP, MDA-MB-231, MCF-7, and Hep G2) and one normal human prostate cell line (PNT2). The pharmacological treatment with CSDE was able to inhibit cell viability of different cancer cell lines (DU 145, PC-3, LNCaP, and MCF-7). DU 145 cells after chestnut shell dry extract treatment also displayed anti-proliferative and apoptosis

induction in AGS gastric cells.

## 11. Toxicity and safety

The leaf extract was toxicity effect was investigated (Neves, 2018) by determination of population growth impairment, generation time, LC50, morphometric changes in *Tetrahymena pyriformis* and MTT test. Generation time, growth and MTT assay were affected by chestnut tree leaves extract and these effects were dosage dependent. The morphometry of the *Tetrahymena pyriformis* cells was also affected. According to the obtained LC50 value, the extract was considered as mildly toxic. In oral administration (infusions and decoctions), the usage of leaf extract has been cautioned since these extracts can be harmful, especially when it comes to children (Neves, 2018, Neves & Cunha, 2019).

## 12. Clinical studies

The use of sweet chestnut extract for topical application was tested by (Almeida *et al.*, 2010). Their study about using leaf extract against UV irradiation in HaCaT cells (human keratinocyte). suggested that the use of the topical formulation prevents and treats oxidative-stress mediated skin diseases. Cerulli *et al.*, (2018) put forth the idea that the extract was isolated compounds such as gallic acid, crenatin and cretanin, can be useful to prevent UV induced cell damage. Carocho *et al.*, (2014b) demonstrated the antitumor activity of decoctions and infusions against HCT15 (colon carcinoma) and HepG2 (hepatocellular carcinoma) cancer cell lines. Sorice *et al.*, (2016) confirmed the induced cytotoxic effect of chestnut extract on HepG2 cells.

## 13. Contraindications: No data available

## 14. Precautions

For toxicity in the aqueous extracts of leaves, Neves (2018) verified that as the chestnut leaves extract concentration increased, the generation time and the population impairment of *Tetrahymena pyriformis* (a biological model) increased at a dosage dependent manner. The author also verified that *T. pyriformis* suffered a biochemical change in a dose dependent response for plant extract concentrations between 4,52 mg/mL and 45,2 mg/mL., that was revealed by the decrease of mitochondrial dehydrogenase activity (Martin & Clynes, 1993). The morphology of *T. pyriformis* was also affected. As the extract concentration increases, the ratio of shortest and longest axis (W/L) changes (B,C,D) and the cells became rounder. At the highest tested concentration (45,2 mg/ml), the cells were round and dead probably due to changes occurring in the microfilament architecture(Kovács *et al.*, 1999). The lethal concentration 50 (LC50) of the tested chestnut crude extract was 0.825 mg/ml. According to Nguta *et al.*, (2011), crude extracts with LC50 values between 0.500 mg mL<sup>-1</sup> and 1.000 mg mL<sup>-1</sup> were mildly toxic.

## 15. Adverse reactions

*Castanea* pollen can cause allergies – particularly in areas where *Castanea* trees are

frequently found. Southern Switzerland (Lugano) is reported to experience the highest *Castanea* pollen loads and hence high *Castanea* allergy rates. It is reported that patients allergic to pollen are affected by oral allergy syndrome (allergy to food resulting from contact between food and the oral mucosa). A reported case of oral allergy syndrome to chestnut appears to be a manifestation of immediate immunoglobulin E-dependent hypersensitivity. It was also reported in a second study that a patient with latex allergy has a high risk of contact urticaria or even anaphylaxis to the related fruits such as chestnut. Class I chitinases are relevant allergens of avocado and chestnut, and could be the panallergens responsible for the latex-fruit syndrome. Almeida *et al.*, (2008) performed skin irritation potential of leaf ethanol: water (7:3) extract by performing an *in vivo* patch test in 20 volunteers. The patch test carried out showed that, with respect to irritant effects, this extract can be regarded as safe for topical application.

16. Marketed formulation, if any: NA

17. References

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1. Botanical Name: ***Catharanthus roseus* (L.) G. Don**

2. Synonym: *Vinca rosea* L.

3. Family: Apocynaceae

4. Common Names

Bengali:	Nayantara
English:	Periwinkle
Gujarathi:	Barmasi
Hindi:	Sada Suhagan, Sadabahar
Kannada:	Batla Hoo, Ganeshana Hoo, Kempu Kaasi Kanigalu
Malayalam:	Banappuvu, Nityakalyani, Savanari, Usamalari
Manipuri:	Saheb- le
Marathi:	Sada-phul
Oriya:	Ainskati
Punjabi:	Rattanjot
Sanskrit:	Nityakalyani, Rasna, Sadampuspa, Sadapushpi
Tamil:	Cutkattu malli, Sudukadumallakai
Telugu:	Billaganneru

5. Description: An evergreen sub shrub or woody herb up to 4 feet high. Leaves oval to oblong, glossy green, hairless, with a pale midrib and a short petiole; they are arranged in opposite pairs. The flowers are white to dark pink with a darker red centre, with a basal tube long and a corolla 2–5 cm diameter with five petal-like lobes. Calyx-lobes are green and very slender about 4 millimeters long. Fruit is a pair of follicles, green.

6. Distribution: Indigenous and to Madagascar and endemic introduced and become naturalized from tropical to subtropical regions of all the states.

7. Part Used: Whole plant.



*Catharanthus roseus* (Photo source: Shukla AN, BSI)

## 8. Medicinal/Therapeutic Uses

In traditional Chinese medicine, extracts from it have been used against numerous diseases including diabetes, malaria, and Hodgkin's lymphoma. Many of the vinca alkaloids were first isolated from *Catharanthus roseus*, including vinblastine and vincristine used in the treatment of leukemia and Hodgkin's lymphoma (Kuruppu *et al.*, 2019). In other words Periwinkle alkaloids have been used in the treatment of leukemia, cancers-breast cancer, lung cancer, uterine cancer, melanomas, Hodgkin and non-hodgkin's lymphoma, malignant lymphomas, neuroblastoma, Wilms tumor, Kaposi sarcoma, mycosis fungoides, to improve cerebral blood flow and treat high blood pressure. It is also use for treating dermatitis, abscesses, eczema, psoriasis, sores, corns, ringworm, scabies, epilepsy, heart tonics and alzheimer's disease.

### 8.1. Uses described in pharmacopoeias and in traditional systems of medicine

It is a very popular herb amongst practitioners of traditional medicine and the herb is widely used in traditional medicine to treat a variety of diseases. Some of the different traditional uses from around the globe are listed below (Renjini *et al.*, 2017; Sain and Sharma, 2013; Sen, 2013):

Sl. No.	Country	Uses
1.	India	The juice of leaves is used as application to bee sting/wasp sting
2.	Philippines	Decoction of leaves is used in diabetes and decoction of young leaves is used in stomach cramps; root decoction is used for intestinal parasitism. Infusion of leaves is used for treating menorrhagia. Crude leaf extracts and root has anti-cancer activity. Roots used for dysentery.
3.	Madagascar	The bitter and astringent leaves are used as vomitive, roots used as purgative, vermifuge, depurative, hemostatic and toothache remedies
4.	Mauritius	The juice of leaves is used for indigestion and dyspepsia
5.	West Indies and Nigeria	The plant is used in diabetes.
6.	Cuba and Jamaica	Flower extract is used for eye wash in infants.
7.	Bahamas	Decoction of flower is used in asthma, tuberculosis and flatulence.
8.	Malaysia	The plant is used in diabetes, hypertension, insomnia and cancer.
9.	Hawai	Extract of boiled plant is used to arrest bleeding.
10.	America	Gargle of plant is used to ease sorethroat, chest ailments and laryngitis.
11.	Africa	Leaves are used for menorrhagia and rheumatism.
12.	China	Used for dysmenorrhea, diabetes & malaria.

## 9. Phytochemical profile

The plant is found to contain various chemical constituent. Both vegetative as well as root are very rich in alkanoids, flavoniods, triterpenoids, tannins, saponin, coumarin, carbohydrates, quinine and phenolic compounds. The flowers part of the plant contains abundant amount of tannins, triterpenoids and alkaloids and have been found to be antidiabetic and wound healing property (Barik *et al.*, 2016). Leaves of are rich in alkaloids and carbohydrates. The root and stem of the plant contains quinones which has antibacterial activities.

## Major chemical constituents

The main active constituents present in these plants' steroid, alkaloids, carbohydrates, flavonoids, triterpenoids, tannins, coumarin, quinone and phenolic compound (Renjini *et al.*, 2017).

Sl. No.	Plant used	Part	Constituents
1.	Whole plant		Vinblastine and vincristine, catharanthin and vindolin, monoterpenoid glycoside, steroid, phenolic, flavonoid and 7-O-methylated anthocyanin
2.	Stem		Alkaloid, carbohydrate, flavonoid, tannin and steroid
3.	Flower		Alkaloid, carbohydrate, saponin, flavonoid, tannin and steroid
4.	Root		Alkaloid, carbohydrate, saponin, flavonoid, tannin, steroid triterpenoid, ajmalicine and serpentine
5.	Leaf		Alkaloid, vinblastine and vincristine, carbohydrate, saponin, flavonoid, tannin, steroid, triterpenoid, chlorogenic acid, loganic acid, secologanin and vindoline

## 10. Pharmacological Studies

Studies on different pharmacological activities like antioxidant property, anti-diabetic activity, anti-cancer activity, anti-microbial activity, anti-ulcer property, hypotensive property, anti-diarrheal property, wound healing property, hypolipidimic effect and memory enhancement activity have been carried out (Barik *et al.*, 2016; Gajalakshmi *et al.*, 2013; Kumar & Ragunathan, 2015; Nisar *et al.*, 2016; Retna & Ethalsha, 2013; Sen *et al.*, 2013;).

### 10.1. Experimental pharmacology

Sl. No.	Pharmacological activity	Plant parts and method used	Doses	organism
1.	Antidiabetic	Fresh leaf, flower, leaf powder suspension, methanolic, aqueous extract, dichloromethane: methanol (1:1) extract	0.5-1.0 ml/kg or 500 mg/kg body weight	Normal and alloxan diabetic rabbit, normal and streptozotocin-induced diabetic rat, 0 male wistar rat, adult albino rabbit, adult female albino rat of wistar strain
2.	Hypolipidemic Effects	Ethanolic, petroleum-ether, ethyl acetate and chloroform extract of leaf	0.5-1.0 ml/kg body weight	Normal and streptozotocin-induced diabetic

3.	Antihyperglycemic activity	Hydroalcoholic extract of flower, leaf , stem and root, leaf powder, leaf dichloromethane and methanol extract	100-500 mg/kg for 20 days	Wistar diabetic rat, alloxan-induced hyperglycemic rat, male wistar albino rat
4.	Hypoglycemic Activity	Hydroalcoholic extract of flower, leaf , stem and root	100-500 mg/kg	Rat, fasted normal rats, streptozotocin (STZ) induced diabetic rat
5.	Anticancer activity	Methanol extract	<15 µg/ml	Different cell types in vitro
6.	Hypoglycemia	Leaf juice	0.5-1.0 ml/kg body weight	Rabbit
7.	Hypotensive activity	Leaf extract (hydroalcoholic or dichloromethane-methanol)	-	Laboratory animal
8.	Body weight gain	Whole plant extract	Alloxan (500mg/kg)	Rat
9.	Cytotoxic Activity	Water, n-hexane, chloroform and methanol extract	60 µg/ ml	Human Colorectal CarcinomaCell Line (HCT 116)
10.	Antiangiogenesis effects	Crude decoction	200mg/ml water	-
11.	Lowering blood glucose levels	Ethanic, aqueous, dichloromethane and methanol extract of leaf and flower	-	Several animal, diabetic rat
12.	Total triglyceride decreasing	Leaf juice	1.0 ml/kg	Rat
13.	LDL-cholesterol decreasing	Leaf juice	1.0 ml/kg	Rat
14.	VLDL-cholesterol decreasing	Leaf juice	-	Rat

15.	Antibacterial activity	Dichloromethane: methanol(1:1) extract	-	<i>B. cereus, B. pumilis, B. subtilis, S. aureus, E. faecalis, K. pneumoniae, E. coli, P. aeruginosa, P. vulgaris, Streptococcus sp., S. thphi, P. aeuroginosa, K. oxytoca, Proteus mirabilis, S. typhimurium, S. paratyphi</i>
16.	Antihelminthic Activity	Ethanol extract of whole plant	200 mg/ml	Resistant strain of helminth parasite
17.	Cytotoxic effects	Aqueous extract of leaf	2.55-2.38 µg/ml	Jurkat cells and normal peripheral blood mononuclear cells (PBMCs)
18.	Antidiarrheal activity	Ethanolic leaf extract	200 and 500 mg/kg	Wistar rat
19.	Antimicrobial and wound healing activity	Ethanolic flower extract	100 mg kg <sup>-1</sup> day <sup>-1</sup> of the ethanol extract	Rats

## 10.2. Clinical pharmacology

Vinblastine is a drug used in the elective regime for the metastatic treatment of testicular cancer. The estimates of half-life after vinblastine administration to patients were 4 min, 1.6 h, and 25 h, which indicate a faster drug distribution in most tissues and a subsequent slower terminal elimination process. Distribution and initial cleaning phase for vincristine are kinetically comparable to the ones observed for vinblastine; half-lives for those phases have been reported at 4 min and 2.3 h in studies with vincristine. The terminal elimination phase for vincristine is reported to be three to four times longer than the one estimated for vinblastine, and the slow elimination of vincristine from the neuronal susceptible tissue suggest that it plays a role in neurotoxicity commonly seen in clinical adjustments with vincristine but not with vinblastine. Hepatic metabolism and bile excretion play major roles in the elimination of both vinblastine and vincristine in humans, small quantities of vincristine and vinblastine, in the order of 10% of the administered dose, are excreted with no alterations through urine. The renal clearance of vinblastine is reported as being less than 10% of the total elimination of the serum. It has been reported that vinblastine inhibits a polymorphic cytochrome P-450 in human

hepatic microsomes, but the necessary concentrations were higher than those observed in clinical adjustments. It is recommended that vinblastine and vincristine doses must be reduced in patients with liver disease. Vincristine is conventionally administered intravenously, in adults, with a dose of 1.4 mg/m<sup>2</sup>, the total dose must not exceed 2 mg in each administration. Sulkes and Collins (??? reference) have commented on the adjustments that can be provided for conventional doses of vincristine and other drugs. Of particular importance is the possibility that some patients can show a good clinical response and relatively low toxicity in dose regimes involving the cautious use of large quantities of vincristine. The initial dose of vinblastine for adults is 3.7 mg/m<sup>2</sup>, with a range of the typical growing dose of 5.5–7.4 mg/m<sup>2</sup>, administered weekly (Barrales-Cureño *et al.*, 2019).

## 11. Toxicity and safety

Madagascar periwinkle can be dangerous if consumed orally. It can be hallucinogenic and is cited as such in the Louisiana State Act 159 (Nejat *et al.*, 2015). All of the Madagascar periwinkle alkaloids have neurotoxic activity especially vincristine; cases of neurotoxicity have been reported with the use of vincristine in patients with acute lymphoblastic leukemia. Vincristine and vinblastine are highly toxic antimitotics, blocking mitosis in metaphase after binding to the microtubules. A study reported on the development of peripheral neuropathy with use of vincristine at normal dosage in 10 of 20 children. Peripheral neuropathy has been reported in cats and dogs, along with involvement of the bone marrow, kidney, and GIT. Study reports of liver damage in rabbits after taking 0.1g/kg of an aqueous leaf extract for 9 days. Study showed an LD<sub>50</sub> of methanol leaf extract at 2.1g/kg in mice. Prolonged treatment at repeated dose of 0.5g and 1.0 g/kg extract cause diarrhea and mortality in rats. Study reports of accidental poisoning of sheep fed ad libitum amounts of leaves and flowers. Acute toxicity occurred within 24 hours with all animals manifesting salivation, in coordination, staggering, dyspnea, anorexia, bloody diarrhea and dehydration, with all animals dying within two days of onset of manifestations.

The drug used traditionally in prescribed doses may be considered safe. The LD<sub>50</sub> for vinblastine in mice is 17 mg/kg iv and for vincristine in mice is 5.2 mg/kg ip (Paarakh *et al.*, 2019).

## 12. Clinical studies

Terpenoid indole alkaloids (TIAs) have been applied clinically since the end of the 1950s as major drugs in the treatment of acute lymphoblastic leukemia, non-Hodgkin lymphomas, myeloma and Hodgkin lymphoma. Terpenoids, the largest group of phytochemicals, traditionally used for medicinal purposes in India and China, are currently being explored as anticancer agents in clinical trials. Terpenoids (also called

“isoprenoids”) are secondary metabolites occurring in most organisms, particularly plants. More than 40000 individual terpenoids are known to exist in nature with new compounds being discovered every year. A large number of terpenoids exhibit cytotoxicity against a variety of tumor cells and cancer preventive as well as anticancer efficacy in preclinical animal models (Paarakh et al., 2019).

### 13. Contradictions

Two of the common anti-cancer drugs which are derived from this plant are vincristine and vinblastine (they are named after *Vinca*) (Loh, 2008). The Main side effects of these drugs are peripheral neuropathy, hair loss, hyponatremia and constipation.

### 14. Precautions

Periwinkle is UNSAFE for anyone to use, but people with certain conditions are especially at risk for harmful side effects.

Pregnancy and breast-feeding: It is not safe to use periwinkle during pregnancy and breast-feeding. Constipation: Don't use periwinkle during constipation as Periwinkle has a drying effect on tissues. This means it can make constipation worse.

Low blood pressure: Periwinkle can lower blood pressure. If you already have low blood pressure, using periwinkle can make it drop too low. Don't use it.

Surgery: Periwinkle can lower blood pressure. There is a concern that it might interfere with blood pressure control during and after surgery. Stop using periwinkle at least 2 weeks before a scheduled surgery.

### 15. Adverse reaction

Many side effects have been reported for these drugs comprising myelo suppression, alopecia, abdominal cramps, abdominal pains, constipation, nausea/vomiting, paralytic ileus, ulcerations of the mouth, hepatocellular damage, kidney impairment, pulmonary fibrosis, urinary retention, amenorrhoea, azoospermia, orthostatic hypotension, and hypertension (Nejat et al., 2015). The dosage and administration must be carefully controlled to reduce side effects.

### 16. Marketed formulations

The two key pharmaceutical dimeric alkaloid compounds, vinblastine (VBL) and vincristine (VCR) exist mainly in the aerial parts of the plant in extremely low concentrations, the latter quantitatively much less than the former.

Vincristine sulfate, originally known as leurocristine, is the only effective antileukemic drug that reduces white blood cell count drastically; since the 1950s, it has increased the survival rate of children with leukemia from 20% to 80%. It is one of the most expensive plant products on the market with considerable side effects (Nejat *et al.*, 2015).

Vinblastine similarly decreases the quantity of white blood cells in the blood. Vinblastine sulfate has now been marketed for more than 40 years as an anticancer drug. It has proven effective against Hodgkin's disease (Nejat *et al.*, 2015). Vincristine sulfate and vinblastine sulfate are being sold for a total US\$ 100 million per year. Developing food stuff incorporated by fresh leaves of Madagascar periwinkle gives rise to the economic importance of the herb while such products possess both pharmaceutical and nutritional properties, simultaneously. These injectable drugs and their semisynthetic analogues such as vinorelbine (VRLB) and vindesine (VDS) interfere with the division of cancer cells.

Navelbine (5'-noranhydrovinblastine) is a semisynthetic vinca alkaloid with complete microtubule depolymerization ability, broader antitumor activity, and a lower neurotoxicity than vinblastine (VBL) and vincristine (VCR) because it selectively interferes with tubulin assembly (Binet *et al.*, 1990). Fully synthetic vincristine is far less efficient (only 20% efficiency) compared to the natural product derived from Madagascar periwinkle, and hence the importance of the species and its bioactive compounds is unchallenged owing to their complex structures (Robert Verpoorte *et al.*, 2004). The other valuable therapeutic alkaloid "ajmalicine" is a constituent of hypotensive drugs employed in the treatment of high blood pressure. Two to three hundred tons of MP roots is required for 3600 Kg annual world production of ajmalicine (Nejat *et al.*, 2015).

Table: The name of Vinca alkaloids, branded drug names and its therapeutic uses.

Sl. No.	Vinca alkaloid	Related drug	Therapeutic uses
1.	Vincblastine	Velban	Hodgkins disease, testicular germ cell cancer
2.	Vincristine	Oncovin	<i>Leukemia, lymphomas</i>
3.	Vinorelbine	Navelbine	Solid tumors, lymphomas, lung cancer
4.	Vindesin	Eldisine	Acute lymphocytic leukemia

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1. Botanical Name: ***Cissampelos pareira* L. var. *hirsuta* (Buch.-Ham. ex DC.) Forman**

2. Synonym: NA

3. Family: Menispermaceae

4. Common Names

Assami:	Tubuki lota
Bengali:	Akaleja
English:	Velvet leaf
Gujarati:	Karemdhiu
Hindi:	Akanadi
Kannada:	Kodupalli
Kashmiri:	Butter bail
Malayalam:	Katuvlli
Marathi:	Pahad mud
Oriya:	Akarnamini
Punjabi:	Baphbel
Sanskrit:	Patha
Tamil:	Appatta, vatta-tiruppi
Telgu:	Adavibankateega
Urdu:	Pahata

5. Description: It is slender, tomentose climber. Leaves peltate, broad, triangularly broad-ovate, or orbicular, obtuse, mucronate, base cordate or truncate, tomentose on both sides; petiole pubescent. Flowers are small in size, pedicels filiform. Male flowers clustered in the axil of a small leaf; sepals are 4 in number, obovate-oblong, hairy outside; petals 4 in number, united to form a 4-toothed cup, hairy outside; stamens 4, column short, anthers connate, encircling the top of the column. Female flowers clustered in the axils of orbicular, hoary imbricate bracts, on 5–10 cm long racemes; sepal 1, petal 1; carpel 1, densely hairy; style shortly 3-fid. Drupe subglobose, compressed, hairy-pubescent, red when fresh, black when dry, endocarp transversely ribbed, tuberculate. Seeds are horseshoe-shaped.<sup>1</sup>
6. Distribution: It is distributed throughout warm parts of Asia, East Africa, and America. Found in tropical and subtropical regions of India.
7. Part Used: Whole Plant



*C.pareira* L. var. *hirsuta* (DC.) (Photo Source : Priyanka Ingle, BSI)

## 8. Medicinal /Therapeutic Uses

### 8.1. Uses described in pharmacopoeias and in traditional systems of medicine:

#### a. Pharmacopoeias

The Ayurvedic Pharmacopoeia of India attributed blood purifying properties to the root and indicated it in lactal disorders.(Khare,2008) The therapeutic uses of Patha according to the Ayurvedic Pharmacopoeia of India are in the treatment of abdominal pain, diarrhea, skin diseases, pruritus and fever (Aiyer,1951).

#### b.Traditional systems of medicine

In the traditional folk medicine the roots are used against a lot of ailments. They have a bitter taste and possess diuretic, purgative and antiperiodic properties. Furthermore they are judged to be good against dyspepsia, diarrhea, dropsy, and cough, urinary difficulties like cystitis, dysentery, asthma and heart diseases. Mainly extracts of the roots are used (Agarwal *et al.*, 2009). In the simplest cases leaves are good as an antiseptic against inflammation and can be put on wounds in order to heal sores (Neuwinger,1996). In a new report on screening African plants one can find the simple instruction to treat malaria, fever, sexually transmitted diseases, snake bites and conjunctivitis, like that: "Boil the ground root in water about 10 minutes and drink the filtrate" (Tshibangu *et al.*, 2002) It is an Ayurvedic medicinal plant used traditionally for the treatment of a number of diseases. It is said to be bitter, astringent, anthelmintic, carminative, stomachic, digestive, anti - inflammatory, diuretic, febrifuge, expectorant , galactogogue and bitter tonic . It is useful in dyspepsia , abdominal pain, diarrhea, dysentery, fever, cough, coryza, asthma and lactation disorders (Database

on Medicinal Plants Used In Ayurveda, Vol2, Central Council for Research in Ayurveda and Siddha ,Department of Indian System of Medicine and Homoeopathy, New Delhi ) (5), Labour pain (Singh *et al.*,1996), Dysmenorrhea (Kamrup) (Gogoi & Borthakur,2001) Liver diseases and jaundice, Antifertility (Jain,2004)

#### 8.2. Uses supported by clinical data

The Ayurvedic drug Patha is one such Drug used in the treatment of abdominal pain, diarrhea, skin diseases, pruritus and fever (Aiyer,1951).

#### 8.3. Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data: No data available

#### 8.4. Special uses in North East India

- a) Disease-Cough, Parts used: Root
- b) Disease-Dropsy, Parts used: Root
- c) Disease- Diarrhea, Parts used: Root
- d) Disease- Urinary disease, Parts used: Root (Rama *et al.*,2017)

#### 8.5. Dosage forms used in tradition

Generally accepted instructions for the use and dosage are not available.(mmh-mms.com). Whole plant can be used to make decoction and is taken orally daily once for 2-3 months (Ryakala *et al.*, 2010).

### 9. Phytochemical profile

#### Major chemical constituents

Alkaloids, viz. hayatine, hayatinine, hayatidine and other bisbenzylisoquinoline alkaloids, some non-nitrogenous components, e.g., quercitol and sterol (root); cyclanoline chlorides, a non-phenolic tertiary alkaloid (tetra hydroisoquinoline chromophore), alkaloids viz., seepeerine, berberine, cissampeline, pelosine (or berberine ), hayatin, hayatinin, I- curine and d- isochondrodendrine along with a saponin, quaternary ammonium bases, d-quercetol and sterol, a base with a dihydroisoquinoline nucleus, cycleanine, hayatinin (4"-0- methyl berberine ) and hayatidin -4" - 0 - methyl berberine ), three water soluble bases viz., menismin iodine, cissamin chloride and pareirin, cissamine chloride, cissampareine, five unidentified tertiary alkaloids, -4"-0-methyl curine, tetrandrine (an alkaloid), dehydrodicentrine, dicentrine and insularine, bis (benzylisoquinoline), alkaloids viz., tetrandrinemono-N-Z'-oxide, isochondodendrine and chondo curine and an alkaloids DL- curine dimethiodide (daijisong) (root and root bark); cycleanine, 1- berberine, hayatidin, hayatinin, hayatin and d- quercitol (leaves); tropoloisoquinoline alkaloids (plant).(Singh and Nishteswar 2013) Anthraquinones,Phenols,Flavanoids and terpenoids are present. (Njeru *et al.*, 2015).

## 10. Pharmacological Studies

### 10.1. Experimental pharmacology

This plant extract for treating dengue virus infection (Bhatnagar *et al.*, 2017). The ethanolic extract was administered at two different doses (250 and 500 mg/kg) to the mice after an over-night fast. Test animals were administered orally with the drugs half an hour prior to acetic acid (0.6% v/v in water, 0.1 ml/10 g, ip) administration. The mice were placed individually in glass beakers 5 min after acetic acid injection and were then observed for 15 min and the number of writhing was recorded for each animal. The number of writhes in each treated group was compared to that of a control group (distilled water), while diclofenac (10 mg/kg) was used as a reference substance. [% inhibition= (reaction time control-reaction time treated/reaction time control) ×100].

Anti-inflammatory test: Long Evans rats were randomly divided into four groups, each consisting of five animals, of which group-I was kept as control giving only distilled water. Group-II was given ketorolac (10 mg/kg) as standard. Group-III and group IV were given the test sample at the dose of 250 and 500 mg/kg, respectively. Half an hour after the oral administration of the test materials, 1% carrageenan was injected to the left hind paw of each animal. The volume of paw edema was measured at 0.5, 1, 2, 3 and 6 h using plethysmometer after administration of carrageenan. The right hind paw served as a reference of non-inflamed paw for comparison. The average percent increase in paw volume with time was calculated and compared against the control group. Percent inhibition was calculated using the formula: % Inhibition of edema=  $(V_c - V_t/V_c) \times 100$ , where  $V_c$  and  $V_t$  represent average paw volume of control and treated animal, respectively.

The antipyretic activity: Was evaluated using Brewer's yeast-induced pyrexia in rats. Adult Wistar rats were selected, weighed and divided in three groups of five animals each and they were fasted 18 h prior to commencement of experiment but water was provided ad libitum. Fever was induced by injecting 20 ml/kg of 20% aqueous suspension of Brewer's yeast in normal saline below the nape of the neck and rectal temperature was recorded by clinical thermometer immediately before (-18 h) and 18 h after (0 h) Brewer's yeast injection. Prior to the experiment, the rats were maintained in separate cages for 7 days and the animals with approximately constant rectal temperature were selected for the study. Paracetamol (100 mg/kg) was used as standard drug for comparing the antipyretic action of extract. The extract at the doses of 500 mg/kg was administered ip, one group was administered with paracetamol (100 mg/kg) i.p. control group was given 0.5 ml normal saline. The rectal temperature was measured at 1, 2 and 3 h after drug administration by using digital thermometer. Percent reduction in rectal temperature was calculated by considering the total fall in temperature to normal level. The institutional guidelines for the care and use of laboratory animals were followed. All values are expressed as mean $\pm$ SEM (standard error of mean). Comparisons were made using one-way ANOVA with Dunnett post hoc test. Statistical significance of  $P<0.05$  was used in all cases. Again ethanolic extract at 250 and 500 mg/kg dose exhibited anti-inflammatory activity in a dose-

dependent manner with the percent inhibition of 46.7 and 40.9%, respectively, as compared with the control group.

Furthermore, the ethanolic extract at a dose of 500 mg/kg body weight exhibited significant ( $P<0.05$ ) antipyretic activity. The body temperature of the experimental animals started to fall in 2 h following administration of the extract and lasted for 3 h. However, the response was not comparable to that of antipyretic activity of paracetamol. So, even though it has not been evaluated in depth for pharmacological properties, but in our study its ethanol extract has been shown to have significant analgesic, anti-inflammatory and antipyretic properties.(Reza *et al.*, 2014).

#### In-vitro antioxidant activity

##### Assay for antiradical activity with DPPH

Antiradical activity was measured by a decrease in absorbance at 516 nm of a methanolic solution of colored 1, 1-diphenyl-2-picrylhydrazine brought about by sample. A stock solution of DPPH was prepared by dissolving 4.4 mg in 3.3 mL methanol. Test medium includes 150  $\mu$ L of DPPH solution along with different concentration (20, 40, 60, 80 and 100  $\mu$ g/ mL) of samples in 3 mL methanol. Blank was performed in the same way with no sample added. Decrease in absorbance, in presence of sample was noted after 15 minutes. An IC<sub>50</sub> was calculated as the concentration which brought about a 50% reduction in absorbance compared to blank.

##### Assay for superoxide radical scavenging activity

The assay was based on capacity of the sample to inhibit blue formazon formation by scavenging the superoxide radicals generated in riboflavin-light-nitro tetrazolium (NBT) system. The reaction medium contains 2.5 mL of phosphate buffer (pH7.6), 100  $\mu$ L riboflavin (20  $\mu$ g), 200  $\mu$ L EDTA (12mM), 100  $\mu$ L NBT (0.1 mg) and different concentrations (10, 20, 30, 40 and 50  $\mu$ g/ mL) of sample contained in 100  $\mu$ L of methanol. The reaction was started by illuminating the reaction mixture for 5 minutes. The absorbance was measured at 590 nm. Blank was performed in the same way with 100  $\mu$ L of methanol instead of test substance. An IC<sub>50</sub> was calculated as the concentration which brought about a 50% reduction in absorbance compared to blank.

##### Measurement of effect on lipid peroxidation on rat liver homogenate

Rat liver homogenate was prepared by homogenizing the tissue in chilled Tris buffer(10 mM, pH 7.4) at a concentration of 10% w/v. Lipid peroxidation was induced in the liver homogenate by Iron-ADP complex in the presence of ascorbic acid. The incubation medium constituted of 0.5 mL of the liver homogenate (10% w/v), 100  $\mu$ M FeCl<sub>3</sub>, 1.7  $\mu$ M ADP, and 500  $\mu$ M of ascorbate and different concentrations of samples in 2 mL of total incubation medium. The medium was incubated for 20 min. at 37°C. Extent of lipid peroxidation was determined by estimation of malondialdehyde (MDA) content. Results were expressed in terms of decrease in MDA formation by the sample extract. Ascorbic acid was used as the positive control. (Bafna & Mishra, 2010).

## 10.2. Clinical pharmacology

Clinical relevance of Cipa extract as a DENV antiviral ,since the data so far showed that Cipa extracts have potent pan-DENV inhibitory activity, it was considered worthwhile to explore the feasibility of its therapeutic use. As DF is normally treated with paracetamol, it would be important to ascertain the nature of any interaction between Cipa and this drug. Dengue disease predisposes some patients to hemorrhagic manifestations and tends to be associated with lowered platelet counts. In this context, it also becomes important to assess if Cipa would have any effect on RBCs and platelets. These concerns were addressed in the following experiments. A type-1 assay was carried out in which DENV-3 was pre-incubated with serial dilutions of a Cipa extract. It was observed that DENV-3 infectivity was inhibited progressively as the Cipa extract concentration increased, with an IC<sub>50</sub> value of 6.1µg/ml. The addition of up to 100µg/ml paracetamol into the DENV-3/Cipa extract pre-incubation mix did not significantly affect the inhibitory profile of Cipa. The calculated IC<sub>50</sub> values in the presence of paracetamol at 1, 10 and 100µg/ml were, respectively, 8.4, 7.4 and 8.5µg/ml. Paracetamol by itself at all concentrations tested did not have any effect on DENV infectivity (plaque counts obtained with DENV-3 alone and DENV-3 plus paracetamol at 100µg/ml were, 43±3 and 45±4, respectively; n = 3). The next experiment examined the effect of Cipa extract on the antipyretic activity of paracetamol using the Wistar rat pyrexia model. Interestingly, this experiment revealed that Cipa extract possessed intrinsic antipyretic effect. When rats, in which fever was induced by subcutaneous injection of brewer's yeast, were treated with Cipa extract, the fever was suppressed at an efficiency that was comparable to that of paracetamol. Interestingly, co-administration of Cipa extract with paracetamol had a synergistic effect, resulting in a more pronounced decrease in body temperature.

In the next set of experiments, whole blood from human volunteers was collected and platelets counts obtained before and after 1–4 hours post-mixing with Cipa extract. In the control sample, blood mixed with vehicle (saline), platelet counts declined steadily over time. Cipa extract-treated blood samples manifested no statistically significant change in platelet counts with respect to their cognate controls, up to 2 hours At four hours, the Cipa extract-treated samples displayed significantly higher( $p<0.05$ ) platelet counts, compared to corresponding saline-treated control. The apparent platelet-protective effect of Cipa extract is intriguing and merits further investigation. Essentially similar results were observed at 2 and 10 µg/ml Cipa extract concentrations, indicating that Cipa extract did not affect platelets adversely. The effect of Cipa extract on platelets was also evaluated in an in vivo experiment using Wistar rats. In this experiment, platelet counts were determined in blood drawn from rats which had been given Cipa extract orally. The results up to 4 hours post-treatment, Cipa extract (up to 1000 mg/kg body weight), did not affect platelet counts significantly ( $p>0.05$  at the highest dose of Cipa extract treatment for 4 hours). The effect of Cipa extract on erythrocytes was also assessed, both in ex vivo and in vivo assays, as done for platelets above. Incubation of freshly collected human erythrocytes with Cipa extract at concentrations upto 400 µg/L did not cause

discernible hemolysis. The blood samples, withdrawn from the Wistar rats (given Cipa extract, described above), were also analysed for erythrocyte cell counts. This analysis, once again revealed that Cipa extract (at concentrations as high as 1000 mg/kg body weight), did not affect erythrocyte counts in the blood of Wistar rats up to 4 hours post-administration. The difference in erythrocyte counts between the treated and untreated rats was not statistically significant ( $p>0.05$ ). We also analyzed total leucocyte and differential counts in the blood of Cipa treated Wistarrats and found no significant difference. A hallmark of severe dengue disease is the elevation of inflammatory cytokines which are implicated in triggering events that culminate in vascular permeability and hemorrhage .To test if Cipa extract had any effect on the secretion of inflammatory cytokines; PBMCs were isolated from blood and incubated with LPS to induce cytokine release. These cells were then treated with Cipa extract and the release of pro-inflammatory cytokines monitored using commercial ELISA kits. This experiment showed that the secretion of TNF- $\alpha$  and IL-1 $\beta$  was efficiently suppressed by Cipa extract with IC50 values of  $6.1\pm1.3$  and  $5.7\pm2.7$   $\mu$ g/ml, respectively. An MTT assay showed that at these concentrations, Cipa extract has no discernible cytotoxicity in both cell lines tested (CC50 = 78.9 $\mu$ g/ml in HepG2; >200 $\mu$ g/ml in LLCMK2). These data suggest that Cipa extract possesses anti-inflammatory activity in addition to the antipyretic activity documented in the experiment above(Sood *et al.*,2015).

#### 11. Toxicity and safety

Roots are the most used parts of this plants. Mainly they contain alkaloids of different structures. All these, alone or together, are toxic. But when used only for short terms in folk medicine and when extracted only by water there no sincere toxic effects could be found. The application seems to be harmless. But sub-acute and chronic toxic effects cannot be excluded. In higher concentrations the alkaloids of this plant is used as poisons in hunting and fishing.(Mmh-mms.com.)

#### 12. Clinical studies: NA

#### 13. Contraindications: NA

#### 14. Precautions

Because of the toxicity of all alkaloids in this plant -alone or all together- all uses of the roots and the whole plant must be advised again, except skin sores in short time treatment.(Mmh-mms.com)

#### 15. Adverse reactions: NA

#### 16. Marketed formulation: NA

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1. Botanical Name: ***Citrullus colocynthis* (L.) Schrad.**

2. Synonym: *Cucumis colocynthis* L.

3. Family: Cucurbitaceae

4. Common Names

Assam:	Mahakal
Bengali:	Indrayan, Makal
Bihari:	Pair
English:	Colocynth, Bitter apple
Gujarati:	Indrak, Iadranan, Indravana
Hindi:	Indrayan, Makal
Kannada:	Pavamekkekayi, Tumtikayi
Malayalam:	Peykommitti
Marathi:	Indrayan, Kaduvrindavana
Punjabi:	Ghorumba, Kaur-tumba, Tumba, Tumbi
Rajasthan:	Ghorumba, Kaur-tumba, Tumba, Tumbi
Sanskrit:	Chitraphala, Indravarooni, Mahendravaruni
Tamil:	Peykkumutti, Verittumatti
Telugu:	Etipuchcha, Paparabudama
Trade:	Colocynth
Urdu:	Indrayan.

5. Description: A perennial trailing herb with woody tuberous root. Tendrils simple, rarely bifid, slender, glabrous. Leaves alternate, elongate-ovate in outline, distinctly scabrid-hairy beneath, smooth except on the nerves above, palmately deeply 3-5-lobed, ultimate lobes pinnately lobulate with central lobe longest, long-ovate in outline; petiole rather densely rough-hairy; probracts lanceolate-elliptic, caducous. Male flowers on long pedicels; calyx campanulate, lobes c. 5 mm broad; corolla pale yellow, ovate-acute. Female flowers on longer pedicels than male, receptacle-tube short, lobes lanceolate; ovary hairy, subglobose or obovate. Fruit globose, smooth, longitudinally green striped, epicarp thin, filled with a dry spongy very bitter pulp. Seeds numerous, ovate-oblong, yellowish brown, not margined.

6. Distribution: Native of Turkey, Tropical and Subtropical North Africa and Asia; found in tropical regions of Maharashtra: Ahmednagar, Pune, Karnataka: Kerala and Tamil Nadu.

7. Part Used: Whole plant



*Citrullus colocynthis* (L.) Schrad

## 8. Medicinal/Therapeutic Uses

### 8.1. Uses described in pharmacopoeias and in traditional systems of medicine

Plant part	Medicinal and Therapeutic Uses	Reference
Seed	Seed oil: Bowel complaints, Epilepsy, Hair growth Pulp: Malaria	Mahesh et al 2014
Fruits	Whole: Acute stomach ache (with salt), Dropsy (with sugar), Urticaria, constipation and toxæmia, dental carries and tooth-ache, deafness, tumors, leucoderma, ulcers, dyspepsia, asthma, bronchitis, urinary discharge, enlargement of spleen, tuberculosis glands of the neck, dyspepsia, constipation, anaemia and throat diseases Pulp: Anti-bacterial Juice: Hepatitis, Ease of child-delivery, reproductive ailments Powder: Abortifacient	
Root	Whole: Inflammation of mammary glands, joints, amenorrhea, ease of child delivery, Ascites, jaundice, urinary disease and rheumatism, enlarged abdomen in children, amenorrhea Paste: Wound healing (anti-biotic and antimicrobial)	
Leaves	Jaundice and asthma	
Fruit and Root	Mixed Paste: Snake poison, Boils and Pimples	
Whole Plant	Glycosidic extract (50mg/kg): Lowering glucose level, Indurations of the liver	

#### Traditional uses:

Fruits were also traditionally used as an ant diabetic medication (tropical and subtropical countries), abortifacient, anti-oxidant and to treat gastrointestinal disorders such as indigestion, constipation, dysentery, gastroenteritis and colic pain (Borhade et al., 2013; Mahesh et al., 2014).

It finds further traditional uses in tribal areas of Rajasthan in reproductive ailments, oedema, leprosy, common cold, cough, asthma, bronchitis, jaundice, joint pain, toothache, wound, mastitis, bacterial infections, cancer, diabetes, hypertension and high cholesterol(cardio-vascular). Dried fruit pulps, fruits, roots and leaves (Mahesh et al., 2014).

The traditional medicinal applications have inspired many pharmacological investigations. Several extracts and isolated compounds have been evaluated for their biological activities, especially anticancer and antidiabetic activities. There seems to be an interest in developing new anticancer/ antitumor drugs from this plant due to its high contents of cucurbitacins (Abdullah et al., 2014).

As per Ayurveda and Siddha system of medicine is Tikta –rasam (bitter in taste), ushna veeryam (heat as the potent element), katu vipaka (obstructs the excretion process), purgative, diuretic, lagu (light in digestion), puerperal disorders, abortifacient, ascites and dropsy. Oils from seeds are used in hair growth and maladu (male infertility) (Borhade et al., 2013).

#### 8.2. Uses supported by clinical data

Diabetes and hypoglycaemic, hypolipedemic, anti-cancer (human laryngeal cancer cell lines) and ant proliferative property (human breast cancer cell lines), anti-oxidant, anti-inflammatory and analgesic, antibacterial and anticandidal, hair tonic, insecticide (*Aphis craccivora*), larvicide (*Aedes aegypti*, *Anopheles stephensi*, *Culex quinquefasciatus*) (Borhade et al., 2013).

#### 8.3. Traditional/Folklore uses described in folk medicine, not supported by experimental or clinical data

Multiple gut disorders (Abdullah et al., 2014), anti-ulcerogenic, airways disorders such as bronchitis, cough and asthma, cardiovascular disorders (Borhade et al., 2013). Diseases that have been mentioned for treatment with traditional Iranian Medicine (TIM) but that have not evaluated in modern phytotherapy until now include sciatica, paralysis, asthma, chronic cough, tinnitus, epilepsy, elephantiasis, and scorpion and snail bite (Roja et al., 2012).

#### 8.4. Special uses in North East India

In Manipur, it is used to alleviate symptoms of diabetes, liver ailments such as jaundice and gastro-intestinal ailments. The whole plant or parts of the plant is boiled and consumed.

8.5. Dosage forms used in tradition (Mahesh et al.,2014).

Abdominal pain	Equal quantities of fresh “Colocynth” roots and black pepper ( <i>Piper nigrum</i> ) are ground with a little water to make a fine paste. One g paste is given three times a day for three days
Amenorrhea	Fresh roots boiled in cow’s milk in the ratio of 1:8. Five ml milk is administered orally twice a day for forty-one days
Wounds	Fresh root paste obtained by grinding fresh roots with a little water, is applied to wounds thrice a day till it heals up completely
Constipation	Decoction of fresh fruit is prepared in water in ratio of 1:6. Five ml decoction is administered orally at bed time for three days
Dental Carries	A decoction obtained by boiling chopped ripe fruits of “Colocynth” in water in the ratio of 1:6 is used as mouth wash twice a day for seven days
Leucoderma	Fresh leaf juice is applied to the skin diseases twice or thrice in a day. Seed oil is applied to depigmented areas every third day. The therapy is continued till the pigments reappear and become stable.
Rheumatism	Fresh root of “Colocynth” and “Aswagandha” ( <i>Withania somnifera</i> ) is taken in equal quantities and ground to a fine paste. Two gm. paste mixed with 5 gm. honey is administered orally twice a day till complete cure is achieved. This therapy is considered to be very effective and it is claimed that the patient begins to improve in two days of therapy.
Snake bite	Fresh roots are ground to a fine paste. Two gm paste is applied to a “Pan”/betel leaf and is given orally within two hours of snake bite.
Abortifacient	Two gm paste is given orally once a day
Stomach ache	The fruits are dried and ground to make powder. Two g powder is given orally twice a day for 2 days
Jaundice	Fresh fruit pulp dried in shade, grind to powder. Two g powder is given orally twice a day for 3 days
Diabetes	Pulp of ripe fruits is trampled by naked feet till feeling of bitter taste appears in the mouth for 15 days(Rajasthan) It is prescribed for diabetes in several cities of Iran by traditional healers in a different range of doses from 300 to 800 mg/day dry fruit
Malaria	Pulp of seeds eaten twice a day for 2 days
Inflammation of mammary glands	A fine fresh root paste, obtained by grinding the roots with a little water, is applied twice daily on inflamed mammary glands till complete cure is obtained

The acceptable dosage of fruit in traditional Iranian Medicine (TIM) is from 0.6 to 1.75g per day. In modern phytotherapy, 0.1–0.4g/ day is allowed to be administered. The acceptable dosage for other parts of the plant is 120–300 mg up to 600 mg/day of seed and 0.2 to 0.4g/day of root powder.<sup>30</sup> The difference between TIM and modern phytotherapy in acceptable dosage may be due to administering fruit with its correctives such as Arabic gum, gum tragacanth, and myrrh gum in TIM (Roja et al.,2012).

## 9. Phytochemical profile

### 9.1. Major chemical constituents

The phytochemical study gives valuable information about the chemicals present in the plant. The behaviours of leaf powder upon treatment with different chemical reagents were also analysed. The various qualitative chemical tests showed the presence of diterpenoids, saponin, sterols, flavonoids, carbohydrate and alkaloids. Aromatic acid, gums and mucilage and tannin were totally absent in the leaf, root, and seed of this plant (*Uma et al.,2014*).

Several bioactive compounds from fruit have been recorded in the literature. They are grouped as glycosides, flavonoids, alkaloids, carbohydrates, fatty acids, and essential oils chemical constituents. Cucurbitacins have been reported as the main components (*Abdullah et al.,2014*).

The main chemical contain of fruit pulp colocynthin (the bitter principle upto 14 %), colocynthein (resin), colocynthetin, pectin gum. Seed contain a fixed oil (17 %) and albuminioids (6 %). Other clinically investigated chemical constituents are tabulated below (*Borhade et al., 2013*).

Part	Clinical content (reported/investigated)
Seed	1. Fatty acid like Stearic, Myristic, Palmitic, oleic, Linoleic, Linolenic acid. 2. Protein 8.25 % and rich content rich in lysine, leucin and sulfo amino acid. 3. Vitamin B1, B2 and Niacin. 4. Mineral like Ca, Mg, K, Mn, Fe, P and Zn.
Aerial part and fruit	Flavoid glycoside quercetin, Flavone-3-glucoside viz iso-vitexin, iso-oretine and iso-oretine-3-methyl ether.
Fruit	1. Cucurbitane type triterpen glycoside viz colocynthoside A & B. 2. Cucurbitane type triterpen glycoside viz cucurbitacin E 2-O-beta-D-glucoside and its aglycone Cucurbitacin E. 3. 2-O-beta-D-glucopyranosyl-16alpha-20R-dihydroxy-cucurbita-1,5,23E,25(26)-teraen-3-11-22-trione. 4. 2-O-beta-D-glucopyranosyl-cucurbitacin B and 2, 25-di-o-beta-D-glucopyranosyl-cucurbitacin L.

## 10. Pharmacological activities (as per available literature)

### 10.1. Experimental pharmacology

#### Anti-inflammatory

Belsem Marzouk and et al study aqueous extracts of fruit and seed at immature state for anti-inflammatory activity using the carrageenan induced paw oedema assay in rats. The best anti-inflammatory activities were obtained with immature fruits from south Tunisia. Therefore, it could be a potential useful product suitable for further evaluation for inflammatory diseases (*Borhade et al.,2013*).

### Anti-candidal and antibacterial activity

Rasool Khatibi and et al assess *in vitro* antibacterial and Anticandidal activity of aqueous and diluted acetone extracts. All extracts showed activity against all strains with antibacterial (*Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Enterococcus faecalis*) and Anticandidal (*Candida glabrata*, *Candida albicans*, *Candida parapsilosis* and *Candida krusei*) properties (Borhade et al.,2013).

### Antioxidant

Saba AB and et al isolated Cucurbitacins are triterpenoid steroids. This property lies in their ability to scavenge free-radicals. Reports also show that cucurbitacins adequately inhibit lipid peroxidation and oxidation (Borhade et al.,2013).

### Hypoglycaemic

Agarwal V and et al examine the effect of root on the biochemical parameters of normal and alloxan-induced diabetic rats. The aqueous extract of roots showed significant reduction in blood sugar level (Borhade et al.,2013).

### Anti-inflammatory and analgesic activities

Marzouk B and et al screen the analgesic and anti-inflammatory activities of aqueous extracts from roots and stems of the plant and from fruits and seeds at different maturation stages. All extracts displayed analgesic and anti-inflammatory activities at different doses without inducing acute toxicity (Borhade et al.,2013).

### Anti-aloepecia

Dhanotia R and et al evaluated for hair growth activity in androgen-induced alopecia in albino mice by testosterone administration intramuscularly for 21 days. Petroleum ether extract was applied topically for its hair growth-promoting activity. The treatment was also successful in bringing a greater number of hair follicles in anagenic phase than the standard finasteride. The result of treatment with 2 and 5% petroleum ether extracts were comparable to the positive control finasteride. The petroleum ether extract and its isolate are useful in the treatment of androgen-induced alopecia (Borhade et al.,2013).

### Mosquito larvicidal activity

The larval mortality was observed after 24 h exposure. All extracts showed moderate larvicidal effects; however, the highest larval mortality was found in whole plant petroleum ether extract of *C. colocynthis* (Borhade et al.,2013).

### **Effects on reproductive system and fertility**

Qazan WSH and et al study toxic effect (400 mg/kg/body weight) on the reproductive system after administration to female Sprague-Dawley rats weighting 250-300 g for two time periods 4 and 12 weeks. Rats receiving 12 weeks treatment showed a decrease in ovarian weights and a decrease in viable foetus's number. These results indicate that long- term exposure of female rats causes adverse effects on the reproductive system and fertility (Borhade et al.,2013).

### **Growth inhibitory activity on breast cancer cells**

Studies are reported on the effects of cucurbitacin glucosides extracted from *Citrullus colocynthis* leaves on human breast cancer cell growth causing both cell cycle arrest and apoptosis suggestive of therapeutic value against breast cancer cells (Borhade et al.,2013).

### **Wound healing**

The wound healing study showed that the ointments from the methanolic extract resulted in an improved wound closure rate and significant reduction in healing time as compared with control group in experimental rats. The estimation of hydroxyproline indicates that a significant increase in hydroxyproline content of granulation tissue is responsible for synthesis of collagen, which is the predominant protein responsible for the wound healing (Sateesh et al.,2018).

### **Analgesic Activity**

The analgesic effect was tested for concentrations ranging from 2 to 8mg/kg, except immature fruits; to which we decrease the concentration to 0.1 mg/kg. The administration of all tested extracts induced a dose-dependent antinociceptive activity. The immature fruits and seeds possess the highest analgesic properties; the most active of them were immature fruits as well as at 0.1 mg/kg (93.52%). Stem extracts were as active as those of roots. The lowest activity was observed for ripe fruits (Belsem et al.,2009).

### **10.2. Clinical pharmacology**

#### **Type II diabetic clinical trial**

Huseini et. al., (2009) conducted 2-month clinical trial in 50 type II diabetic patients using powder two groups of 25 each under standard anti-diabetic therapy, received 100 mg fruit capsules or placebos three times a day, respectively. The patients were visited monthly and glycosylated haemoglobin (HbA1c), fasting blood glucose, total cholesterol, LDL, HDL, triglyceride, aspartate transaminase, alanine transaminase, alkaline phosphatase, urea and creatinine levels were determined at the beginning

and after 2 months. The results showed a significant decrease in HbA1c and fasting blood glucose levels in treated patients. Other serological parameters levels in both the groups did not change significantly. No notable gastrointestinal side effect was observed in either group (Borhade *et al.*,2013).

## 11. Toxicity and safety

In the acute toxicity and histopathological effect of saponin extracted from whole plant on mice, Diwan *et al.*, (2000) reported the median lethal dose (LD50) to be 200 mg/kg, which indicate that the studied plant constituent is not toxic when comparing the LD50 values of most bioactive pharmaceuticals currently used in therapeutics (Abdullah *et al.*,2014).

It has been demonstrated to be responsible for diarrhea in treated animals and colitis in humans. The membranolytic activity of saponin an ingredient of the pulp extract is believed to be the main pathophysiological mechanism for intestinal damage (Hamid *et al.*,2013).

It is highly toxic as indicated by acute toxicity studies in white mice. The LD50 was calculated as 1000mg/kg bw. All test animals expired within four days of experimentation. Histopathological studies on Heart, Kidneys and Liver also indicated Gross changes in histology of Heart, Liver and Kidneys. As the drug is used in a number of herbal drug formulations it is advisable that it should be used very cautiously or where ever possible its use should be avoided (Jahanzeb *et al.*,2016).

The absence of any significant changes in aspartate transaminase, alanine transaminase and alkaline phosphatase activity, and in levels of urea and creatinine, indicate that at the doses given, the extracts did not cause any damage to liver or kidney function. Furthermore, the absence of significant gastrointestinal disturbances observed in the present study following administration, indicates that it is safe at a dose of 300 mg/day treatment to diabetic patients for 2 months (Husseini *et al.*,2009).

## 12. Clinical Studies

### Anti-diabetic

A total of 50 type II diabetic patients (aged 40–65 years), registered at the diabetic clinic registry of Shariati Hospital, were selected and enrolled in a study in various cities of Iran. The patients were admitted by investigators and informed about the rationale and main aims of the study. They were prescribed different range of doses from 300 to 800 mg/day dry fruit (Husseini *et al.*,2009). All the patients completed 2 months' therapy. The demographic and paraclinical characteristics of two groups at the beginning of the study are summarized in Table 1(Husseini *et al.*,2009).

Table 1. The demographic and some of the paraclinical characteristics of placebo and *C. colocynthis* treated groups at beginning of the study.

	Group		P value
	<i>C. colocynthis</i> (n=25) (mean $\pm$ SD)	Placebo (n=25) (mean $\pm$ SD)	
Age (year)	53.3 $\pm$ 5.6	55.1 $\pm$ 5.4	0.623
Duration of disease (year)	4.7 $\pm$ 2.4	5.1 $\pm$ 3.7	0.381
Weight (kg)	66.2 $\pm$ 5.4	67.1 $\pm$ 4.9	0.801
Glucose (mg/dL)	189.2 $\pm$ 27	172.0 $\pm$ 24	0.240
HbA1c (%)	10.4 $\pm$ 1.9	9.1 $\pm$ 1.9	0.032
Total cholesterol (mg/dL)	211.9 $\pm$ 37	194.7 $\pm$ 43	0.051
Triglyceride (mg/dL)	171.5 $\pm$ 74	192.7 $\pm$ 83	0.373

Most of the patients in the treated group were satisfied with the therapy, having apparently good gastrointestinal status. The average finding of patient's blood parameters in the two groups at the beginning and after 2 months of the study are summarized in Table 2.

Table 2. The average serological parameters at begining and after 2 months of the study in placebo and treated groups.

	Group (n = 25)			
	<i>C. colocynthis</i> (mean $\pm$ SD)		Placebo (mean $\pm$ SD)	
	Begining	After 2 months	Begining	After 2 months
Glucose (mg/dL)*	189.2 $\pm$ 27	173.9 $\pm$ 34	172.0 $\pm$ 24	176.6 $\pm$ 32
HbA1c (%)*)	10.4 $\pm$ 1.9	9.0 $\pm$ 2.4	9.1 $\pm$ 1.9	9.1 $\pm$ 1.6
Total cholesterol (mg/dL)	211.9 $\pm$ 37	204.8 $\pm$ 40	194.7 $\pm$ 43	202.6 $\pm$ 36
LDL cholesterol (mg/dL)	126.2 $\pm$ 28	118.0 $\pm$ 46	108.7 $\pm$ 24	115.0 $\pm$ 31
HDL cholesterol (mg/dL)	69.3 $\pm$ 20	62.5 $\pm$ 17	65.6 $\pm$ 21	55.6 $\pm$ 18
Triglyceride (mg/dL)	171.5 $\pm$ 74	170.2 $\pm$ 40	192.7 $\pm$ 83	215.5 $\pm$ 97
Urea (mg/dL)	13.9 $\pm$ 3.1	15.7 $\pm$ 4.7	15.0 $\pm$ 3.8	14.7 $\pm$ 3.5
Creatinine (mg/dL)	0.91 $\pm$ 0.1	0.92 $\pm$ 0.1	0.087 $\pm$ 0.0	0.94 $\pm$ 2.5
Aspartate transaminase (U/L)	25.8 $\pm$ 8.2	28.4 $\pm$ 7.1	27.6 $\pm$ 6.0	28.7 $\pm$ 5.1
Alanine transaminase (U/L)	34.9 $\pm$ 7.1	31.3 $\pm$ 1.1	33.0 $\pm$ 12	32.5 $\pm$ 8.1
Alkaline phosphatase (IU/L)	182.8 $\pm$ 52	171.5 $\pm$ 43	165.0 $\pm$ 62	175.0 $\pm$ 60

\*Fasting blood glucose and glycosylated hemoglobin (HbA1C) levels significantly decreased in the treated group compared with the begining of the study (0.015 and 0.003, respectively) and compared with the placebo group (0.029 and 0.023, respectively)

The present study showed the beneficial effect on the glucose profile in patients with type II diabetes. The treatment significantly lowered the glycosylated haemoglobin and fasting blood glucose levels in diabetic patients (Husseini *et al.*,2009).

#### Hypolipidemic

Rahbar AR and et al investigate the hypolipidemic effect of beyond the hypoglycaemic impact on human. A daily intake of 300 mg day (-1) of powdered seeds can lower the triglyceride and cholesterol concentration significantly in nondiabetic hyperlipidaemia patients. Serum cholesterol levels dropped from 940.7 to 230.41 (75.55%) and further to 119.2 (87.32%) by the end of the experiment (Borhade *et al.*,2013).

#### 13. Contraindications

It is abortifacient; thus, it is contraindicated during pregnancy. It is considered a traditional poison and over-dose to be avoided. Not to be administered to children and weak patients. The drug and its preparation cause drastic irritation of the gastro-intestinal mucosa and haemorrhage. The toxic dose of fruit pulp is 0.5-1g, while fatal dose is 4g (Mahesh *et al.*,2014).

#### 14. Precautions

It is recommended in TIM (Traditional Iranian Medicine) to administer equal weights of starch, Arabic gum, myrrh gum, or gum tragacanth. In addition, it should be ground carefully until it is completely powdered, because if there is any unground particle present, it can cause inflammation of the gastrointestinal tract. It is also harmful for slender people, and it should be administered with fruit juice for these people (Roja *et al.*,2012).

#### 15. Adverse Reactions

The most reported adverse events are rectorrhagia (Hamid *et al.*,2013),diarrhoea, inaction of intestine, and liver impairment. It causes headache, abdominal cramps, and nausea in very cold weather and dysentery and inflammation in very hot weather (Mahesh *et al.*,2014).

#### 16. Marketed formulation, if any

Allopathic formulation is rare but widely available in herbal and ayurvedic formulation like Yuvika indrayan jadd - indrain jadd (Yuvika Herbs), Colocynthis 30C (Rxhomeo), LIFERR Indrayan Phal (Liferr-Sinhal Herbs), Boiron colocynthis 5CH Granules (Boiron Srl), SBL Colocynthis Mother Tincture Q (SBL), Ointment with Colocynths and various herbs (Hemani), ADEL Colocynthis Dilution 200 CH (Adel Pekana Germany).

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1. Botanical Name: *Citrus hystrix* DC.

2. Synonym: NA

3. Family: Rutaceae

4. Common Names

English: Khaffir lime, Makrut lime, Mauritius papeda

Garo: Chambil

Khasi: Sohkwit

5. Description: A medium-size tree up to 20 feet high. Leaves dark red when young; petiole winged, apex rounded to truncate; leaf blade ovate, longer (rarely same length) and 0.5-1cm wider than winged petiole, tertiary veins conspicuous, margin apically conspicuously and sparsely crenate, apex narrowly obtuse. Flowers white and pinkish red outside. Stamens around 30; filaments distinct. Style short, thick. Fruit lemon yellow, ellipsoid to sub-globose, slightly coarse or smooth, oil dots numerous and prominent, apex rounded; pericarp thick; sarcocarp in 11-13 segments, very acidic and slightly bitter. Seeds numerous ridged; embryo solitary; cotyledons milky white.

6. Distribution: Native to tropical Southeast Asia and southern China. In India tropical to subtropical regions.

7. Part Used: Fruit, leaves and rind of fruits



Figure1: *Citrus hystrix*DC.  
(Source: Photograph by Tangmo)

## 8. Medicinal/Therapeutic Uses

### 8.1. Uses described in pharmacopoeias and in traditional systems of medicine

It is used by the traditional healers in the silent valley of Kerala, India reported a total of 102 species of plants that were commonly used for medicinal purposes and *Citrus hystrix* was used for the treatment of cancer, skin generation, dandruff and hair loss (Yabeshet al., 2014).

### 8.2. Uses supported by clinical data

**Anti-cancer:** A work was carried out to examine the *in vitro* cytotoxicity activity from crude khaffir lime leave on leukemia cell lines viz., HL60, K562, Molt4, U937 using different extraction fractions. The result showed that the highest cytotoxicity activity was exhibited in ethyl acetate fraction with IC<sub>50</sub> values of 19.0±0.6, 35.3±1.4, 21.8±0.4, and 19.8±1.0 µg/respectively (Chueaghongthong et.al., 2011).

### 8.3. Traditional /Folklore Uses described in folk medicine

**Leaves and Fruit:** Decoction of the leaves and fruits are used for treating arthritis, diabetes, gouts, gastrointestinal and fever and is given orally (Abdul Rahman et al., 2018).

**Leaves:** It used for treating flu, fever, hypertension, abdominal pains and babies diarrhea (Fortin et.al., 2009).

### 8.4. Special uses in North East India

**Meghalaya:** Whole fruit or juice is taken orally for treating food poisoning (Upadhaya et.al., 2016).

**North-East India:** Fresh fruits, bottled juice and dried fruit peel were being used by local people for edible purposes against gastritis problems. Juice mixed with sugar is used as a squash and relished by local people as it gives soothing effect to the stomach, fresh fruits and dried fruit peels are used in non-vegetarian preparations to give a typical acidic flavour to curries (Hazarika, 2012).

**Karbi Anglong District, Assam:** The rind of *C. hystrix* was used as a condiment by the people (Teron, 2019).

### 8.5. Dosage forms used in tradition

The juice is drink orally for treating cancer, while is used as a topical for the treatment of dandruff, hair loss and skin generation (Yabeshet.al., 2014).

## 9. Phytochemical profile

### Major chemical constituents

- Leaf Oil: It has been reported that Makrut oil consisted of several components and the most active component was  $\alpha$ -terpineol, followed by terpinene-4-ol, and limonene, while citronellal was found to be the major component (80.04%) in Makrut leaf oil (Srisukhet *et al.*, 2012). Investigation on the chemical composition Swangi revealed that citronellal was the major compound found in leaf oil (81.49%); twig Oil (78.64%) and peel oil (16.80%) respectively (Sato *et al.*, 1990).
- Fruit and Peel Oil: Six were identified from peel oil and thirty seven compounds from fruit oils and out of which the major compounds found in peel oil were  $\beta$ -pinene (27%), Limonene (24.7%) and Sabinene (13.8%); while in fruit oil the compounds include  $\alpha$ -terpineol (15.8%),  $\beta$ -pinene and Limonene (9.1%) respectively (Safian *et al.*, 2005).

## 10. Pharmacological Studies

### Experimental pharmacology

**Anti-diabetic activity:** Evaluation of *C. hystrix* leaf flavonoids rich extract (CLE) as anti-cataract effect in STZ-induced diabetic rats reveals that the extract significantly reduces the fasting blood glucose (FBG) as well as in mitigating the diabetic cataract (Umran *et al.*, 2020).

**Anti-bacterial:** Isolation and screening of anti-bacterial activity against human pathogenic bacteria from two Citrus species *viz.*, *C. hystrix* and *C. limon* using agar diffusion and methanolic fruit peel extraction showed that both the species have antibacterial properties that can be explored as viable, alternative source to commercially available antibiotic drugs (Ajithkumar & Panneerselvam, 2012).

**Stimulating activity:** Investigation on the chemical composition of khaffir lime oil and the evaluation effect of the compound on autonomic nervous system parameters and behavioral parameters in healthy humans report that khaffir lime oil has stimulating/activating effects that provide evidence on its use in medicines, such as causing reduction in blood pressure or in relieving depression and stress in humans (Hongratanaorakit & Buchbauer, 2007).

**Antiviral activity:** Four species *viz.*, *Citrus hystrix*, *Erythroxylum laurifolium*, *Obertia cifolia* and *Sneckoam bavilla* out of the thirty six medicinal plants collected from La Reunion Island, showed antiviral activity against Herpes simplex virus type-1 (HSV-1) (Fortin *et al.*, 2002).

### 10.1. Clinical pharmacology

Cardio protective effect: Observation of the histopathological changes in cardiac and hepatic tissues from peel extract of *C. hystrix* rat model showed that *C. hystrix* peel ethanolic extract (ChEE) has a potential as a cardio-protector agent in chemotherapy (Putri et al., 2013).

Antipyretic and anti-nociceptive activities: *In vivo* study to evaluate the anti-pyretic, anti-nociceptive, gastrointestinal and acute toxicity effect from different leaf extract in Swiss albino mice showed that leaf extracts exhibited anti-pyretic and anti-nociceptive activities (Barai et al., 2015).

### 11. Toxicity and safety

The leaf extract performed using different extraction methods did not induce any acute toxicity effect when administered orally to Swiss albino mice (Barai et al., 2015).

Excessive exposure to peel oil may cause skin irritation. And contact with sap may cause skin irritation.

12. Clinical studies: Not been reported.

13. Contraindications: No data available.

14. Precautions: No data available.

15. Adverse reactions: No data available.

16. Marketed formulation, if any: No data available.

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1. Botanical Name: ***Curcuma longa* L.**

2. Synonym: *Curcuma domestica* Valeton

3. Family: Zingiberaceae

4. Common Names

Assamese:	Halodi
Bengali:	Halud, Halada, Haldi
English:	Turmeric
Gujarati:	Halada, Haldi
Hindi:	Halada, Haldi
Kannada:	Arisina, Arasana
Malyalam:	Manjal
Marathi:	Halada, Haldi
Sanskrit:	Haridra
Tamil:	Manjal
Telugu:	Haridra, Pasupu

5. Description: A rhizomatous herbs up to 30 cm high; rhizomes conical, deep orange-yellow inside, strongly aromatic. Leaves 4-6, distichous; petiole 40 cm long; oblong-lanceolate, tapering at both ends, margins wavy, glabrous, pubescent towards the extreme tip; ligule short, near the lamina. Inflorescence central; peduncle 15 cm, concealed within the leaf sheaths; spike 8-10 cm long with a distinct white coma. Coma bracts 8-10, 7 × 3.5 cm, spreading. Fertile bracts 30, compactly arranged, lower half of adjacent bracts fused to form pouches, tip recurved, pale green, outer surface minutely pubescent, inner surface glabrous. Lower bracts subtend cincinni of two flowers, upper bracts one flowered. Flowers white, glabrous; lobes unequal; dorsal lobe larger, concave, white, hooded, hood hairy, lateral lobes linear, white, glabrous. Labellum trilobed, middle lobe emarginate, light yellow with a broad, median dark yellow band. Lateral staminodes linear, tip slightly incurved. Anther-thecae 4 mm long, spurred; spurs 3 mm long, parallel. Epigynous glands two, 5 mm long. Ovary 5 mm long, tricarpellary, syncarpous; ovules many on axile palcenta, pubescent towards the tip. Style long, filiform; stigma blipped.

6. Distribution: Native to Indian subcontinent and south east Asia; In India, turmeric is cultivated throughout tropical regions.

7. Part Used: Leaves and rhizomes.



*Curcuma longa L.*

## 8. Medicinal /Therapeutic Uses

### 8.1 Uses described in pharmacopoeias and in traditional systems of medicine

Turmeric has been used for many conditions in traditional medicine in India, Pakistan and Bangladesh. Its rhizomes can be prepared in various ways and is reputed to alleviate asthma and coughs. In Ayurveda it is used to treat edema, wounds, allergy, respiratory inflammations, and skin disorders including acne, black spots, and

blemishes. In traditional Chinese medicines severe abdominal pains are also treated by turmeric (Goel *et al.*, 2008). Turmeric has been used in Unani medicine for conditions such as liver obstruction and jaundice and has been applied externally for ulcers and inflammation. Roasted turmeric is being useful in the treatment of dysentery. Turmeric has also been used as ingredients in tooth powder or paste.

8.2. Use supported by clinical data: Traditional use clinical data are not available.

8.3 Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

Oral administration of hot water extract of the dried rhizome is supposed to slow lactation, regulate fat metabolism, help symptoms of diabetes, diarrhea and liver diseases, and as a tonic to calm the stomach. The regular intake of fresh juice on an empty stomach has been used to prevent stomach disorders. The hot water extract of the dried rhizome was also reputed to have an abortion-promoting effect when taken orally or in the form of a pessary. The dried rhizome has found its application on fresh wounds and insect stings, and also helps the healing process in chickenpox and smallpox. Turmeric is being used externally as a remedy to improve complexion of the skin and to remove hair, as a tonic to alleviate itching. Inhalation of turmeric smoke is believed to provide relief from hiccups. Pieces of the rhizomes are added to water to make an infusion and used in baths which improves skin tone and reduces hair growth.

8.4. Special uses in North East India

In Tripura, rhizomes of the plant used to treat skin infection and menstrual pain problem (Sen *et al.*, 2011). The rhizomes are also used in the treatment of Anemia, leucoderma, migraine injury, jaundice, Hepatitis-B, duodenal ulcer, food poisoning, urinary infection, boils, malaria, intestinal disorders, fungal infection in legs, fungal skin damage (lichen) and cold allergy on skin etc. (Velayudhan *et al.*, 2012). The tribal communities in the north eastern states chewed rhizomes for getting relief from asthma (Tushar *et al.*, 2010).

8.5 Dosage forms used in tradition: Decoction, extract, powder and paste.

## 9. Phytochemical profile

It is rich in phytochemicals like, tannins, alkaloids, phenols, steroids, flavonoids, phlobatannin, cardiac glycosides, terpenoids, triterpenes and saponins (Deb *et al.*, 2013; Oghenejobo *et al.*, 2017).

Major chemical constituents:

The principal phytoconstituents of turmeric are known to be diarylheptanoids (e.g. curcumin, demethoxycurcumin and bisdemethoxycurcumin), sesquiterpenoids (e.g. α-

curcumene,  $\beta$ -atlantone, curcumol and dehydrocurdione), diterpenoids, polysaccharides and phenolic acids (Yuan *et al.*, 2017). In addition, the rhizomes contain  $\alpha$ -phellandrene, sabinene, curcuminoids, demethoxycurcumin,  $\alpha$ -phellandrene cineol, borneol, zingiberene. Curcumin (diferuloylmethane) is responsible for the yellow colour of the turmeric (Ashraf *et al.*, 2017).

## 10. Pharmacological Studies

### 10.1. Experimental pharmacology

- Curcumin has lipoxygenase- and COX-2- inhibiting properties, thus it exhibits potent and promising anti-inflammatory activity. It has been seen effective in decreasing both acute and chronic inflammation in *in-vitro* and *in-vivo* studies.
- Curcumin has been seen effective as anticoagulant. It inhibits adrenaline-induced platelet and collagen aggregation (Srivastava *et al.*, 1985).
- Curcumin exhibits potent galactose-induced cataract activity. It reduced blood sugar level in rat given alloxan. Curcumin also decreases complications related glycation end products induced in diabetes mellitus (Kumar *et al.*, 2011).
- Curcumin inhibits 5a-reductase, which is proved to convert testosterone to 5a-dihydrotestosterone, which is seen inhibiting the flank organs enlargement in hamster. It also inhibits motility of human sperm and is also given in combination to treat in fertility (Rithaporn *et al.*, 2003).
- Due to the increase in the activity of the enzyme nitric oxide synthase and an increase in the levels of beta transforming growth factor, the topical administration of curcumin on diabetic rat has been successfully demonstrated for wound healing process (Kumar *et al.*, 2011).
- Various clinical and animal studies have demonstrated the ability of curcumin to inhibit different stages of carcinogenesis including inhibition of tumor promotion, angiogenesis, and tumor growth. Curcumin has been observed to inhibit cell proliferation and tumor growth in colon and prostate cancer (Kumar *et al.*, 2011).
- It has promising in cardiovascular effects, as well as a potent antimicrobial agent. Hence it is alternatively considered as miraculous herb in Ayurveda and other traditional medicine systems.
- Curcumin has demonstrated wide range antiviral activity against different viruses such as influenza virus, Respiratory syncytial virus (RSV), Herpes simplex 1 (HSV-1) papillomavirus virus (HPV), and Human norovirus (HuNoV) (Li *et al.*, 2019; Mathew *et al.*, 2018; Mounce, *et al.*, 2017; Pécheur, 2014).

- Oral administration of aqueous extracts of rhizome to mice from 140-560 mg for 14 days resulted in inhibition of mono amine oxidase (MAO). A activity while oral administration of 560 mg aqueous extracts resulted in inhibition of MAO B activity in mouse brain. These results demonstrated that consumption is related to antidepressant effects *in vivo* (Yu, Kong *et al.*, 2002).
- However, studies have also noted that the efficacy of curcumin relies not on the amount of curcuminoids ingested, but rather on the degree of curcuminoid absorption (Shimatsu *et al.*, 2012)

## 10.2. Clinical pharmacology

- Administration of curcumin with gemcitabine to patients with advanced pancreatic carcinoma revealed curcumin's anti-proliferative property and its interaction with several intracellular signal transduction pathways that activate and enhance the anti-tumor effect of gemcitabine thereby showing potential of curcumin as a promising compound for treatment of patients suffering from pancreatic cancer (Bar-Sela *et al.*, 2009).
- One study investigated the effect of curcumin consumption by healthy men and postmenopausal women on vascular endothelial function. Results demonstrated that curcumin intake improved vascular endothelial function by reducing oxidative stress and improving resistance artery endothelial function (Santos-Parker *et al.*, 2017). This study showed antioxidative capability of curcumin.
- A randomized clinical trial conducted on 112 patients with this extract (80% Turmerosaccharides and 20% Curcumin extract) demonstrated significant improvement in the knee pain and effusion-Synovitis of knee Osteoarthritis (Wang *et al.* 2019).
- A formulation containing *C. longa* and *Boswellia serrata* extracts (CB formulation) was evaluated for safety and efficacy in 54 osteoarthritic patients and directly compared with the selective COX-2 inhibitor, celecoxib. The observations related to this study demonstrated the extract safe with no dose related toxicity (Kizhakkedath, 2013).
- In a clinical study, the effects of curcumin compared to phenylbutazone or placebo for spermatic cord edema after surgery for inguinal hernia or hydrocele was evaluated. Forty-five patients (ages 15-68) received 400 mg curcumin. The results showed improvement in anti-inflammatory activity as measured by spermatic cord edema, spermatic cord tenderness, operative site pain, and operative site tenderness (Jurenka, 2009).

## 11. Toxicity and safety

Due to extremely poor bioavailability has not showed any toxicity to animals or human at recommended dose (Chainani-Wu *et al.*, 2003).

## 12. Clinical studies

Curcumin isolated from its rhizome is also used in rheumatism, liver disorders, anorexia. Several clinical studies have reported the efficacy of various curcumin formulations in improving condition of patients suffering from inflammatory bowel disease, chronic pancreatitis, hyperlipidemia, rheumatoid arthritis, cardiovascular diseases and cancer (Aggarwal, *et al.*, 2009; Basnet *et al.*, 2011; Jurenka, 2009 & Yang *et al.*, 2005).

- A clinical study on the effect of curcumin consumption on patients with acute coronary syndrome (ACS) reported that consumption of curcumin in low-doses resulted in effective reduction of Low density lipoproteins (LDL) and an increase in High density lipoproteins (HDL) in ACS patients (Alwi *et al.*, 2008).
- A daily intake of 500 mg curcumin capsules by ten healthy volunteers for seven days resulted in 33% decrease in serum lipid peroxides and a 12% decrease in total serum cholesterol levels indicating the positive impact of curcumin consumption on serum cholesterol levels and cardiovascular health (Soni *et al.*, 1992).
- The anti-cancer effect of curcumin consumption has been seen in some clinical trials, mainly as native chemoprevention against colon and pancreatic cancer (Bimonte *et al.*, 2016; Khan *et al.*, 2020).

## 13. Contraindications

Drug-Herb interaction can be seen while given with chemotherapy agents. According to reports 1 g curcumin daily for two weeks caused enhancement of CYP2A6 activity and inhibition of CYP1A2 function.

## 14. Precautions

- Not to be given in raw form to the patients undergoing chemotherapy (Chen *et al.*, 2010).
- Dose limit should not be crossed more than 2-2.5 g per day per person (Bar-Sela *et al.*, 2011).
- Contact may cause an allergic skin reaction in some people.

## 15. Adverse reactions

Overdose may cause stomach pain, fever, and blood pressure fluctuations.

## 16. Marketed formulation, if any

There are many marketed products of Curcumin. Some of them are given below:

- Curcumin C3 Complex by sports research used as anti-inflammatory and antioxidant. Curcumin 500 by Bio Nutrition used as Digestive Health, Immune Health, Joint Function, anti-inflammatory, anti oxidant.
- Curculas tablet manufactured by Estrellas Life Sciences Pvt Ltd containing curcumin 500 mg with Piperene is beneficial as anti-inflammatory, anti oxidant
- COPRIL capsules with same composition manufactured by PCD Pharma is also exhibiting results in nervous system along with its anti-inflammatory, anti oxidant uses.
- Onco-Norm manufactured by SAPIENS LABS and marketed by Med-Biologicals.
- Nenucun marketed by antra Pharma is also being used as dietary supplement.
- There are many other Ayurvedic, Unani, Traditional medicine system, Allopathic medicine based on curcumin used as dietary supplement, anti-inflammatory, antioxidant, prevent cancer, joint function.

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1. Botanical Name: ***Dillenia pentagyna* Roxb.**

2. Synonym: NA

3. Family: Dilleniaceae

#### 4. Common Names

Assamese:	Okshi, Oua, Ou-bonsolta
Bengali:	Ban Chalta Cach, Boncholta
English:	Dog Teak
Gujarati:	Karmal, Hin, Karmal, Kallai,
Hindi:	Aggai, Karmal
Kannada:	Kaadu Kanigalu, Koolateegu, Madathaega, Malegeru
Khasi:	Dieng-Soh-Bar
Malayalam:	Pattippunna,Kondappunna,Kattupunnakai,Kodapunna,
Marathi:	Piwala Karmal, Nepali, Tatera, Tantri
Oriya:	Railgatcho
Sanskrit:	Aksikiphala, Punnaga
Tamil:	Kalluccilaikay, Nay-t-tekku, Punnai Vakai, Naitekku
Telugu:	Revada, Chinna Kalinga, Partake, Ravadi chettu

5. Description: A medium-size deciduous tree, up to 50feet high. Leaves simple, alternate, spiral, clustered at the tip of branchlets, estipulate; petiole sheathing, stout, glabrous, winged; obovate to oblong-lanceolate, scarious, base acute or attenuate, apex obtuse, margin serrate, rarely entire, glabrous above, puberulent beneath; lateral nerves many, parallel, prominent, intercostae scalariform, faint. Flowers bisexual, fascicled on old branches, yellow, fragrant; bracts hairy; sepals obovate or elliptic, glabrous, accrescent; petals 5, obovate, obtuse, bright yellow; stamens numerous, yellow in 2 series, outer series with 60-90 stamens, inner series with up to 10 stamens; carpels 5-10, cohering at the axis, arranged on the narrow conical receptacle, unilocular, ovules many; styles free, 4 mm long. Fruit aggregate of berries, drooping, subglobose, indehiscent, fleshy, yellow, orange or red, subtended by persistent sepals. Seeds numerous, ovoid, black, glabrous, exarillate.

6. Distribution: China to Indo-Malaysia. In India, the plant is distributed in Punjab to Assam, South India, Andaman, Gujarat, Mizoram and West Bengal.

## 7. Part Used: Bark, Leave and Fruit



*Dillenia pentagyna* Roxb.  
(Photo S.L. Meena, BSI)

## 8. Medicinal/Therapeutic Uses

### 8.1. Uses described in pharmacopoeias and in traditional systems of medicine

Traditionally, the plant has been used by the local people of Mizoram to treat stomach ailments, inflammation and diabetes (Zothanpuia & Kakoti, 2017).

### 8.2. Uses supported by clinical data

A work was done to evaluate and validate the *in vitro* and *in vivo* anti-inflammatory activity that has been used in the folklore medicine of Mizoram to treat various ailments including inflammation. It was found that methanolic stem bark extraction of the plant could inhibit the inflammation effect which occur due to the presence of the constituents namely betulinic acid and  $\beta$ -sitosterol that actively interact with the inflammatory mediators and suppress the inflammation when evaluated *in vitro* and *in vivo* (Zothanpuia & Kakoti, 2017).

### 8.3. Traditional/Folklore Uses described in folk medicine

Fruit: The fruits are used as a medicine for Dropsy therapy (Nyman *et al.*, 1998).

Bark: It is used for treating swelling of the body and tick bites (Ghimire & Bastakoti, 2009).

Leaves, bark and roots: These are used for treating cuts and wounds, bone fracture, bleeding piles, diabetes, dysentery diarrhoea skin diseases, breast cancer and body pain (Dubey *et al.*, 2009).

### 8.4. Special uses in North East India

Meghalaya: Bark is used for the treating rheumatic pain, diabetics and stomach ache (Hazarika *et al.*, 2015).

Mizoram: Bark and wood is used for treatment of cancer and ulcer (Rai & Lalramnghinglova, 2010).

### 8.5. Dosage forms used in tradition

Bark: Decoction from the bark is orally taken for diabetes, while the paste made from the bark is applied on rheumatic pains (Rai & Lalramnghinglova, 2010). Decoction made from the stem bark is used for treating arthritis and gout (Singh, 2017). Stem bark juice is used among the Tharus of Nawalparasi district in Central Nepal against tick bites (Ghimire & Bastakoti, 2009). Two spoonful of bark decoction are orally taken for diabetics and for stomach ulcer (Hazarika *et al.*, 2015). The stem bark powder of 5-10g is mixed with water and given thrice a day for three months in case of diabetes and is also given for the treatment of diarrhoea and dysentery until it is cured. Filtrate obtained from pounded bark of 10g is mixed with 10g of crystal sugar and given to pregnant women for ease in delivery (Dubey *et al.*, 2009). 500g of the bark is boiled in water for 2-3 hours and given at 100ml twice a day before meal for treating hypertension (Khiangte & Lalramnghinglova, 2017).

Stem bark: Decoction from the stem bark of the plant is used for the treatment of stomach-ulcer and stomachic (Lalramnghinglova, 2016).

Leaves: The leaf juice is used as topical treatment for healing wounds (Prasad *et al.*, 2008). Paste made from leaves is applied daily on cuts and wounds as well as in bone fractures until cured. Leave decoction is used once a day daily to cure skin disease as well as for relieving body pain. 5-10g of leave powder is given to women for treating breast cancer (Dubey *et al.*, 2009). Decoction of the leaves for 10 ml, 2-3 times a day daily is taken orally for treating chest pain. 20ml bark decoction for 3-5 times daily is

given orally for the treatment of cancer. Leaf juice is applied externally for curing wounds (Sharma *et al.*, 2001).

Root: 25-50ml of root decoction is taken orally twice daily to relief body pain and cancer (Dubey *et al.*, 2009).

## 9. Phytochemical profile

### Major chemical constituents

- Stem: Two new flavonoids glycosides *viz.*, naringenin 7-galactosyl(1→4)glucoside and dihydroquercetin 5- galactoside isolated from stem tissues (Srivastava, 1981). A new saponin constituent from the stem is named as α-L-rhamnopyranosyl-3β-hydroxy-lup-20(29)-en-28-oic acid was isolated (Tiwari *et al.*, 1980).
- Stem bark: Methanolic extraction from the stem bark showed the presence of flavonoids, triterpenoids, steroids, phenolics, saponins, fixed oils and others exerting varied pharmacological activities (Zothanpuia & Kakoti, 2017).
- Bark, leaves, sepals, fruits and seeds: Phytochemical screening form different parts namely bark, leaves, sepals, fruits and seeds using different organic solvents *viz.*, chloroform, ethanol, and n-hexane was done and the result showed that constituents *viz.*, alkaloids, flavonoids, phenolic, terpenoids, tannins and saponins were extracted from the bark, leaves, sepals, fruits and seeds. The result also showed that phenolic compounds was higher in ethanolic extract of bark and leaves as compared to the other parts of the plant, while found that total flavonoids compounds was higher in the bark (Patle *et al.*, 2020).

## 10. Pharmacological activities

**Antiviral:** Stem bark has been reported to possess antiviral activity against Raniket disease virus (Aswal *et al.*, 1996 & Dhawan, 2012).

**Anti-tumour activity:** Evaluation on 5 plants collected from Mizoram (*Dillenia pentagyna*, *Ageratum conyzoides*, *Blumealan ceolaria*) and Meghalaya (*Potentilla fulgens* and *Taxus baccata*) were tested for their anti-tumour activity in Inbred Swiss albino mice against murine ascites Dalton's lymphoma *in vivo*. The result revealed that methanolic extraction from the stem bark of *D.pentagyna* exhibited significant inhibitory effects against Dalton's lymphoma cells (Rosangkima & Prasad, 2004).

**Anti-hyperglycemic activity:** Hydro-alcoholic extract of the fruit at a dose of 400 mg/kg body weight was found to exhibit a significant anti-hyperglycemic in the induced diabetic rats (Yadav *et al.*, 2017).

### 10.1. Clinical pharmacology

A study was made to investigate the antitumor and antimutagenic activity from the stem bark in murine model. The result denoted that methanolic extract from stem bark at a dose of 20mg/kg bw/day showed anti-tumour activity (%ILS~70%) against ascites Dalton's lymphoma, while antimutagenic activity was reported from a dose of 100mg/kg bw/day by inhibiting cisplatin (CIS) and benzo[a]pyrene (B[a]P) that induces chromosomal aberrations and sperm abnormality (Prasad *et al.*,2009).

11. Toxicity and safety: Not available.
12. Clinical studies: Not available.
13. Contraindications: Not available.
14. Precautions: Not available.
15. Adverse reactions: Not available.
16. Marketed formulation, if any: Not available.

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1. Botanical Name: *Dioscorea bulbifera* L.

2. Synonym: NA

3. Family: Dioscoreaceae

4. Common Names

Bengali:	Banalu, Gaichaalu, Kukuralu;
English:	Air potato, Air yam,
Gujarati:	Dukkarkanda,
Hindi:	Kandukanda, Ratalu, varahikanda,
Kannada:	Kuntagenasu,
Konkani:	Karamdo
Malayalam:	Kattukachil;
Marathi:	Manakund, kadu-karanda,
Sanskrit:	Varahikanda, Aluka, Shukara,
Tamil:	Kodikilangu, Pannukilangu;
Telugu:	Chedupaddu-dumpa, Malakakayapendalamu.

5. Description: A large climbing shrub with tuberous root stocks. Leaves ovate-suborbicular, base deeply cordate, apex acuminate to shortly caudate, membranous, glabrous, basally 9-11-ribbed; petiole to 20 cm long. Bulbils frequent in leaf axils and in inflorescence. Male flowers in slender, axillary panicled spikes, pendulous; bracteoles ovate, acute. Perianth light green; lobes 6, biserrate, linear-oblong. Stamens 6 free. Female spikes 1-3 together; staminodes 3; ovary triquetrous, 3-locular, ovules 2-per locule; styles 3; stigma 2-fid, reflexed. Capsules oblong, 3-winged.

6. Distribution: Native of the tropics of the old world; found in tropical regions; 700-900m altitude range. It is common throughout India ascending to 6,000 ft. in the Himalayas.

7. Part Used: Bulbils and tuber.



*Dioscorea bulbifera L*

## 8. Medicinal / Therapeutic uses

It is used for memory enhancement, anti-aging, constipation and fever (Odugbemi, 2008), its infusion used to apply cults and sores due to the presence of high tannins that is used to hasten the healing of wound in flamed membrane (Anona& Regiana, 2018). Bulbil of the plant has high content of steroidal saponin called diosgenin that is used against anti-fertility activity (Sajeela *et al.*, 2011). In addition to this plant used as contraceptives, sexual vigour remedy and piles treatment, ulcers, syphilis, leprosy, cough and diabetes (Ikiriza *et al.*, 2019) and antiviral activity against HIV and hepatitis B virus (Chaniad, 2016).

### 8.1. Uses described in pharmacopoeias and in traditional system of medicine

It has been reported that raw tubers are used for enhancing appetite (Kumar *et al*, 2017). Tubers are used as intestinal colic, relieving dysmenorrhea, reducing acidity,

used against rheumatoid arthritis; relieve inflammation, asthma, menopausal problems, labour pain, and prevention of early miscarriage, hernia, reliving the pain associated with child birth (Kumar et al., 2017). Bulbis of the plant is used to reduce the throat pain (Mbiantcha et al., 2011), boiled tubers are consumed orally to reduce body heat. Root paste mixed with cow milk taken for curing asthma and cough. For treatment of typhoid extract of tubers taken with wild turmeric (*Curcuma aromatic*). Tubers of the plant are boiled and given for abdominal pains. Dry tubers in the size of pea pieces are given early morning with water 3 days for curing piles (Kumar et al., 2017).

#### 8.2. Uses supported by clinical data: No data available.

#### 8.3. Traditional /folklore uses described in folk medicine

It is a prime staple medicinal-food substitute for most rural and local people of the state of India. The rural and local people use as food supplements make them edible by different traditional practices. Tuber powder prescribed with honey and milk for anti-aging effect and causes cell and tissue rejuvenation. It improves sperm and semen quantity, quality and used for impotency and infertility as male/female reproductive tonic. It also improves voice, digestion, strength, and immunity with balancing Kapha and Vata. Tubers are used in leprosy, asthma, cough, cold, tuberculosis, contraceptive, constipation, indigestion, abdominal pain, muscular pain, bone fracture, dysentery, sore throat, struma, wounds, boils, cuts, injury, carbuncle, and tumour and also used as refrigerant to reduce body heat during summer. Tubers are also used for the treatment of purgative, deflatulent, aphrodisiac, rejuvenating and tonic anthelmintic, haemorrhoids, scrofula, worm infestations, general debility and polyuric. Fresh tuber decoction cures laryngitis in children, insect bite, ring worm, goitre, and fever. Root powder is used as component of local medicine for tuberculosis (Kumar et al., 2017).

#### 8.4. Special uses in North East India

In Assam tubers are roasted, cooked as vegetables, as pig fodder. Root powders are used as a remedy for tuberculosis, diseases of lung, spleen, improving digestion and metabolism. Bulbils are used for remedies of typhoid in children, fresh tuber decoction used against laryngitis in children, insect bite, ring worm infection, fever and goitre (Dutta et al., 2015). Sikkim tubers and leaves are used as vegetables, tubers are used as remedy for aphrodisiac, stomach ache, improves appetite. Manipur it is used as antidiabetic and remedy for diarrhoea, tubers are used as vegetables. Tubers are used as remedies for piles, diabetics, dysentery and pyloric ulcer in Mizoram (Laha et al., 2016). In Meghalaya boiled and cooked tubers are used as food, one teaspoon of tuber powder is given orally once as single dose to cure abdominal pain. Nagaland tuber of the plant is used for the treatment of jaundice, headache, diuretic, and anthelmintic. Leaves are used for steam distillation for the treatment of conjunctivitis (Ozukum et al., 2019).

## 8.5. Dosage forms used in tradition

One spoonful of root powder, tuber paste is given with Curcuma aromatic, root paste given with milk.

## 9. Photochemical profile

Phytochemical profile reveals that the presence of saponins, tannins, flavinoids, sterols, sterols, tannins, flavinoids, polyphenols and glycosides (Ghosh *et al.*, 2015), steroid saponin (Tapondjou *et al.*, 2013). Phytochemical profile of this plant is varied depending on the geographical location type of plant part and solvent system used for extraction. It has been reported that 70% of ethanol extract showed the presence of flavonolaglycones, namely kaempferol-3, 5-dimethyl ether, caryatin, catechin, flavanol glycosides such as quercetin-3-O- galacto pyranosid, myricetin-3-O-galactopyranoside, and myricetin-3-O-glucopyranoside. In addition to this steroid spogenins namely diosbulbisins A, B, C, and D, diosbulbin N, P and O, spirostaneglycosides of diosbulbisides A,B and cholestan glycosides of diosbulbisiode C are abundantly found in ethanolic extract of zhizome (Tang *et al.*, 2014; Tapondjou *et al.*, 2013). Diosbulbin B is a demethylditerpenoid found as main component in chloroform fraction. Carotenoides such as zeaxanthin, leutin, neoxantins are commonly found (Ghosh, 2015), Compound of clerodanediterpenoides, bafoudiosbulbins A, B,C, F and G also present (Kuete *et al.*, 2012). Phytoalexin called demethyl batatasin IV and nor diterpenoid diosbulbin D .Dioscoreanosides of A,B,C,D,E,F,G,H,I,J, and K also found in this plant (Tapondjou *et al.*, 2013).

## 10. Pharmacological Studies

Several reports demonstrated that it has antidiabetic potential and frequently used in Indian and Chinise system as anticancer, antioxidant, antimicrobials, analgegesic, antiinflmatory and immunomodulatory function (Ghosh *et al.*, 2013). Diosgenin acts as inhibitor of  $\alpha$ -amylase and  $\alpha$ -glucosidase inhibitor. Ethanolic and ethyl acetates of the plant extract showed highest inhibition of 72% and 82% against  $\alpha$ -amylase and  $\alpha$ -glucosidase respectively. GC-TOF-MS analysis of ethyl acetate extract indicated presence of high diosgenin content. Molecular docking studies showed that Diosgenin interacted with two catalytic residues (Asp352 and Glu411) from  $\alpha$ -glucosidase. This studies highlighted diosgeninas novel drug candidate for type II diabetes mellitus (Ghosh *et al.*, 2014).Plant has potential activity against HIV. Studies showed that anti-HIV activity of 7 compounds of ethyl acetate and water fraction from bulbils. Flavanoid, myricetin showed potent anti-HIV-1 integrase activity (IC<sub>50</sub> value 3.15Mm), and 2, 4,6,7-tetrahydroxy-9,10-dihydrophenanthrene (IC<sub>50</sub> value 14.2Mm). These compounds have potential interaction with IN active site of enzyme. These compounds interacted with Asp64, Thr66, His67, Glu92, Asp116, Gln148, Glu152, Asn155, and Lys159, which are involved in both the 3'-processing and strand transfer reactions of integrase enzyme (Chaniad *et al.*, 2016; Okon, 2013, Ahmed *et al.*, 2009). Methanolic extract along with six isolated compounds such as

bafoudiosbulbins A, B,C,F, G and 2,7dihydroxy -4- methoxyphenanthrene from bulbils are tested for against mycobacterium and Gram negative bacteria involving multidrug resistance(MDR) phenotypes expressing active efflux pub. Results showed that extract has activity against 15 tested microbes. Activity of the samples on many MDR organisms such as *Enterobacter aerogenes* EA289, CM64, *Klebsiella pneumoniae* KP63 and *Pseudomonas aeruginosa* PA124 was better than that of chloramphenicol. Hence the crude extract as well asbafoudiosbulbins C can be used as potential antimicrobial drug to fight against MDR bacteria (Kuete, et al., 2012). Studies highlighted the green silver nanoparticle synthesized and the extract showed synergistic potential for the enhancement of antibacterial activity of broad-spectrum antimicrobial agent (Ghosh et al., 2012).Ghosh et al., (2015) synthesized nanoparticles of platinum palladium bimetallic and synthesized nanoparticles showed anticancer activities in Hela cells with 75% cell death along with enhancing antioxidant scavenging activity against 2,2-diphenyl-1-picrylhydrazyl, superoxide, nitric oxide, and hydroxyl radicals. From the methanolic extract evaluated for cell inhibition and antioxidant properties (Chen et al., 2013).

#### 10.1. Experimental pharmacology

Studies conducted for the effect of polysaccharides on cervical cancer. The oral treatment of polysaccharides (DBLP) at concentration of 100-150mg/kg in U14 cervical tumour bearing mice treated with Cyclophosphamide (CTX) (25 mg/kg). DBLP alone also inhibited tumour (25.6% at 100 mg/kg or 37.6% at 150 mg/kg), CTX+DBLP combination produced tumour inhibition rates of 5.6 -9% higher than CTX alone. While tumour itself and CTX treatment reduced thymus and/or spleen/body weight. Whereas DBLP alone or CTX + DBLP combination attenuated this reduction. DBLP lowered peripheral blood T-cell subpopulation CD4+/CD8+ ratio, and DBLP+CTX combination attenuated CTX effect in lifting CD4+/CD8+ ratio. Tumor itself and CTX treatment heightened oxidative stress whichwas attenuated by DBLP treatment, and DBLP+CTX combination suppressed CTX-induced oxidativestress. Combination use of DBLP with CTX can potentially enhance CTX anti-tumor effect and can attenuate CTX-induced immunosuppression and oxidative stress in U14 cervical tumor-bearing mice (Cui et al., 2016).The anti-hypernociceptive properties of ethanol extract of *D. bulbifera* tested in persistent inflammatory and neuropathic models of pain in mice model and result highlighted the plant is equipped with pharmacological analgesics properties and probably anti-inflammatory properties (Mbiantcha, 2011).

#### 10.2. Clinical pharmacology: Not yet done.

### 11. Toxicity and safety

The curative properties for various diseases have been reported but it has toxic effect especially liver toxicity. Disocene and diosbulbin B from Chinese plant root are responsible for the liver toxicities, abdominal pain, coma and even death. Hepatotoxicity of the plant is reported for methanolic extracts and its chloroform

fractions (Ma *et al.*, 2011). Hepatotoxic effect mediated by the plant is mainly due to changes in the metabolites such as elevated levels of creatine, taurine, dimethylglycinacetate and glycine and decreased level of urea, hippurate and succinate 2-oxoglutarate (Liu *et al.* 2010). Study showed that toxicity can be reduced by autoclaving. During autoclaving hydrogen cyanide present in the plant material is reduced by 93% and 75% reduction in total free phenolics. Other component such as amylase inhibitor, trypsin inhibitor, tannins and oxalates are reduced (Santhakumari *et al.*, 2008).

Hepatotoxicity can be reduced combination with other plant it has synergistic effect on detoxification. Niu *et al.*, (2015) reported that scutellarin from *Scutellaria barbata* prevented diosbulbin induced liver injury through attenuating NF-Kb mediated hepatic inflammation and ameliorating liver oxidative stress injury.

#### 12. Clinical studies: not yet reported.

#### 13. Contraindications

*Dioscorea* contains chemicals like the drug digoxin. Consuming this plant along with digoxin might increase the effect of digoxin and increase the risk of side effect.

#### 14. Precautions

Do not eat raw plant as medicine. It contains chemicals like digoxin (lanoxin), which causes irregular heartbeat. Certain chemicals of the plant cause seizures. Female should be taken care while consuming this plant it will affect fertility.

#### 15. Adverse reactions: NA

#### 16. Marketed formulation:

Ajamamsa Rasayanam, Narasimha Churna, Pancha Nimbadi Churna, Vastyamayantaka Ghrita, Varahytadighurdam and substitute for Riddhi and Vridhhi drugs of Astavarya in Ayurveda.

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1. Botanical Name: ***Elaeocarpus tectorius*** (Lour.) Poir.

2. Synonym: *Craspedum tectorium* Lour.

3. Family: Elaeocarpaceae

4. Common Names

Assamese : Agong, Bolrogong

Garo : Poreng, Seleng

Khasi : Dieng-sohkhylam, Dienglasw

5. Description: Tree up to 50 feet high. Leaves simple, alternate, spiral; petioles thickened at both ends, often with 2 glands near apex, glabrous; elliptic-oblong to ovate-oblong, broadly cuneate to rounded at base, acute to acuminate at apex, repand-serrate, veins prominent beneath, coriaceous, rusty pubescent when young, glabrous; secondary nerves 12-14 pairs. Inflorescences in axillary; flower buds oblong-ovoid, acute; Flowers white; grey puberulous; sepals lanceolate or ovate, acute, densely villous along margins; petals, cuneate-oblong or obtiangular, laciniate at apex, ciliate along margins; stamens 50; filaments glabrous or minutely puberulous; anthers, oblong, puberulous, rarely with a few bristles at apex; disc thick, 5-lobed, tomentose; ovary, oblong to ovoid, downy, 3-loculed; styles hairy. Fruits ellipsoid or oblong-ovoid, greenish-yellow; pyrenes 2-3 locular, with 2 longitudinal grooves prominently rugose. One seeded.

6. Distribution: It is distributed to India, Sri Lanka, Myanmar, Indo-china, Malaysia. In India found in tropical and sub-tropical region, grows in evergreen forests at 1000-2000 m altitude.

7. Part Used: Leaf, Bark and Fruit.



*Elaeocarpus tectorius* (Lour.) Poir.

## 8. Medicinal Therapeutic Uses

The methanolic extract of the leaf is shown to have an effect on the respiratory problems. The fruits show efficient activities and can be recommended as an herbal drug formulation for treating urinary tract infection (UTI) (Manoharan *et al.*, 2019).

### 8.1 Uses described in Pharmacopoeias and traditional systems of medicines

Traditionally, tribal communities utilize the fruits to treat various microbial infections and diseases including rheumatism and piles (Nayagam *et al.*, 1993, Mundaragi *et al.*, 2017).

### 8.2 Uses supported by clinical data: Not available

### 8.3 Traditional uses described in Folk medicine:

Traditionally this plant has been used for the treatment of pneumonia, ulcers, piles, rheumatism, leprosy (Nayagam *et al.*, 1993)

### 8.4 Special uses in Northeast India: Not available

### 8.5 Dosage forms used in tradition: Not available

## 9. Phytochemical profile

The major chemical constituents found in the fruits are Glucose, fructose, flavonoids, sterols, tannins, fatty acid, and various phenolic compounds such as gallic acid, trans cinnamic acid, vanillic acid, p-coumaric acid, ferulic acid, syringic acid. Some of the volatile compounds in methanolic extract are also present such as 5-hydroxymethylfurfural, 1,6-anhydro-D-glucopyranose, 1,5-D-mannitol (Muthuswamy, 2014). Four phenethylamine-containing alkaloids were isolated and identified from the leaf crude extract. Tectoricine possesses isoquinuclidinone ring system that

incorporates a phenethylamine moiety, while tectoraline is an alkamide moiety (Ezeoke *et al.*, 2018). Ogundele & Das (2019) reported four fatty acids, three diterpenoids, one triterpene alcohol, two fatty alcohols, three phaeophytins, one phytosterol, one sesquiterpene, and three hydrocarbons from the hexane extract of the leaves.

## 10. Pharmacological activities (as per available literature)

### 10.1 Experimental pharmacology

In the methanolic extract the total flavonoid & phenolic content was recorded as 1.25mg CE/g DW and 10.96 mg CE/g DW which also proves the high reducing power. The antioxidant and nutraceutical value were reported by the (Mundaragi *et al.*, 2019). The stem and stem bark biological activity tests such as antibacterial, antifungal, antiviral, effect on respiration, on the uterus, diuretic, central nervous system, and anti-inflammatory were carried out in rat model system and its effect is promising (Abraham *et al.*, 1986). Manoharan *et al.*, (2019) showed efficacy against UTI.

### 10.2 Clinical Pharmacology: Not available

11. Toxicity and safety: The LD<sub>50</sub> test of the bark, stem and leaf is 175mg/kg, 1g/kg and 464mg/kg respectively. (Abraham *et al.*, 1986)

### 12. Clinical studies: Not available

### 13. Contraindications: Not available

### 14. Precautions: Not available

### 15. Adverse reactions: Not available

### 16. Marketed formula if any: Not available

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1. Botanical Name: ***Elephantopus scaber* L.**
2. Synonym: NA
3. Family: Asteraceae
4. Common Name:

Bengali:	Hasti pod
English:	Elephant foot, Prickly leaved elephant foot,
Garo:	Achaksn Hindi: Samdudri, Ban Tambaku,
Kannada:	Hakkarike
Khasi:	Kynbat-skur-sniang
Malayalam:	Anayatiyan
Sanskrit:	Gojivha,
Tamil:	Yaanaichhuvadi
Telugu:	Enugabira
5. Description: A rosette, perennial, scabrous; rootstock creeping herbs up to 60 cm high.. Leaves sessile, in radical rosettes; obovate, oblong-lanceolate, cuneate-attenuate at base, subacute at apex, margin serrate; cauline leaves alternate, few, undersurface pale-brown tomentose. Heads solitary, glomerate, terminal, each subtended by 3-8-cordate, foliaceous, conduplicate, bracts. Involucral bracts 4-seriate; outer subulate; inner lanceolate. Florets pink-purple. Fruit achenes truncate, 10-ribbed, pilose; pappus 1-seriate, white, comprising 4-5-bristles.
6. Distribution: Widely distributed in tropical areas of Africa, America, and Asia. In India(Assam, Andaman & Nikobar). Its natural habitat is subtropical or tropical moist mountain forests.
7. Part Used: Whole Plant



*Elephantopus scaber* L. (Photo A N Shukla, BSI)

#### 8. Medicinal /Therapeutic Uses:

It is mucilaginous and is considered a cardiac tonic, an astringent, an alternative, a febrifuge, a diuretic and an emollient (Panda, 2004) reported it as potent antimicrobial drug of natural origin. Anti-asthematic (Sagar & Sahoo, 2012).

##### 8.1 Uses described in pharmacopoeias and in traditional systems of medicine:

It has been used in traditional medicine to stimulate diuresis, reduce fever and eliminate bladder stones, as well as to treat nephritis, edema, dampness, chest pain, pneumonia, scabies, arthralgia and leukemia (Ho *et al.*, 2009). Anti-asthematic (Sagar & Sahoo, 2012). As per the traditional claims, roots were used as an antipyretic, cardio tonic and diuretic (Nadkarni, 1954). Decoction of roots and leaves is used as emollient and given in dysuria, diarrhea, dysentery and in stomachic pain (Kirtikar & Basu, 1991). The aqueous extract of leaves is applied externally to treat eczema and ulcers (Chopra *et al.*, 1956). It is used in traditional folk medicine for the treatment of nephritis, oedema, dampness, pain in the chest, fever, scabies, arthralgia due to wound and cough of Pneumonia. It is also used as a tonic, febrifuge, and diaphoretic against cough, bronchitis, and asthma (Kabiru & Por, 2013).Studies reveal various pharmacological

activities attributed to its phytochemical content which include analgesic, anti-inflammatory, antidiabetic, antiasthmatic, antimicrobial and wound healing properties (Kabiru & Por, 2013).

#### 8.2 Uses supported by clinical data:

Chan *et al.*, (2015) reported potential therapeutic effect for colorectal cancer.

#### 8.3 Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data:

The root decoction is given to orally to prevent inflammation after child birth, it ease the gastric related problem. It is used to treat hepatitis, cough related abnormalities; root paste is used by the local people as antivenome (Wan *et al.*, 2009).

#### 8.4 Special uses in North east India:

People of North east use this plant as a medicinal herb against various diseases such as, diaphoretic, diuretic, pulmonary diseases emmenagogue, emollient, febrifuge and tonic. A decoction is used to treat fungal skin diseases. It is also used to treat conditions such as oedema, asthma, coughs and; dyspepsia, diarrhea, urethral discharges and venereal diseases.

#### 8.5 Dosage forms used in tradition:

Used for the treatment of toothache as a toothbrush (Achuta *et al.*, 2010). Also, the whole plant has been reported to be useful for curing insomnia, diabetes, bronchitis, viral or bacterial infection, leukaemia, rheumatism, snake bite, diuresis, antipyresis, to eliminate bladder stones and for filariasis. The leaves crushed and mixed with salt is used to treat dysentery (Achuta *et al.*, 2010), while the water extract of the leaves is applied externally to treat eczema and ulcers (Daniel, 2006; Jasmine & Daisy, 2008).

### 9. Phytochemical profile:

The phytochemical study showed that it is a rich source of bioactive molecules which are broadly classified as terpenoids & flavonoids, quinones, phenols, alkaloid, steroids, glycosides & essential oils. (Ahmed *et al.*, 2009) identified stigmasterol, lupeol, stearic acid, deoxyelephantopin isomers, analogue 1 and analogue 2 of deoxyelephantopin by soxhlet extraction. Phytochemicals such as deoxyelephantopin, 11,13, dihydrodeoxyelephantopin, lupeol, epifriedelinol and stigmasterol have been isolated from this plant (Ho *et al.*, 2009). A compound isolated from different solvent fractions of the plant includes elephantopin, triterpenes, stigmasterol epifriedelinol and lupeol. Other compounds are copaene isopropyl dimethyl hexahydronaphthalene, cyclosativene and zingiberene from the essential oils (Kabiru & Por, 2013, Sridhar *et al.*, 2012) reported

aqueous extracts contains carbohydrates, tannins, saponins, proteins and flavonoids while the methanol fraction contains alkaloids in addition to the phytochemicals present in the aqueous fraction (Kabiru & Por, 2013, Ahmad *et al.*, 2009) isolated stigmasterol, lupeol, stearic acid deoxyelephantopin isomers, analogue 1 and analogue 2 of deoxyelephantopin compounds by using n-hexane (polar) and methanol (non polar) solvent from roots, leaves and stem. Ho *et al.* (2009) reported Cyclosativene, Copaene, Isopropyl dimethyl hexahydronaphthalene, zingiberene, trimethyldimethylene-decahydronaphthalene, caryophyllene, dimethyl-6-(4-methyl-3-pentenyl), norpinene – $\beta$  sesquiphellandrene,  $\beta$  caryophyllene, Isocaryophyllene,  $\alpha$ -santalol Ledol,  $\alpha$ -bisabolol, caryophyllene oxide, cadinol, bisabolol, Isopropyl dimethyl- tetrahydronaphthalenol, hexahydrofarnesyl acetone, hexadecanoic acid, phytol and octadecadienoic acid.

## 10. Pharmacological Studies:

Most of the major studies only involved the bioactivities of the compounds especially deoxyelephantopin (Ho *et al.*, 2009). Major sesquiterpene lactones Isolated from ethyl acetate fraction are Deoxyelephantopins show anti-cancer activity by inducing both intrinsic and extrinsic apoptotic pathway in Human colorectal cancer cell line HCT116 (Chan *et al.*, 2015). Anti-asthmatic (Sagar & Sahoo, 2012). The aerial parts and leaf extract from petroleum ether, chloroform & methanol which is 0.1-1.5mg/ml is effective against multidrug resistance bacteria like *Salmonella paratyphi A*, *Klebsiella pneumonia*, *Staphylococcus aureus*, *Salmonella typhimurium* (Jenny *et al.*, 2014). The ethanol extract and deoxyelephantopin isolated from the plant were observed to promote healing of wounds in rat, (Singh *et al.*, 2005).

### 10.1 Experimental pharmacology:

**Antimicrobial:** The acetone extract contain a terpenoid, which is identified as 6-[I-(10,13-dimethyl 4,5,8,9,10,11,12,13,14,15,16,17- dodecahydro- 1Hcyclopenta[a] phenanthren -17-yl) -ethyl] -3-methyl-3,6- dihydro-2 H-2- pyranone ,had shown the activity against multi drug resistant bacteria which produce Extended spectrum Lactamase (ESBL) (Jenny *et al.*, 2014; Jasmine *et al.*, 2007). Jenny *et al.*, (2014) reported effectiveness against multidrug resistance bacteria, antimicrobial (Avanti& Neeta, 2005; Ganga Rae *et al.*, 2012), antimicrobial (Sridhar *et al.*, 2012),

**Antidiabetic:** A new steroid with aniline was identified in the acetone extract found to reduce glucose level in blood of hyperglycemic rats(Jasmineet *al.*, 2007), methanol extract, acetone extract and aqueous fractions showed excellent hypoglycemic effect (Daisy *et al.*, 2009, Daisy & Jasmine, 2008).

**Antiviral:** The aqueous extract of the leaves & root is shown to possess an inhibitor having anti-HIV-1 RT activity, its mode of action is noncompetitive with respect to the

substance (ditto) (Wawa & Kwantrairat, 2014), one of the important sesquiterpene compound sesquiphellandrene isolated and it shows anti-rhinoviral activity (Wang *et al.*, 2004).

**Hepatoprotective activity:** The hepatoprotection activity is seen in the ethanol extract of the whole plant against alcohol induced liver damage in mice (Hoet *et al.*, 2012; Hung *et al.*, 2011; Sheeba *et al.*, 2012; Kabiru & Por, 2013).

**Antiasthmatic:** The ethanolic extract of leaves 250-500mg/kg has significantly reduce the bronchospasm by increasing synthesis of collagen & the rate of wound contraction (Sagare *et al.*, 2012)

**Antioxidant activity:** Antioxidant properties of plant (Ganga Rao *et al.*, 2012), root (Sheeba *et al.*, 2012; Kabiru & Por, 2013).

**Antitumor:** Antitumor effect of the isolated sesquiterpene lactones was reported by (Lee *et al.*, 1975, Fuchino *et al.*, 2001; Kabiru & Por, 2013).

**Other activity:** Antidiarrheal and cardio tonic activity (Muthiumani *et al.*, 2010; Kabiru & Por, 2013), wound healing (Singh *et al.*, 2005).

## 10.2 Clinical pharmacology:

Xuet *et al.*, (2006) reported antitumor activities of sesquiterpene lactone deoxyelephantopin.

## 11. Toxicity and safety:

The aqueous or hydroalcoholic extract of the whole plant were higher than 2-6g/kg when administered orally or intraperitoneal which proves its low acute toxicity (Poliet *et al.*, 1992). Hence the extracts could be nontoxic for oral administration to a concentration 5g/kg in mice (Battuet *et al.*, 2012). The following safety test was reported: Arsenic: Not more than 5.0 mg/kg; Mercury: Not more than 0.5 mg/kg; Lead: Not more than 10.0 mg/kg; Cadmium: Not more than 0.3mg/kg. In the practice of traditional medicine, it should not be prescribed for pregnant women and should be prescribed at low concentration for children (Bhattarai, 1989; Poli *et al.*, 1992).

## 12. Clinical studies:

A clinical study on diuretic effect was carried out in 10 human individual volunteers, the quantity taken was 7.5g/100ml, no significant changes were observed. (Wright *et al.*, 2007; Laranja *et al.*, 1991)

## 13. Contraindications: not available

14. Precautions: Breastfeeding and Pregnant women should avoid its use.

15. Adverse reactions: Not mentioned

16. Marketed formulation if any: No product (either crude extract or the compounds isolated from the plant can be found in the international market (Ho *et al.*, 2009).

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1. Botanical Name: *Eryngium foetidum* L.

2. Synonym: NA

3. Family: Apiaceae

4. Common Names

Assamese:	Man-dhonia, Jangali Memedhu, Brahma memedhu,
English:	Long coriander, spiny coriander, Mexican coriander
Hindi:	Ban dhana
Sanskrit:	Phiranga
Manipur:	Awa phadikom

5. Description: An spreading very aromatic, glabrous, perennial herbs up to 40 cm high with tuberousroots; stems dichotomously branched, deeply striate. Leaves simple; basal spatulate, spinous and toothed; lamina, oblanceolate-spatulate, cuneate at base, obtuse at apex, margin spinous-toothed; cauline sessile, palmately 3-5-partite; lobes oblong, spinous toothed. Flowers white, in oblong-cylindrical umbels; bracts spinulose, stellate-pubescent; calyx teeth rigid, acute; petals white. Fruit ellipsoid.

6. Distribution: It is native to Mexico, the Caribbean, Central and South America, but is cultivated worldwide, sometimes being grown as an annual in temperate climates. It is introduce and cultivated many states from tropical to temperate places.

7. Part Used: Whole Plant.



*Eryngium foetidum* L.

## 8. Medicinal/ Therapeutic Uses

In China this plant is widely used for the treatment to reduce inflammation around the body (Paul, et.al., 2011, Nataraj, et.al., 2020, Seraj,et.al., 2012, Wang, et.al., 2012). Treat any type of body pain due to injury, rheumatic pain, crushed leaves and applied twice daily in the morning and evening for 2 hours at a time to painful areas for 7 days (Seraj, et.al., 2012). Six communities register the plant as being useful for female reproductive problems such as infertility, childbirth complications, menstrual pains, ease of delivery, postpartum abdominal pains, and vaginal infections and as an emmenagogue (Paul et.al., 2011).

In Carribean island dry leaves were used to cure diarrhea, stomach ache, cold, fever nausea, malaria. Leaves, roots and fruits are crushed and taken even for snake bite, high blood pressure and stomachache trouble(Prakash et.al., 2014). It is used for the treatment of diabetes, rheumatism, several anti-inflammatory, respiratory (cold, asthma, cough, sinusitis), and stomach disorders (Thomas et.al., 2017).

### 8.1. Uses described in pharmacopeias and in traditional system of medicine

It is a commonly used traditional spicy herb distributed in the tropical parts of the world. It has long been used to treat fever, vomiting, diarrhea, hypertension, arthritic pain, constipation, asthma, stomachache, worms, infertility complications, snake bites, diarrhea, and malaria. Phytochemicals such as lutein,  $\beta$ -carotene, chlorogenic acid, kaempferol, and caffeic acid were reported from the plants (Swargiray et.al., 2016).The traditional uses recorded for this herb, are numerous and mainly medicinal. In Tropical

America and the West Indies where the plant is indigenous, the prevailing use of the plant is to treat fevers, colds, vomiting, the flu and as food (Janwitthayanuchit et.al., 2016, Dawilai, et.al., 2013). In Surinam a treatment for colds is even prescribed for babies. Here a decoction of the leaves is used to bathe the child and a small amount of the mixture is given to drink. For fever the leaves and roots are mixed with coconut oil (*Cocos nucifera*) and the child is rubbed (Paul et.al., 2011). In Chinese traditional medicine it widely used for treatment of inflammation(Erdem et.al., 2015).

Ancient tribes such as those of Mexico, the Caribs of the Caribbean, the Rama midwives of Nicaragua and the Apantani Indians of India used various preparations of the plant mainly for pains such as stomach aches. However, it is noted that a possible side effect resulting from consumption of the crushed plant material is constipation. Six communities register the plant as being useful for female reproductive problems such as infertility, childbirth complications, menstrual pains, ease of delivery, postpartum abdominal pains, and vaginal infections and as an emmenagogue. In Brazil a decoction of the whole plant is used to ease delivery, but is contraindicated for pregnancy because it is reported to provoke uterine contraction. Costa Ricans regard the plant as an aphrodisiac but no mention is made of the affected sex(Paul et.al., 2011).

Other notable ailments for which this plant has been used includes hypertension, rheumatism, asthma, digestive problems, diarrhea, headache, eye disease, poisoning, venereal disease (VD), diabetes, as a vermicide, fits, pain, malaria and snake bites. The plant extracts were hardly effective when tested for activity against fibroblast cell lysis after treatment with *Heterometrus laoticus* scorpion venom(Paul et.al., 2011, García et.al., 1999, Janwitthayanuchit et.al., 2016).

## 8.2. Uses supported by the clinical data

- Pain relief is generally known to reduce inflammations around the body parts such as bone joints, muscle contractions and a host of other pains. To efficiently use this plant as a pain reliever; cut out the leaves and boil them, apply the hot water on the body parts or drink(Erdem et.al., 2015).
- Roots decoction is taken as a sudorific, diuretic, febrifuge, abortifacient, stomachic and stimulant.
- Juice or a decoction of the leaves is used as a stimulant, as a laxative and as a remedy for colds and fever.
- The leaves are febrifuge, laxative.
- The hexane extracts from the leaves can reduce the edema, induced by 12-O-tetradecanoylphorbolacetate (TPA) in the mouse, in a similar proportion in acute and chronic assay(Wang et.al., 2012).

- In Malaysia decoction were prepared from the leaves to cure abdominal pain, digestive ailments, and vaginal infections. Leaves, roots and fruits are crushed and taken even for snake bite.

### 8.3. Traditional/ Folklore Uses described in folk medicine, not supported by experimental or clinical data

Leaf decoction is used in traditional medicine as vulnerary, hypotensive and for digestive troubles. The crushed leaves are placed in the ear to treat pain, and are used for the local treatment of arthritic processes (García et.al., 1999).

In China it is widely used for the treatment of inflammation and several diseases as traditional medicine (Erdem et.al., 2015, Nataraj et.al., 2020). In Thailand people used to treat toothache and digestive problems. In Caribbean countries it has been traditionally used for venereal and gastrointestinal problems. In northern part of Iran leaves were used for its multiple beneficial effects on human health. Peoples used to cure diarrhea and headache in Turkey. From the leaves decoction and infusion were prepared to cure fever, flu, diabetes, hypertension, constipation diuretic, anti-convulsant, cold, muscular pain in South East Asia. In Caribbean island dry leaves were used to cure diarrhea, stomach ache, cold, fever nausea, malaria. Leaves, roots and fruits are crushed and taken even for snake bite (Nataraj et.al., 2020).

### 8.4. Special uses in North East India

- In Northeastern region of India especially it is used as a food, the leaves are added to curries, chutneys, stews, cooking non-vegetable and soups as a flavouring agents and medicine (Sinha & Singh, 2019). In Assam the local name “gongar dhundia” is one of the most commonly used traditional plants of lower Assam used as medicine and food(Swargiray et.al., 2016).
- It is used for garnishing as it has a strong flavor and is also used as a salad in a Northeast India (Sinha & Singh, 2019).

### 8.5. Dosage forms used in tradition

In tradition dosage forms used in liquid, paste and oil form.

According to the Study of the Bede community traditional medicinal practitioners of Porabari village in Dhaka District, Bangladesh treat any type of body pain due to injury, rheumatic pain, crushed leaves and applied twice daily in the morning and evening for 2 hours at a time to painful areas for & days (Seraj et.al., 2012; Sinha & Singh, 2019).

The leaves, stem , seed and roots part used to treat infusion fever, flu, diabetes, hypertension, diuretic, anti- convulsant, constipation colds, heat, muscular pain, diarrhea, snake bite, aerie, malaria, abdominal pain, postpartum abdominal pain fever, digestive ailments, virginal infection, cold fever stomach ache, asthma rheumatism, eye disease, VD remove pains. (Paul et.al., 2011), (Nataraj et.al., 2020).

The paste from the leaves and stem is applied on the forehead as remedy for headache. Decoction prepared from leaves is used to cure common cold in babies. The baby is bathed in small amount of decoction and a little amount of the decoction is drunk. To cure fever in child, the leaves and the roots. It is mixed with blauwsel and coconut oil and the body of the baby is rubbed with it (Sinha & Singh, 2019). Here a decoction of the leaves is used to bathe the child and a small amount of the mixture is given to drink. For fever the leaves and roots are mixed with coconut oil (*Cocos nucifera*) and the child is rubbed (Paul et.al., 2011).

Paste form crushed the leave and stem is applied on the forehead as a remedy for headache and Roots of the plant take oral treat in stomach trouble (Prakash et.al., 2014).

## 9. Phytochemical profile

1. Phytochemical screening of mentholic extracts is found alkaloids, flavonoids phenol, antharaquinones, steroids (Swargiray et.al., 2016; Janwitthayanuchit et.al., 2016).

The major chemical constituents fresh leaves contains 87% moisture, 6.5% carbohydrate, 3.3% protein, 0.6% fat, 1.7% ash, 0.06% Phosphorous, 0.02% iron, Vitamin A (10 IU/100g), vitamin B2 (60 mg/100 g), vitamin C (150-200 mg/100g). On a dry weight basis leaves consist of 0.1–0.95% volatile oil, 27.7% crude fiber, 1.23% calcium, and 25 ppm boron . It also contains saponins, flavonoids and essential oil, while the root contains triterpene saponins, monoterpene glycosides, and phenolic compounds such as phenolic acids, coumarin derivatives, terpene aldehyde esters, acetylenes, essential oils and oligosaccharides (Nataraj et.al., 2020; Wang et.al., 2012).

## 10. Pharmacological Studies

Bioactivity and pharmacological properties have been evaluated for antihelmintic, anti-convulsant, anti-inflammatory, analgesic, antimalarial and antibacterial properties that were reported from traditional use. One major limitation of these tests is that they were done in vitro or on animal models and therefore lack the clinical data which determine their suitability for human use.(Paul et.al., 2011; Janwitthayanuchit et.al., 2016).

### Anthelmintic activity

In Jamaica, the refined plant extracts rich in eryngial (E-2-dodecenal) appeared to be remarkably antihelmintic during in vitro screening using *Strongyloides stercoralis* (infective larvae) as the test organism. This is an important observation, because *Strongyloides stercoralis* (threadworm) infection is clinically the most severe parasitic disease of humans in the Caribbean region, and this skin-penetrating parasite is the cause of long-enduring, low-grade internal infections. The research findings of Forbes et al., in (2002) were elaborated into a US patent application on new methods for treating infectious diseases in humans and other mammals, which were caused by parasitic

trypanosomes, bacteria and fungi and by parasitic nematodes. These discoveries suggest a possible role in veterinary medicine (Paul et.al., 2011; (Janwitthayanuchit et.al., 2016).

#### Anti-convulsant activity

It is used extensively in traditional medicine to treat fits in Jamaica. A pharmacological evaluation using 3 mL of an aqueous extract prepared at a concentration of 110 g/250 mL demonstrated anti-convulsant activity in rats with picrotoxin-induced (4.5 mg/kg i.p.) convulsions. In a review entitled "Phytotherapy in Epilepsy". The aqueous extracts, boiled or that obtained by steam distillation of the leaves and stems, when administered intraperitoneally to rats, were shown to be as effective in treating epilepsy as the phenobarbitone control. Epilepsy is a disorder of the nervous system which depending on severity can lead to death of the patient. The results which present evidence of anti-convulsant activity in the plant extracts have been available since 1986 yet, to date the component(s) responsible for this activity have not been explored. (Paul, et.al., 2011, (Janwitthayanuchit et.al., 2016).

#### Anti-inflammatory and analgesic activity

An organic extract from the leaves rich in stigma sterol (95%), was shown by Garcia et al. to display topical anti-inflammatory activity on chronic and acute inflammation in effects. For a number of tropical plants these properties are displayed by polyphenolic compounds. Preliminary evaluation of the blood glucose lowering effects of the plant (at 351 mg/kg and 176 mg/kg) on three animal models (normoglycaemic rats, streptozotocin-induced diabetic rats and normal rats) subjected to the oral glucose-tolerance test, revealed that a single (acute) oral dose of the leaf extract does not cause significant reduction in the level of glucose of the models tested. Also the polyphenolic content of the plant was not significant. These results suggest that the plant is not likely to be a candidate in the management of blood sugar of diabetic patients.(Paul et.al., 2011; García et.al., 1999).

#### Antibacterial activity

The *in vitro* bactericidal effects of several plant extracts against plant pathogenic bacteria from mango (*Mangifera indica*), sunflower (*Helianthus annuus*), papaya (*Carica papaya*) and banana (*Musa* sp.), the greatest effects were found with coriander against the *Erwinia* genus of Enterobacteriaceae. However when subjected to *in vitro* tests against Helicobacter species isolated from gastric biopsy samples, methanol extracts showed only weak activity when applied at a concentration of 1 mg/mL. In yet another study by Kubo et al., pure E-2- dodecenal ("eryngial") showed potent activity (minimum bactericidal concentration, MBC of 6.25 µg/mL) (34 µM), against *Salmonella choleraesuis* at all growth stages. Since the extracts from the aerial part of the plant were negative when screened broadly for antimicrobial activity, and displayed limited toxicity against brine shrimp (6.7% compared to the lapachol control which showed

100% toxicity) , the observed antibacterial activity maybe highly specific, targeting only a limited number of organisms(Paul et.al., 2011; Janwitthayanuchit et.al., 2016).

#### Antimalarial activity

The whole plant extracts were tested for *in vitro* anti plasmodial activity against *Plasmodium falciparum*. The results (IC<sub>50</sub>N25 µg/mL) suggest that the potential of this plant as an antimalarial drug for humans is low despite the claims of traditional use. Interestingly in the screening of the aqueous extract of the entire plant against various species of Plasmodium, activity was only reported against *P. gallinaceum* which infects chickens thereby suggesting another possible veterinary use(Paul et.al., 2011; Janwitthayanuchit et.al., 2016).

#### Anti-diabetes activity

Folklore reports make moderate mention of the plant in the treatment of diabetes. An ideal anti-diabetic compound should possess both hypoglycemic and antioxidant properties, with no adverse effects. For a number of tropical plants these properties are displayed by polyphenolic compounds. Preliminary evaluation of the blood glucose lowering effects of the plant (at 351 mg/kg and 176 mg/kg) on three animal models (normoglycaemic, streptozotocin-induced diabetic rats and normal rats) subjected to the oral glucose-tolerance test, revealed that a single (acute) oral dose of the leaf extract does cause significant reduction in the level of glucose of the models tested. Also the polyphenolic content of the plant was not significant. These results suggest that the plant is not likely to be a candidate in the management of blood sugar of diabetic patients(Paul et.al., 2011).

Other: Yagi et al., has obtained a Japanese patent for having developed a skin-whitening agent in which *E. foetidum* is of four plants used. The preparation is to be used for sunburns, freckles, liver spot and related instances where skin-whitening is required. The exact role of the plant extract in this preparation is uncertain(Paul et.al., 2011).

#### 10.1. Clinical Pharmacology

- It is one of four plants used in a Japanese patent for having developed a skin whitening agent.
- The hydromethanolic extracts possess strong antidiabetic activity. This shows the extract could be a good alternative to other medicines used for treating diabetes(Singh et.al., 2014).
- The leaf extracts are used in rural India for treating hepatic issues (Yuhlung and Bhattacharyya, 2014; Singh et.al., 2014).

#### 11. Toxicity and safety

Consumption at high dose for long term and its toxic effect have never been reported. Therefore, it should be studied scientifically for its toxicity in order to establish suitable

dose for human consumption in the form of supplement or herbal products(Janwitthayanuchit et.al., 2016).

An Oral acute toxicity study as per OECD guidelines 423 was performed on the extracts to check for any mortality or behavioral changes in Swiss albino mice up to a dose of 2000 mg/ kg body weight (n=5).This indigenous plant in the amelioration of hepatotoxicity and poses no signs of morbidity or mortality up to a dose of 2000 mg/kg body weight with the drug (Chakraverty et.al., 2016).

## 12. Clinical studies

- The leaves are packed with flavonoids, tannins and many triterpenoids. These compounds demonstrate antibacterial and anti-inflammatory properties which are effective against malaria parasites and other microbes like bacteria and fungi.
- Essential oil studies extracted from the leaves have demonstrated strong antioxidants activities. This aromatic herbs contains a high amount of ascorbic acid (vitamin C) that acts as an antioxidants and help in scavenging free radicals. This makes the herb an effective part of the treatment of diabetes and other disorders caused due to oxidative stress in the body.
- Treats oedema: oedema or edema refers to the swelling of a small body part or entire body due to injury or inflammatory. Other reasons include pregnancy, infections and medications. In a study these leave help to reduce oedema due to the presence of stigmasterol, beta- sitosterol, brassicasterol and terpenic compound.
- The plant has several medicinal properties; a study demonstrates the anticonvulsant property of cilantro due to the present of bioactive compounds such as eryngial, flavonoids and tannins in the plants. And pain reliever all type of pain include ear pain, headache, pelvic pain, joint pain, and muscle pain,

## 13. Contraindications

It has immense healing power in many cases but few cases are contraindicated. In Brazil a decoction of the whole plant is used to ease delivery, but is contraindicated for pregnancy because it is reported to provoke uterine contraction(Paul et.al., 2011; Rodrigues et.al., 2007).

## 14. Precautions

Chronic toxicity study demonstrated that EF diet at 0.8% (35 times of human consumption) did not affect hematological and biochemical parameters, but 73 and 155 times of human consumption, some abnormality signs that led to the significant increase in the serum BUN level were produced, which strongly correlated with kidney histopathological lesion. Consequently, the consumption of leaves at high dose for a

long time may cause kidney lesion. No sufficient studies talk about the safe dose during pregnancy or breastfeeding. Consult a doctor before using it.

#### 15. Adversely reaction

Adversely side effect has noproven. However it may cause allergic reaction to some people or interact with drugs. Over consumption may lead to certain adverse effects. Daily consumption for 24 weeks may causekidney dysfunction, considering it is taken higher dose (around 35 times more than the normal dose (Janwitthayanuchit et.al., 2016)and also a possible side effect resulting from consumption of the crushed plant material is constipation (hardening of tool) (Paul et.al., 2011; Rahmatullah et.al., 2009).

#### 16. Marketed formulation, if any:

- Extract rich in eryngial has been patented for the treatment of parasites in humans and other mammals (Nataraj et.al., 2020).
- *Eryngium foetidum* is one of four plants used in a Japanese patent for having developed askin-whitening agent (Wang et.al., 2012).

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1. Botanical Name: ***Hibiscus rosa-sinensis* L.**
2. Family: Malvaceae
3. Synonym: *Hibiscus arnottii* Griff. ex Mast.
4. Common Names

Assam:	Joba
Bengali:	Joba
English:	Chinese hibiscus, Shoe flowers
Gujarati:	Jasuva
Hindi:	Jasum, Jasut
Kannada:	Dasavala
Malayalam:	Chembarathi
Marathi:	Dasindachaphula, Jasavanda
Oriya:	Mondaro
Punjabi:	Jasum
Sanskrit:	Japa, Java, Rudra pushpam
Tamil:	Semparuthi
Telugu:	Java pushpamudasana

5. Description: An erect evergreen shrub up to 20 feet high. Leaves simple, alternate, spiral; Stipules filiform, hairy; ovate or elliptic-ovate, tapering at base, acuminate at apex, serrate-dentate along margins, glabrous or with few hairs on the veins beneath; secondary nerves 3-5 pairs. Flowers solitary, axillary on upper branches; pedicels sparsely stellate pilose, articulate near apex; Epicalyx lobes 5-8, filiform, connate at base, 8-15 mm, sparsely stellate, apex obtuse or acute, Calyx campanulate, stellate puberulent, lobes 5, ovate to lanceolate. Flowers pinkish to red, with or without dark centre; petals 5, twisted, obovate, pilose abaxially, apex rounded; staminal column ca. 4-8 cm long, exserted, antheriferous near the apex; anthers monothealous, reniform. Fruit a capsule, glabrous, apex beaked.
6. Distribution: Tropical Asia, China, Nepal, Pakistan, Africa. Now it is widely cultivated as ornamental plants throughout India.
7. Part Used: Leaves parts, flower, stems.



*Hibiscus rosa-sinensis*

## 8. Medicinal/ Therapeutic uses

### 8.1. Uses described in pharmacopoeias and in traditional systems of medicine

It has been used in Siddha medicine, a traditional Tamil system from South India, for many centuries. Hibiscus extracts have been used for ages in Ayurveda to cure many ailments. The plants have the natural health benefit that can be used to cure diseases naturally. They are used to cure ailments such as cough cold, hair loss and hair greying also. The flowers and leaves of this plant play a major role in hair treatment. These are ground into a fine paste with water and this is generally used as a shampoo plus conditioner. The plant also helps to improve the overall texture and health of hair. Hibiscus is a sweet sour herb and is used in the preparation of herbal teas. It acts as an antioxidant and also helps in the reduction of cholesterol levels. It has also been used in the traditional medicine for treating colds, loss of appetite, disorders of the respiratory tract. The plant is beneficial as a mild laxative, expectorant and diuretic. It is found to have emmenagogue effects which can stimulate menstruation and in some women, cause an abortion (Al-Snafi, 2018; Diana et al,2015).

### 8.2. Uses supported by Clinical Data

Components of hibiscus have shown potential as a chemo-preventative agent against tumor promotion in laboratory and animal studies. These components also possess anti-inflammatory properties. Research reveals little or no clinical data regarding the use of hibiscus as a chemo-preventive agent. Studies on consumption

of hibiscus leaf tea have proved to reduce blood pressure in many people suffering with high blood pressure. Hence it is recommended for regular dietary consumption to reduce blood pressure. Hibiscus leaf tea is very effective in lowering LDL cholesterol levels. Its content helps in preventing buildup of plaque on the inside of arteries, thereby lowering your cholesterol levels. Hibiscus leaf contains lots of vitamin C which when consumed in the form of tea to cure cold quickly. (Gupta et al, 2009).

### 8.3 Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

In medicine, Roots and leaves, were anodyne and emmenagogue. They were used to regulate menstruation and stimulate blood circulation. Leaves were also used as abortifacient and to stimulate expulsion of placenta after childbirth. Flower is used for regulation of menstrual cycle, for liver disorders, high blood pressure as antitussive, in stomach pain, for eye problems, as abortifacient and as an aphrodisiac. Young leaves and flowers were used in headache. Decoction of leaves, root and fruits were helpful in treatments of arthritis, boils and coughs. Fruits were employed externally in cases of sprains, wounds and ulcers. The leaves are used for the treatment of dysentery and diarrhea, to promote draining of abscesses and as analgesic in the traditional medicine of Cook Islands, Haiti, Japan and Mexico. Flowers of the plant were used in diabetes, epilepsy, bronchial catarrh and leprosy. The flowers have been reported in the ancient Indian medicinal literature with beneficial effects in heart diseases. Petals were used to stimulate thicker hair growth and to prevent premature graying, hair loss and scalp disorders. (Babita et al. 2019)

### 8.4. Special uses in North East India

In North eastern region usually used as dried root powder is mixed water and orally for irregular menstruation, flower paste is also used as for hair fall and dandruff. In Manipur mainly used as cough, syphilis, gonorrhea, constipation, roots decoction with sugar candy is good in urinary disorder, menstrual disorder and as a health tonic. Leaf paste softens inflamed parts. Flower paste reduces pain caused by external wounds and sores. Petals infusion is good for alimentary tract.

### 8.5. Dosage forms used in tradition

Leaf paste – 10g -20 g

Flower Powder- 10 g

Hibiscus powder - ½ - 1 teaspoon a day or as per your requirement.

Hibiscus oil- 4-5 teaspoons or as per your requirement.

For High blood pressure-Hibiscus tea made by adding 1.25-20grams or 150mg/kg of Hibiscus to 150ml to 1000ml of boiling water has been used. The tea is steeped for 10-30 minutes and taken one to three times daily for 2-6 weeks.

## 9. Phytochemical profile

The presence of phytochemicals in methanolic extracts of hibiscus flower and leaves. The phytochemical analyses showed the presence of alkaloids, glycosides, flavonoids, saponins, tannin and phenols in hibiscus leaf extract, while hibiscus flower extract contained alkaloids, saponins, protein, phytosterols and carbohydrate. (Udita *et al*,2015).

## 10. Pharmacological Studies

Anti-bacterial activity, Antifungal activity, Antioxidant activity, Anti-fertility activity, Hair growth promoting activity, Anti-diabetic activity, Anti-inflammatory activity, Immune response activity.(Vincenta *et al*,2016)

Table 1: List of pharmacological effects of *Hibiscus rosa-sinensis*

Pharmacological activity	Part used	Extract/fraction	Dose tested/route of administration	Animals/cell line culture
Anti-fungal	Leaves	Methanolic	80 µg/ml	<i>Aspergillus niger</i> , <i>Candida albicans</i>
Anti-oxidant	Leaves	Aqueous 70% ethanol	500 µg/ml	DPPH and hydrogen peroxide radicals superoxide hydrogen peroxide, nitric oxide radicals
Anti-cancer	Leaves	Oil extract 90% methanol  Methanolic Ethyl acetate	75 µg and 125 µg 250 µg IC50 87.6 ± 0.91 µg/ml	Oral cancer cell lines KB (ATCC CCL-17) HT-29 colorectal AGS cell lines K-562 leukaemic cancer cells
Anti-diabetic	Leaves	Alcoholic Ethanolic Methanolic	2 mg/kg bw 400 mg/kg	NOD mice Alloxan induced diabetes in rats Streptozotocin induced diabetic rats
Wound healing Activity	Flower Leaves	Ethanolic Aqueous Methanolic	120 mg /kg 0.01g/ml 200 mg/kg, p.o.	Sprague Dawley rats Sprague Dawley rats Swiss albino mice
Anti-inflammatory	Leaves  Flower, leaves	Hydroalcoholic  Ethanol	200 mg/kg, p.o. 100 mg/kg	Acetic acid induced colitis in male Wister rats carrageenan induced paw edema Sprague-Dawley rats

Cardioprotective	Leaves	Aqueous	200 mg/kg	Hypertensive and non-hypertensive albino rats
Anti-pyritic	Leaves	Aqueous	500 mg/kg b.w	mice
Hepatoprotective	Leaves	Ethanoic	30 mg/kg b.w.	Piroxicam induced liver toxicity in Swiss albino mice

## Medicinal Applications

### Anti-bacterial activity

The methanol extracts prepared from the leaves were shown to have antimicrobial activities against *Pseudomonas aeruginosa*, *Escherichia coli*, *Enterobacter aerogenes*, and *Streptococcus pyogenes*. Using well diffusion method and after an incubation period of 24 hours at 37° C, the maximum observed zone of inhibition was  $13 \pm 00$  mm and it was against *E. coli* followed by  $12 \pm 00$  mm against both *S. aureus* and *E. aerogenes* at 80 µg/ml concentration of leaves methanolic extract .These microorganisms were obtained from infected skins, and the chemical compounds responsible for the antibacterial activity may be due to flavonoids, tannins, terpenoids, saponins, or alkaloids identified in the study. (Asmaa et al., 2018)

### Antifungal activity

The antifungal activity of root, leaves, and flowers ethyl alcohol extracts was also investigated. It was reported that using disc diffusion method, the growth of both *Candida* with many petals methanol extracts, and 0.19 from and yellow with 5 petals ethanol extracts. On the other hand, the samples orange/pink with many petals methanol extracts and red with five petals ethanol extracts exhibited least antioxidant activity as 1.17 and 4.49 respectively.

### Antioxidant activity

In another investigation, the ferric reducing antioxidant power (FRAP) and DPPH inhibition assays were used to determine the antioxidant potential of *Hibiscus rosa sinensis* flower extracts. Antioxidant activities of extracts were dependent on extraction solvents. Aqueous extracts contained high amounts of tannins and anthocyanins, and exhibited strong antioxidant effect (Khan et al., 2017)

### Anti-diabetic activity

The antidiabetic potential of ethyl acetate extract of petals of *Hibiscus rosa-sinensis* was investigated in diabetic rats. Extract was administrated at dose level of 25mg/kg as per body weight. Levels of Hepatotoxicity marker enzymes were restored in serum and glycogen level was normalized because of regulation of glycogen metabolizing enzymes activities (Khan et al., 2017)

### Anti-fertility activity

In another study, the powder mixed with propelyne glycol was orally subjected to albino Wister rats before mating. This treatment resulted in 100% inhibition of implants in pregnant rats, compared with overall that was used as positive control. The group treated with propelyne glycol as negative control, gave 100% deliveries on full term compared to 0% from groups treated with overall extract. The phytochemical analysis of the aqueous extract showed that steroids and saponins could have contributed to this anti-fertility activity. Similarly, flowers have also lowered progesterone and estrogen levels in pregnant female albino Wister rats. This has led to endometrial changes that in turn disrupted the estrous cycle, and caused non-receptive conditions preventing blastocyst implantation.

### Hair growth promoting activity

The petroleum ether leaf extract was proven to be a good hair growth promoter in a study involving Wister albino rats. After 14 days, the 5% w/w extract ointment resulted in  $4.91 \pm 0.261$  mm hair length compared to  $6.06 \pm 0.431$  mm in 2% minoxidil treated group, and  $2.21 \pm 0.108$  mm in negative control group. The extract also contributed to  $1937 \pm 37.84$  hairs per cm<sup>2</sup> area, while Minoxidil gave  $2315 \pm 05.78$  hairs per cm<sup>2</sup> area. The alopecia was induced by exposure to sonic stress, and there were no side effects such as erythema or edema, compared to synthetic hair growth promoting ointment. Similarly, 5% hydroalcoholic leaves extract ointment exhibited  $5.97 \pm 0.13$  mm hair length, and  $2058 \pm 19.23$  hairs per cm<sup>2</sup> area.

### Anti-inflammatory activity

In male wister rats, hydroalcoholic leaves extract had an ameliorative effect on 4% acetic acid induced colitis via rectal administration. The 7 days treatment with 200 mg/kg, p.o. of extract reduced the ulcer area of colon to  $20.67 \pm 2.40$  mm<sup>2</sup>, as compared to  $10.00 \pm 1.23$  mm<sup>2</sup> from prednisolone treatment group taken as positive control, and  $41.67 \pm 1.96$  mm<sup>2</sup> from negative control group. The phytochemicals that were present such as steroids, polyphenols, alkaloids, and flavonoids, might have contributed to this activity.

### Immune response activity

The effect of aqueous extracts of flowers on immunomodulation was studied by intraperitoneally injecting 500 mg kg<sup>-1</sup> BW of extract in male Swiss albino mice. After 15 days of treatment, cytokine IL-1 $\alpha$  serum levels increased by 14.27% and IL-2 levels decreased by 32.70% in comparison to control group. The antibody titre also increased to 2.39 ng ml<sup>-1</sup> compared to 1.73 ng ml<sup>-1</sup> in control group. Moreover, the extract increased the macrophage yield and viability, as well as the phagocytic index to  $76.76 \pm 1.40$ , which is only  $72.85 \pm 1.07$  in control group. HPTLC chromatogram proved that it contains alkaloid and flavonoids.

## 10.1 Clinical Pharmacology

A clinical study on 30 patients suffering from hypertension and hypercholesterolemia with a Siddha drug, *Anna Pavaala Sindhooram*, containing *Japa* (*Hibiscus rosa-sinensis*) as one of the ingredients, indicated that the drug is efficacious in reducing the cholesterol, phospholipids and triglycerides

Clinical trials were conducted with *Vidangadi yoga* (an herbal preparation containing *Embeliaribes* seeds, *Hibiscus rosa-sinensis* flowers and *Ferula foetidaoleogumresin*) for its antifertility activity.

The drug was found to be quite effective with no toxic effects.

*Hibiscus* tea is a great source of anti-oxidants, which help fight free radicals and reduce oxidative damage, the dose of antioxidants in hibiscus tea might be able to slow this process, lower inflammation in the body, and keep your skin looking dewy and youthful. Studies have shown that drinking hibiscus tea offers heart- healthy benefits, such as lowering blood pressure. 'In a study in The Journal of Nutrition, adults with high Blood pressure who consumed three servings of 8 glasses of hibiscus tea daily for six weeks saw a decrease in their overall blood pressure'. Hibiscus tea contains vitamin C, a strong antioxidant that we know is responsible for keeping our immune systems healthy. It shows increased concentration of detoxifying enzymes in the liver, it conclude that hibiscus tea is a proven method for kidney stone prevention in humans. (V.M. Jadhav *et al*, 2009)

## 11. Toxicity and Safety

*Hibiscus* plants are considered "toxicity category 4." This means that the plant and its blossoms are considered nontoxic to humans. They are not only nontoxic, they are also considered to have health benefits.

*Hibiscus* is generally considered safe. But more research is needed to determine a safe dosage for pregnant or breastfeeding women, children, and people with liver or kidney disease. (Al-Snafi, 2018).

## 12. Clinical Studies

Clinical studies have shown that the high dose of antioxidants in hibiscus tea might be able to slow this process; lower inflammation in the body, drinking hibiscus tea offers heart- healthy benefits such as lowering blood pressure. One small study showed that hibiscus tea increased HDL (good) cholesterol. Decreased LDL (bad) cholesterol and triglycerides. Hibiscus tea is also high in iron a mineral that keeps the immune system balanced and help the body to maintain red blood cells. Both human and animal studies have shown that hibiscus may prevent liver damage and showed an increased concentration of detoxifying enzymes in the liver (V.M. *et al*, 2009)

### 13. Contraindications

Occupational skin symptoms are suspected. Not in Pregnancy.

### 14. Precautions

Hibiscus may lower blood glucose level, making it difficult to control sugar during and after surgeries. So, it is generally advised to avoid Hibiscus supplements at least 2 weeks before surgery. Pregnancy and breast – feeding: Hibiscus is possibly unsafe when taken by mouth in large amounts as a medicine.

### 15. Adverse reactions

Side effects of hibiscus are uncommon but might include temporary stomach upset or pain, gas, constipation, nausea, painful urination, headache, ringing in the ears, or shakiness.

### 16. Marketed formulation if any

Madhukadyavaleha, Siddha drug, *Anna Pavala Sindhooram*, containing *Japa* (*Hibiscus rosa-sinensis*), *Vidangadi* yoga (an herbal prepration containing *Embeliaribes* seeds. *Hibiscus rosa-sinensis* flowers and *Ferula foetidaoleo-gum* resin), *Patrangasava* (used in conditions like pain menstruation, leucorrhea, fever), *Trichup* capsule (provides rich nutrition to hair follicles, encourages fresh growth), *Cutinol* hair oil (hair fall), *Keshrich* oil (used for nourishment of hair, against dandruff and in conditions of alopecia., *kusum Keshya* lotion by ethanolic extract of *Japakusum* (*Hibiscus rosa sinensis* L.) flower (Baby et al ,2015).

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1. Botanical Name: ***Houttuynia cordata* Thunb.**
2. Synonym: *Houttuynia foetida* Loudon
3. Family: Saururaceae
4. Common Names
  - Assamese: Mochondori, Mosundori, Mosondoi, Masundari
  - English: Fish mint, Fish wort, heartleaf, bishop's weed
  - Bengali: *Ghanday jhar*
  - Khasi: *Ja-mynda or Jmyr-doh*
  - Garo: *Machha-turi*
  - Arunachali: *Mumbre, Siiya hamang, Muchandariin*
  - Manipuri: *Toning khokin*
  - Mizo: *Uithinthang*
  - Naga: *Nuichua or Nokana*
5. Description: A perennial herb up to 60 cm high with creeping root stock. Leaves simple, alternate; stipular, usually ciliate, base enlarged and slightly clasping; petiole glabrous; ovate or ovate-cordate, cordate at base, shortly acuminate at apex, entire, chartaceous, densely glandular, usually glabrous, sometimes pubescent at vein axils, usually purplish abaxially; secondary nerves 5-7 pairs. Inflorescences in dense spikes, subtended by an involucres of 4-6 white, peduncles sub-glabrous; involucral bracts oblong or obovate, apex rounded; bract beneath each flower linear, terete, inconspicuous; perianth absent; stamens 3 longer than ovary; Stigma recurved. Fruit subglobose.
6. Distribution: Native to South-east Asia; In India it is found in Assam, Manipur, Nagaland.
7. Part Used: Whole Plant



*Houttuynia cordata*

## 8. Medicinal /Therapeutic Uses

### 8.1. Uses described in pharmacopoeias and in traditional systems of medicine

It was first discovered by Chinese people to have medicinal properties and used it for medical purposes as Traditional Chinese Medicine. It is used for treating pneumonia and SARS (Lau, 2008; Shingnaisui, 2018).

### 8.2 Uses supported by clinical data

Anti-viral, Anti-inflammatory, Immunomodulator (Yang &Jiang, 2009; Wang, 2010).

### 8.3 Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

In Manipur, Nagaland, Sikkim and North Bengal used leaves as anthelmintic and in Arunachal Pradesh herb used for freshness, deep sleep and cardio-vascular disorder (Rathi *et al.*, 2013; Kumar *et al.*, 2014). In China It also used for treatment of lung abscess, lobar pneumonia, malaria, chincough, diarrhea, dysentery, appendicitis, urethritis, infantile diarrhea, heatstroke, cold, tonsillitis, cholecystitis, stubborn dermatitis, boils, wound by the viper (Fu *et al.*, 2013). In Arunachal Pradesh, leaves extract used for treatment of dysentery and crushed

leaves and stems used to treat measles, gonorrhea (Khongsai *et al.*, 2011). In North Eastern India, it is consumed as ethnic side dishes and leaf salad to lower the blood sugar level. Leaf juice is used to treat cholera, dysentery, anemia and purification of blood (Kumar, 2014; Shingnaisui, 2018). The decoction is prepared from whole plant is used both internally and externally. Internally it is used for the treatment of cancer, coughs, dysentery, enteritis and fever. Externally it is used to treat snake bites and skin diseases. In Japan, a beverage is prepared from infusion of the leaves called Dokudami Cha which is mixed with other herbal remedies and are used for removal of free radicals, reducing inflammation and to support the immune system (Shingnaisui, 2018).

#### 8.4 Special uses in North East India

In the North-East India, people of Manipur, Assam, whole plant is eaten raw with traditional dishes and as a medicinal salad for lowering the blood sugar level. In Manipur, *Maiba-Maibi* (Male –Female Traditional Healers of Manipur) used for curing dysentery, muscular sprain, stomach ulcer, anaemia, gastritis, tuberculosis, and pneumonia.

In Nagaland, Whole plant is taken for stomachache, cholera, dysentery and as diuretic. It is also used on skin diseases (Sangtam, 2012).

In Manipur it is eaten for detoxification, boils, allergy, antipyretic, anti-inflammatory, tumors, asthma, analgesic, diuretic, and haemorrhoids (Devi, 2014).

In Arunachal Pradesh extract of tender shoot is taken for stomachache and warmed leaves are packed in banana leaf for snuff or massage to get relief from sinusitis (Kagyung, 2010). The leaf extract is given during dysentery and crushed leaves and stem are used to treat measles, gonorrhoea, and skin troubles (Khongsai, 2011).

In Assam, fresh leaves are crushed and taken raw or stem cooked as a remedy for constipation and indigestion (Ripunjoy, 2013).

In North-East India, it is eaten raw as a medicinal salad for lowering the blood sugar level and is commonly known by the name “Jamyrdoh” by Khasi and Jaintia tribes of Meghalaya (Rathi *et al.*, 2013; Kumar *et al.*, 2014).

#### 8.5 Dosage forms used in tradition

Decoction, paste, fresh raw plants (vegetable)

#### 8. Phytochemical profile

It contains aristolactams, 5, 4-dioxoaporphines, oxoaporphines, amides, indoles, ionones, flavonoids, benzenoids, steroids and several essential oils. Among those few flavonoids such as Quercetin 3-rhamnoside (influenza), Quercetin

(HIV), norcepharadione B (HSV-1), quercetin 7-rhamnoside (porcine epidemic diarrhea virus) exhibited anti-viral potential (Kumar *et al.*, 2014; Fu *et al.*, 2013).

## 10. Pharmacological Studies

Aqueous extract is significantly inhibited replication of SARS coronavirus (SARS-CoV) by blocking 3C-like protease (3CLpro) and RNA-dependent RNA polymerase. Also exhibited immunomodulatory activity by enhancing CD4+ and CD8+ T cells as well as secretion of interleukin – 2 (IL-2) and IL-10 in mouse splenic lymphocytes (Kumar *et al.*, 2014; Lau *et al.*, 2008). The aqueous extract inhibited anti-dinitrophenyl (DNP) immunoglobulin E (IgE) antibody induced local allergic reaction (passive cutaneous anaphylaxis) in mice. Essential oil have exhibited anti-inflammatory potential by inhibiting lipopolysaccharide (LPS) induced cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) expression in macrophages of mouse peritoneal. Aqueous extract inhibited anti-inflammatory potential by inhibiting lipoteichoic acid (LTA) induced tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) in dermal fibroblast. Ethanolic extract exhibited anti-inflammatory effect by blocking nuclear factor-kappa B (NF- $\kappa$ B) in human mast cells. The injection (HCl), containing essential oil, normal saline and tween-80 inhibited pseudorabies herpesvirus, quercetin 7-rhamnoside (Q7R) isolated from *H. cordata* inhibited replication of porcine epidemic diarrhea virus (PEDV), norcepharadione B isolated and inhibited replication of HSV-1 (Kumar *et al.*, 2014). Quercetin 3-rhamnoside (Q3R) exhibited potential antiviral activity of about 86% and 66% against influenza (A/WS/33) virus at concentration of 100  $\mu$ g/ml and 10 $\mu$ g/ml respectively. The Quercetin efficiently inhibited Vpr induced transcription from HIV-LTR and HIV replication, (Fu *et al.*, 2013). Aqueous extract is also exhibited antiobesity, anti-bacterial, anticancer, anti-diabetic, anti-allergic and antioxidant effect (Kumar *et al.*, 2014).

### 10.1. Clinical pharmacology

The injection is used in traditional Chinese medicine and clinically plays unique roles in the therapy of infectious diseases owing to its anti-inflammatory effect and anaphylaxis (Yang & Jiang, 2009; Wang, 2010).

### 11. Toxicity and safety: NA

### 12. Clinical studies

The injection is used in traditional Chinese medicine and clinically plays unique roles in the therapy of infectious diseases owing to its anti-inflammatory effect and anaphylaxis (Yang & Jiang, 2009; Wang, 2010).

### 13. Contraindications

Anti-bacterial medicines, allergic history to *Houttuynia* injection.

#### 14. Precautions

The most common system treated in *Houttuynia* Injection ADR cases was respiratory system and was also the most common site of ADR symptoms. The ADRs of these injections were serious. So, precaution has to be taken to prevent anaphylactic shock. *Houttuynia* injection cannot be used among the children and the patients with allergic history to injection. Improper use among patients beyond indication (i.e reproductive system diseases, gastrointestinal diseases, ophthalmopathy, acute leukemia) (Wang, 2010).

#### 15. Adverse reactions

The adverse reaction of *Houttuynia* injection was reported and use and approval of seven kinds of injective preparations was temporarily suspended since June 1, 2006 by China's State Food and Drug Administration (SFDA). While in September 2006, SFDA again allowed the pharmaceutical companies for reuse only with the intramuscular formulation after re-evaluation of the safety of *Houttuynia* injective preparation. The ADRs of these injections were serious. Multiple systems or organs were involved in ADRs including respiratory system, skin, digestive system, circulatory system and nervous system. Also resulted in several Respiratory diseases, Reproductive system diseases, urinary system diseases, anaphylactic shock (Wang, 2010).

#### 16. Marketed formulation, if any

Plukaow Extract plus by Khaolaor Laboratories Co.LTD., *H. cordata* capsules, Plu Kaow Immunity Antioxidant Herbs Supplement by Herbal one, Supreme Nutrition *Houttuynia* Supreme Capsules by Supreme Nutrition Products.

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1. Botanical Name: ***Ichnocarpus frutescens*** (L.) W.T. Aiton

2. Synonym: *Apocynum frutescens* L.

3. Family: Apocynaceae

4. Common Names

Assam	: Lamkandol, Paharukibandan
Bengali	: Dudhi, Syamalota
English	: Black creeper
Hindi	: Dudhilata, Kalidudhi, Siamalata
Kannada	: Gorwiballi, Karehambu
Malayalam	: Paalvally
Marathi	: Kantebhouri, Krishnasarwa
Oriya	: Madhobi, Soyamnoi, Syamolota
Sanskrit	: Paravalli, Sariva, Syamalata
Tamil	: Paravalli, Udargodi
Telugu	: Illukatte, Nalateage.

5. Description: A much branched extensive climber, with brown-tomentose. Leaves ovate, apex obtusely acute, base rounded, nerves 5 pairs, brown-pubescent below; petiole to 5 mm long. Flowers in terminal or axillary panicled cymes; calyx lobes ovate, acute, pubescent. Flowers white, salver shaped, contracted at mouth, tube hairy inside, throat densely white-villous, lobes twisted, oblong, acuminate; stamens included, anthers deeply sagitate at base, apiculate at apex; carpels free, stigma columnar. Mericarps follicular, to 15 cm long, slender, rusty puberulus. Seeds many, compressed, crowned with long silky coma.

6. Distribution: Indo-Malaysia and Australia. In India distributed all most all states from tropical to subtropical regions.

7. Part Used: Whole Part.



*Ichnocarpus rutescens* (L.) W.T. Aiton

## 8. Medicinal /Therapeutic Uses

### 8.1. Uses described in pharmacopoeias and in traditional systems of medicine:

The leaf gently warmed and applied over swollen regions by the presence of the worm by the tribal of Southern Rajasthan (Joshi, 1991).

Leaves are boiled in oil and applied for headache, tongue ulcers, cramps, night blindness, bleeding, and stomach pain. Root is used as a tonic, blood purifier, and removal of stone from the bladder; dental caries, vomiting, burning sensation, hyperdipsia, seminal weakness, nephrolithiasis, strangury, skin diseases, leprosy, pruritus, vomiting, cephalalgia and general weakness. Flowers and leaf latex juice are applied to cure skin infections. Plants are used in the treatment of rheumatism, asthma, cough, bronchitis, bone fracture, cholera, constipation, dysentery, night blindness, measles, ulcer, vomiting, leucoderma also as febrifuge, blood purifier (Meher et. al., 2018).

Whole plant that can relieve burning sensation on the skin and bleeding disorder and diarrhea (Pandurangan *et al.*,2010). It is used in the indigenous system of medicine in the treatment of fevers, gout, rheumatism, arthritis, epilepsy, venereal diseases, herpes and skin diseases (Anonymous, 1959; Kirtikar& Basu, 1998; Nadkarni, 1982).

## 8.2. Uses supported by clinical data

### Wound Healing activity

The roots extract (hydro-alcoholic) showed wound healing activity significantly in the excision wound model in rats on topical application. Povidone iodine ointment was taken as standard in this study. The results showed that hydro-alcoholic extract of stems on topical application reduced the scar area from  $2.5\pm1.5$  to  $0.0\pm0.0$  cm<sup>2</sup> , hydro-alcoholic extract of leaves on topical application was reduced the scar area from  $2.5\pm1.5$  to  $0.2\pm0.0$  cm<sup>2</sup>, hydro-alcoholic extract of roots on topical application was reduced the scar area from  $2.5\pm1.5$  to  $0.7\pm0.4$  cm<sup>2</sup>, control on topical application was reduced the scar area from  $2.5\pm1.5$  to  $1.2\pm1.0$  cm<sup>2</sup> and standard povidone iodine ointment on topical application was reduced the scar area from  $2.5\pm1.5$  to  $0.5\pm0.02$  cm<sup>2</sup> respectively. The final result revealed that the hydro-alcoholic stems extract has remarkable wound healing potency and appear to explain the traditional use for wound healing in India and offer a scientific support to the treatment of traditional healers (Meher *et al.*, 2013).

## 8.3. Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

Tonic, blood purifier, and dental caries, vomiting, burning sensation, hyperdipsia, seminal weakness, nephrolithiasis, strangury, skin diseases, leprosy, pruritus, vomiting, cephalalgia and general weakness, of rheumatism, asthma, cough, bronchitis, bone fracture, cholera, constipation, dysentery, night blindness, measles, ulcer, vomiting.

## 8.4. Special uses in North East India

Root bark extract is mixed with the root bark of *Zizyphus rugosa* with 1-2 spoonful sugar and administered twice a day for urinary infection (Majumdar *et al.*, 2006).

## 8.5 Dosage forms used in tradition

Decoction of a handful of leaves is used for fever at a dose of 20 ml three times a day (Girachet *et al.*,1994). The dried root powder is used as lactogogue and is administered about 10 g twice a day with a glass of fresh water after the meals by the tribal of Sonaghati of Sonbhadra district, Uttar Pradesh (Singh,2002).

## 9. Phytochemical profile

Ursolic acid, Kaempferol, Trifolin, Mannitol, Flavon, Phenolic acid, Triterpene glycoside(1,4- $\beta$ -D-glucopyranosyl-(1,3)  $\alpha$ -amyrin,  $\beta$ -Sitosterol, alkaloid and Flavonoid (Meher *et al.*, 2013)

## 10. Pharmacological Studies

### Experimental pharmacology

**Anti-urolithiatic activity:** The inhibitory effect of the ethyl acetate extract of the roots on nephrolithiasis induced in the rats was administered with aqueous solution of ethylene glycol (0.75%) for 28 d. It resulted in hyper-oxaluria as well as increased renal excretion of calcium and phosphate. Urinary excretion of oxalate, calcium and phosphate are significantly increased in calculi-induced rats [(2.10  $\pm$  0.08), (8.15  $\pm$  0.33) and (7.2  $\pm$  0.06) mg/dL, respectively] as compared with normal control (saline) rats [(0.34  $\pm$  0.02), (2.916  $\pm$  0.17) and (3.64  $\pm$  0.04) mg/dL, respectively]. When standard drug (Cystone 750 mg/kg p.o.) administered to calculi-induced rats, the excretion levels of oxalate, calcium and phosphate were significantly decreased to (1.00  $\pm$  0.05), (3.916  $\pm$  0.25) and (3.18  $\pm$  0.09) mg/dL respectively (Singh & Singh, 2012).

**Hepatoprotective activity:** Protective and curative effect of polyphenolic extract against carbon tetrachloride and tamoxifen-induced hepatotoxicity in rats was examined. Carbon tetrachloride (1 mL/kg) and tamoxifen (45 mg/kg) given through intraperitoneal route caused liver damage in rats manifested by significant rise in serum enzymes levels, declines in reduced glutathione level and elevations in malondialdehyde levels. The oral administration of polyphenolic extract of leaves in a dose of 200 mg/kg to carbon tetrachloride and tamoxifen-intoxicated rats produced significant increment in the reduced glutathione levels with significant decrement in malondialdehyde and lever transaminases levels. Histopathological changes of liver sections showed that prophylactic and curative treatments with polyphenolic extract resulted in a relatively good protection against both carbon tetrachloride and tamoxifen intoxicated rats. The extract inhibits CYP mono-oxygenase aminopyrine-N-demethylase and aniline hydroxylase, suggesting a plausible hepatoprotective mechanism. The normalization of phenobarbitone induced sleeping time suggests the restoration of liver CYP enzymes. The study shows that hepatoprotective effect of polyphenolic extract is by regulating the level of hepatic microsomal drug metabolizing enzymes (Kumarappan *et al.*, 2011).

**Antioxidant activity:** *In vitro* antioxidant activity of methanolic extract of roots exhibited strong scavenging effects on 2, 2-diphenyl-2-picryl hydroxyl (DPPH) free radicals, nitric oxide, super oxide anion, hydroxyl radicals and lipid peroxidation with IC<sub>50</sub> were (17.4  $\pm$

0.75), (172.8 ± 1.95), (37.4 ± 0.34), (49.2 ± 0.64) and (130.7 ± 2.50) µg/mL, respectively (Pandurangan *et al.*, 2009).

**Analgesic activity:** Analgesic effects of 70% alcoholic extract of leaves stem and roots were performed in Wistar rats of either sex by hot plate and tail immersion methods. Alcoholic extract of stem at a dose of 500 mg·kg<sup>-1</sup> showed higher latency of percentage protection (hot plate, 154.12% and tail immersion 221.33%) in comparison with alcoholic extract of leaf (hot plate, 122.42% and tail immersion 195%) and root (hot plate, 138.66% and tail immersion 214.67% (Mishra *et al.*, 2009).

**Antidiabetic activity:** Antidiabetic activity of aqueous extract of roots was estimated in streptozotocin–nicotinamide -induced type-II diabetic rats. Type-II diabetic rats were administered aqueous root extract (250 and 500 mg/kg, p.o.) of the plant drug or vehicle (gum acacia solution) or standard drug glibenclamide (0.25 mg/kg) for 15 d. Blood samples were collected by retro-orbital puncture and were analyzed for serum glucose level on days 0, 5, 10 and 15 using glucose oxidase-peroxidase reactive strips and glucometer. For oral glucose tolerance tests glucose (2 g/kg, p.o.) was administered to nondiabetic control rats treated with glibenclamide (10 mg/kg, p.o.) and aqueous extracts of root. The serum glucose levels were analyzed at 0, 30, 60 and 120 min. after drug administration. The aqueous extracts of root (250 and 500 mg/kg, p.o.) induced significant reduction ( $P < 0.05$ ) of fasting blood glucose levels in streptozotocin-nicotinamide-induced type-II diabetic rats on 10th and 15th days. In the oral glucose tolerance test, the extract increased the glucose tolerance (Bairik *et al.*, 2008).

**Anti-hyperlipidemic activity:** The polyphenolic extract of leaves were evaluated in alloxan-induced diabetic rats. Diabetes was induced by single intraperitoneal injection of alloxan (150 mg/kg). The polyphenolic extract of the plant (300 mg/kg for 21 days) showed significant decrease in hepatic HMG-CoA reductase activity of alloxan diabetic rats and no significant effects were found in the normoglycemic rats. Polyphenolic extract exhibited significant hypolipidemic effect as evident from correction of hyperlipidemic indicators (TC, TGs, VLDL, HDL and LDL). Oral administration of polyphenolic extract (100 mg/kg) significantly enhanced the release of lipoprotein lipase enzyme significantly. The histopathological studies of aorta in polyphenolic extract treated alloxan-rats revealed almost recovery to normal appearance (Kumarappan *et al.*, 2007).

**Antitumor activity:** *In vivo* antitumor activity of polyphenolic extract of leaves has been assessed on Murine Ehrlich Ascites Carcinoma (EAC) model. *In vivo* study showed a significant decrease in tumor volume, viable tumor cell count and a significant increase of life span in the polyphenolic extract treated group compared to the untreated one. The life span of polyphenolic extract treated animals increased by 53.41% (50 mg/kg)

and 73.95% (100 mg/kg). The result was found comparable with standard drug 5-fluorouracil (86.97%) at a dose of 20 mg/kg.

*In vitro* cytotoxicity study was performed in moncytoid leukemia (U-937) and erythroleukemia (K-562) cell lines and the study indicates that polyphenolic extract of the leaves of the plant at doses of 5, 10 and 20 µg/mL effectively inhibits proliferation of U-937 and K-562 cell lines and result was found comparable with standard drug cytarabine arabinoside at a dose of 20 µg/mL (Kumarappan et al., 2007 and 2009).

#### Antiviral activity

Ethanic extract of the entire plant has been reported to show significant antiviral activity using cell cultured method (Kaij-A-Kamb et al., 1992).

11. Toxicity and safety: NA

12. Clinical studies: NA

13. Contraindications: NA

14. Precautions: NA

15. Adverse reactions: NA

16. Marketed formulation, if any: NA

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1. Botanical Name: *Inula racemosa* Hook. f.

2. Synonym: *Inula royleana* C.B.Clarke

3. Family: Asteraceae

4. Common Names

Gujarati:

Pokharmul,

Kannada:

Puskarmul,

Hindi:

Pokharmula

Kashmiri:

Poshkar,

Malayalam:

Puskkarmulam,

Marathi:

Pushkarmul,

Sanskrit:

Puskaramula, Kasmira, Padma, Sugandhikam

Tamil:

Puskarmulam.

Telugu:

Pushkaramulamu,

5. Description: An erect, stout, herb up to 6 feet high with tomentose. Leaves basal large, lanceolate and stem clasping, lower leaves are narrowed to a winged leaf stack. The abaxial laminal face is densely tomentose. Radical leaves are broad and elliptic with long stalked. The cauline leaves are smaller, oblong and semi amplexicaule. Stem leaves oblong, half stem clasping usually deeply lobed at the base. Flowers – in heads /racemes, very large. Outer bracts broad, tips triangular, bent back, inner bracts linear, sharp pointed. These are shady yellow daisies produced in mid to late summer. These borne on apical spike like cluster. Fruits are cylinder, hairless, achene. Pappus 8 mm long and reddish in colour (Soni and Sharma, 2018).

6. Distribution: Commonly distributed at temperate and alpine western Himalayas at an altitude of 5000 to 14000 ft. from Kashmir to Kumaon, Afghanistan to Nepal. It also found wild among strong alpine scrub vegetation in cold Laddakh (Leh) region of Kashmir (Soni and Sharma, 2018).

7. Part Used: Root and rhizome (Arora et al., 1980).



*Inula racemosa*

## 8. Medicinal/Therapeutic

### 8.1 Uses described in pharmacopoeias and in traditional systems of medicine

Hikka (Hiccup), Kasa (Cough), Swas (Asthma), Parswsula (both side chest pain), Hridrog (Cardiac disease angina & HD), Aadhman (Gastritis) and Pandu (Anaemia). Tibetan medicine - strong antifungal and anti-inflammatory activities (Soni and Sharma, 2018).

### 8.2 Uses supported by clinical data

Protective effects on 4-NQO-induced DNA damage and apoptosis. Anti-atherogenic effect validating the cardioprotective and anti-obesity claims in traditional medicine (Arumugam and Murugan, 2013).

### 8.3 Traditional/ Folklore uses, not supported by experimental or clinical data:

The root is medicinal and considered as specific remedy for cough, dyspnoea, asthma, pleurisy, tuberculosis and chest pain, especially pre cordial pain. The aqueous extract of the fresh or dry roots is given orally in rheumatic pains and liver problems. Externally a paste or liniment is used for relieving pain. The root is also used in veterinary medicine as a tonic. The root forms an important ingredient of several polyherbal formulations for heart diseases and inflammatory conditions of spleen and liver. The root has been traditionally used for the treatment of gonorrhoea; the flower is used in jaundice and ophthalmic afflictions in folklore. Leaves are extensively used for the affections of the respiratory tract such as chronic and acute bronchitis. The dried leaves are smoked as cigarettes in asthma and the juice of fresh leaves have been used for diarrhoea and dysentery and also used as valuable antiseptic, antiperiodic and anthelmintic (Kimothi, 2014).

### 8.4 Special uses in North East India: Not available in literature.

### 8.5 Dosage forms used in tradition: Roots and rhizome powder 1-3 grams (Bhutya, 2011).

### 8.6 Phytochemical Profile: Phytoestrogenic effect

#### Major chemical constituents

Alantolactone (Chi et al., 2016), isoalantolactone (Chi et al., 2016), inunolide (Germacranolide), dihydroisoalantolactone, B-sitosterol, D-mannitol, dihydroxinunolide, neo-alantolactone, inunolise, sesquiterpene lactone (inunol) (Xiaofeng et al., 2020), alantodiene (Kalsi et al., 1989), isoalantodiene (Kalsi et al., 1989), sesquiterpene lactones (Soni and Sharma, 2018; Kimothi, 2014).

## 9. Pharmacological Studies

Anti-inflammatory, analgesic, antifungal (Liu, Mishra and Tan, 2006), antibacterial (Lokhande et al., 2007), hepatoprotective, anti-allergic, antioxidant, anti-asthmatic, adaptogenic, adrenal beta blocking (Tripathi et al., 1988), hypoglycemic and cardioprotective activity (Mangathayaru et al., 2009) and Phytoestrogenic effect (Kalachaveedu et al., 2018).

## 10. Experimental pharmacology

*I.racemosa* modulatory effect on experimental Atherosclerosis in Guinea-Pigs demonstrates the anti-antherogenic effect of *I. racemosa*, thus validating the

cardioprotective and anti-obesity claims in traditional medicine (Mangathayaru *et al.*, 2009).

#### 10.1 Clinical pharmacology

Administration of *Inula* to the patients of Ischemic Heart Disease shows marked improvement in ST depression on ECG, along with that there is reduction in Chest pain and dyspnea also.

#### 11. Toxicity and safety

Studies done to assess the safety and therapeutic profile of the plant extract, Administration of single dose of petroleum ether (60-80 °C), alcohol (95 %) and water extracts of flowers at the limit dose of 2000 mg/kg, p.o did not have any toxic effects. The animals were alive, healthy and active during the observation period. Thus, different extracts emerged safe for administration for further studies (Gautam *et al.*, 2009).

#### 12. Clinical studies

Clinical studies reveal that administration of *Inula* to the patients of Ischemic Heart Disease shows marked improvement in ST depression on ECG, along with that there is reduction in Chest pain and dyspnoea also (Tripathi *et al.*, 1984).

#### 13. Contraindications

People with high BP should take this herb only under medical supervision. Over-dosage may cause low BP (Bhutya. 2011).

#### 14. Adverse reactions

Reported as harmful for individuals with warm temperament. May produce headache. In large doses or long term use, reduces blood volume and harm virility.

#### 15. Adverse reactions: No data available

#### 16. Marketed formulation, if any

Puskarmulasava, Puskaradi Churn, Puskaradikalk, PuskaradiKasaya, BrhatYograjguggulu, Haritakyadi churn, Kankayangutika, Kumaryasav, Dasmularista, Lodhrasava(Soni and Sharma, 2018).

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***Justicia adhatoda L.***

[Internal Code: IBSDM000]

1. Botanical Name: ***Justicia adhatoda L.***

2. Synonym: *Adhatoda zeylanica Medicus*

3. Family: Acanthaceae

4. Common Names

Bengali: Bakas

English: Malabar nut

Gujarati: Alduso

Hindi: Adosa, adalsa, arusha, vasaka

Kannada: Adusoge

Malayalam: Atalotakam

Marathi: Adulsa

Sanskrit: Amalaka, bashika, Vasaka

Tamil: Adadodai, Adutheendapalai

Telugu: Adasaramu.

5. Description: A stiff, evergreen, much-branched perennial shrub with a strong, unpleasant odour, 1.2-6 m tall. Leaves opposite, elliptic-lanceolate or ovate-lanceolate, margins entire, apex acute, 5-30 cm long, hairy, light green above, dark beneath, leathery. Flowers large, white with red or yellow-barred throats, borne in compact, axillary, pedunculate spikes with large bracts. Fruits (capsules) clavate, longitudinally channelled, 1.9-2.2 cm long and 0.8 cm wide, pubescent. Seeds globular.

6. Distribution: Indigenous to Indo-Malaysia, Sri Lanka, Bhutan, Pakistan, Afghanistan and widely spread over India up to an altitude of 2400 m.

7. Part Used: Whole plant leaves, roots, flowers and stem bark are used.



*Justicia adhatoda* L. – Photo by: A. N. Shukla, BSI

## 8. Medicinal/Therapeutic Uses

### 8.1 Uses described in pharmacopoeias and in traditional systems of medicine

It is highly reputed plant species, utilized in indigenous system of medicines in India for over 2000 years (Claeson *et al.*, 2000). In Ayurvedic medicine vasaka has been used for a multitude of disorders including bronchitis, leprosy, blood disorders heart troubles, thirst, asthma, fever, vomiting, loss of memory, leucoderma, jaundice, tumours, Mouth troubles, sore-eye, fever and gonorrhoea. It is useful for the treatment of bronchitis, tuberculosis and other lung and bronchiole disorders. A decoction of the leaves is used to recovery of cough and other symptoms of colds. The soothing action of the plant helps in reducing irritation in the throat and the expectorant will help loosen phlegm deposits in the airway vasaka exhibits antispasmodic, expectorant and blood purifying qualities. The leaves, roots and flowers of the plant are extensively used in indigenous medicine as remedy for cold, cough, bronchitis, and asthma (Singh, 2011).

### 8.2. Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

All the parts has been used for their curative effects from ancient times (Atal, 1980). It has been used in Ayurvedic system of medicine for the treatment of various ailments of respiratory tract in both children and adults. Various parts of the plant are used in Indian traditional medicine for the treatment of asthma, joint pain, lumber pain, sprains, cold, cough, eczema, malaria, rheumatism, swelling and venereal diseases (Jain, 1991).It is used by the European medical practitioners. The fluid extract and tincture were used in England as an Antispasmodic, Expectorant and

febrifuge. It was said to be beneficial in intermittent, typhus fever and Diphtheria (Wren, 1932). In Germany, the leaves are used as an expectorant and spasmolytic agent (Madaus, 1938). In Sweden is classified as a natural remedy and some preparations against cough containing an extract of vasaka are accessible (Farnlof, 1998).

### 8.3. Special uses in North East India

Fumigants from burned bark, leaves and root acts as Mosquito repellent there are tribal practices for repelling mosquitoes in North-East India. It was found that Meitei community in the study area extensively used in ethnomedicine as well as food. Young and mature green leaves are used as traditional medicine to cure many ailments like cough, fever, asthma and dysentery. The ethnic community uses inflorescences and leaves to treat digestion and other health issues.

### 8.4. Dosage forms used in tradition

Cough and bleeding- Take 1 table spoon juice of leaves with honey internally.

Excessive menstruation- Juice of leaves 15ml with 15 gm jaggery twice daily internally

Bleeding piles- Decoction of whole plant with sugar internally

The drug vasaka is often taken in the form of juice extracted from its leaves, mixed with ginger or honey, in doses of 15 to 30. The leaves can be made into a decoction or the dried leaves can be given in powder form in doses of 2 grams. Both the decoction and powder are constituents of many preparations used in the Ayurvedic medicine for various affections of the respiratory tract. The root and the bark have the same medicinal uses as the leaves. A decoction of the bark is given in 30 to 60 ml doses and the powdered root-bark in 0.75 to 2 grams does.

### 9. Photochemical profile

The plant contains active principal component of quinazoline alkaloids such as vasicine, adhatodine, vasicinone and deoxy vasicinone. Vasicol (alkaloids) also isolated from the plant. A new alkaloid and galactoside isolated from the root and characterized as 9-acetoamido-3,4-dihydro pyrido-(3,4-b)-indole and O-ethyl- $\alpha$ -D-galactoside respectively. B-D-glucoside, D-Galactose and deoxyvasicinone have been isolated in addition to sitosterol  $\beta$ -D-glucoside from the roots. Flavonoids found in the leaves are identified as kaempferol, quercetin, vitexin, isovitexin while the phenolic acids were identified as p-hydroxybenzoic acid, syringic acid and p-coumaric acid. Leaves contain free vitamin C, and carotene. Flowers and leaves contain flavones luteoline. Leaves are enriched with mineral elements of calcium, magnesium, potassium, sodium, and iron. The petroleum ether extract from the flowers contained different non-nitrogenous compounds such as triaticontane, B-sitosterol, A-amyrin and B-sitosterol-D-glucoside. Young inflorescence yielded vasicinone. Flowers contains oils containing tridecanoic acid, pentadecanoic acid, and new glucoside identified as 2,4, dihydroxychalcone-4-glucoside. Seed oil contained arachidic (3.1%), behenic (11.2), lignoceric (10.7), cerotic (5), oleic (49.9)

and linoleic acid (11.2). Other alkaloids isolated from the plants are 9-acetamido-3,4-dihydropyrido-(3,4,b)-indole, oethyl-A-D-galactoside, 1,2,3,9, tetrahydropyrrolo (2,1-b)quinazolin-9 (1H)-one, sitosterol-B-D-glucoide, D-galactose and deoxyvasicinone, vasicol, vasicinone, adhatonine and vasicinolone (Khursheed *et al.*, 2010).

## 10. Pharmacological Studies

The phytochemical studies of the various parts revealed the presence of alkaloids, phytosterols, polyphenolics and glycosides as a major class of compounds. Its principal constituents are quinazoline alkaloids with vasicine as its chief alkaloid. The leaves are rich in Vitamin C and carotene and yield an essential oil. Chemical compounds found in leaves and roots of this plant includes essential oils, fats, resins, sugar, gum, amino acids, proteins and vitamin C etc (Dymock, 1972). The leaves also contain a very small amount of an essential oil and a crystalline acid. An analysis published in India in 1956 showed the seeds as containing 25.8% of deep yellow oil composed of glycerides of arachidic 3.1%, behenic 11.2%, lignoceric 10.7%, cerotic 5%, oleic 49.9% and linoleic acids 12.3% and  $\beta$ -sitosterol (2:6%) (Dweck, 1995). Elemental analysis using atomic absorption spectrophotometry revealed the presence of major (K, Na, Ca and Mg) and trace (Zn, Cu, Cr, Ni, Co, Cd, Pb, Mn and Fe) elements (Jabeen *et al.*, 2010). The chemical analysis of various bioactive compounds isolated from leaves and roots were carried out (Gulfraz *et al.*, 2005). From the data, concentration level of protein (8.5 %), vasicine (7.5%), vitamine C (5.2%), and fats (2.5%) were found in roots samples. Whereas, level of such compounds was low in leaves except sugar (16.4%), fiber (5.2%), vasicinone (3.5%), Zn (0.6%), S (1.3%) and Fe (1.2%).

### 10.1. Clinical pharmacology

Ardusi contains numerous bioactive compounds, for instance, vasicinol, 5-hydroxy vasicine, vasicine, vasicine glycoside, deoxyvasicine, vasicinone, adhavasicinone, vasicolinone, adhatodine, anisotine and vasnetine. Vasicine shows bronchodilator activity under *in vitro* and *in vivo* condition, whilst, vasicinone exhibited its effectiveness towards bronchoconstriction *in vivo*. Simultaneous effect of these two alkaloids was preferably administered for bronchodilator activity both under *in vitro* and *in vivo*. A combination of vasicine and vasicinone also showed a significant reduction in cardiac depressant effects. Vasicinone produced from the roots, prevents shrinkage of intestine and cardiac depression in guinea pigs, and transient hypotension in cats, thus displaying decent anticholinesterase activity. Vasicine produces ambroxol and bromhexine that have a pH-dependent growth inhibitory influence on *Mycobacterium tuberculosis*, which suggests that it may play a significant part in the primary treatment of tuberculosis. Both vasicine and vasicinone have sucrose inhibitory activity, signifying that they can be explored as natural antidiabetic agents. It has been reported that vasicine and its derivatives are excreted through urine. By way of intramuscular and intravenous administration, for the first 18 and 22 h, 55% of the excreted product was vasicine, whilst, on oral administration, it was 18% during the first 24 h. The leaves of *A. vasica* possess anti-ulcer activity, which was tested in rats. The ardusi leaves have the highest degree of

anti-ulcer activity (80%) as detected in the ethanol induced ulceration model when compared to that of the actions of pylorus and aspirin. The syrup made from leaves improved symptoms of dyspepsia as well. The leaf extract exhibited antimutagenic activity when cadmium intoxicated mice was treated with the same, wherein, it showed marked decline in inhibition of lipid peroxidation and xanthineoxidase activity. Swiss albino mice when exposed to Cobalt- 60 radiation, was affected with radiation-induced ailment, displaying noticeable effects in histology of testis. This effect was significantly reduced when extract was applied. This suggests that the ardui plant extracts have radio-protective effects on testis.

#### 11. Toxicity and safety

Vasaka is considered safe in recommended usage and dosing. The safety of this herb has not been tested in children and should be avoided, unless directed by a medical professional. Use of this supplement is not recommended during pregnancy (except at birth, and then only under the direction of a medical practitioner.) Care should be exercised when taking this herb with other drugs or supplements that exhibit expectorant or antispasmodic effects.

#### 12. Clinical studies

The efficacy of vasa in the form of syrup against Non-ulcer Dyspepsia (Amiapitta) through a clinical trial has been attempted. This trial showed hopeful results. The drug has reduced the total and free HCL in the patients of hyperacidity and hyperchlorhydria.

#### 13. Contraindications

It is contraindicated to pregnant women. Obstruction of the biliary tract. In cases of gallstones, use only after consultation with a physician. Hypersensitivity to the drug.

#### 14. Precautions

Pregnancy and breast-feeding: It's unsafe to take Malabar nut if you are pregnant. It's also best to avoid use if you are breast-feeding. The effects of Malabar nut on a nursing infant are unknown at this time.

#### 15. Adverse reactions

The main suspected adverse reactions are urticaria (8.3%), rashes (7.4) and contact dermatitis (5.7%)

#### 16. Marketed formulation, if any:

Formulation of vasaka in the market include: Herbilicious Adusa powder, Ayurveda vasaka capsules, Adusa juice, Adusa syrup.

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1. Botanical Name: ***Lagerstroemia speciosa* (L.) Pers.**

2. Synonym: *Munchausia speciosa* L.

3. Family: Lythraceace

4. Common Names

Assam:	Ajar, Thing-dou, Thlado
Bengali:	Ajar, Jarool
English:	Queen crape myrtle, Queen of flowers
Hindi:	Azhar, Jarul
Kannada:	Jarul
Marathi:	Mota-bondara, Taman
Punjabi:	Jarul
Sanskrit:	Syandana
Tamil:	Kadali, Pumaruthu
Telugu:	Varagogu.

5. Description: A medium-size, deciduous tree up to 40 meter high; with smooth bark. Leaves opposite, distichous, spatulate, oblong to elliptic-ovate; stipules are minute or absent. Flowers axillary or terminal panicle, often showy, calyx with funnel or bell shaped, 6(9) lobed, petals often 6, inserted near the mouth of the calyx tube, white to pink or purple in color, clawed, wrinkled, stamens are many in several rows, ovary superior, 3-6 locular with many ovules in each cell. Fruit is large woody capsule on the persistent calyx. Seed has an apical wing.

6. Distribution: It is widely distributed in India, China, Cambodia, Myanmar, Thailand, Vietnam, Indonesia, Malaysia and the Philippines. In India Assam, Kerala, Madhya Pradesh, Meghalaya, Garo hills (Balpakram NP, Darungiri) and Khasi hills.

7. Part Used: Aerial part or entire plant.



*Lagerstroemia speciosa* L. Pers. (Image Credit: Chaya Deori)

## 8. Medicinal / Therapeutic Uses

### 8.1. Uses described in pharmacopoeias and in traditional systems of medicine:

The roots are used as astringent, stimulant, and febrifuge, it was also used for stomach problems. The leaves infusion was used in the treatment of diabetes mellitus and for weight loss. The leaves, flowers, and barks were used as purgative. Decoction of leaf was used for bladder and kidney inflammation, dysuria, and other urinary dysfunctions, in malaria, headache, and cracked heelings for cholesterol deduction, hypertension, and diabetes. Bark decoction was used for gastrointestinal tract disturbance, stomachache, haematuria, and depression. The seeds were also used as narcotics (Al-Snafi, 2019).

### 8.2. Uses supported by clinical data

**Anti-diabetic:** Leaf extracts had reduced the levels of plasma glucose and insulin in hereditary type II diabetic mice (Kakuda *et al.*, 1996). The plasma cholesterol level in treated mice was significantly reduced, but not the plasma triglyceride level, suggesting that leaf extracts restrained or delayed cholesterol absorption in the intestine (Wei *et al.*, 2014).

**Anti-inflammatory:** The protective effect of methanolic extract of leaves (100 and 200 mg/kg bw orally for 7 days) was assessed against dextran sulfate sodium-induced ulcerative colitis in C57BL/6 mice. Both the doses of extract significantly prevented dextran sulfate sodium-induced inflammatory and ulcerative damages of the colon,

reduced lipid peroxidation and also restored the levels of innate antioxidants in the colon tissue (Chaudhary *et al.*, 2017).

**Anti-obesity activity:** Significant reduction of body weight and parametrial adipose tissue weight was observed in obese female KK-AY mice when fed with a hot water leaf extract (Suzuki *et al.*, 1999).

**Anti-diarrheal activity:** The methanolic crude extract of roots was inquired for anti-diarrheal activities in an experimental animal model. The methanolic crude extract are reported to have anti-diarrheal activity and inhibited the mean number of defecations by 32.75% ( $p < 0.010$  and 51.72% ( $P < 0.001$ ) at the dose of 200 and 400 mg/kg bw respectively (Hussain *et al.*, 2014).

The ethanol extract of the dried fruits of exhibited anti-diarrheal activity on castor oil-induced diarrhea in mice, it was found that it can increased mean latent period and decreased the frequency of defecation significantly ( $P < 0.001$ ,  $P < 0.010$ ) at the oral dose of 500 mg/kg bw comparable to the standard drug loperamide at the dose of 50 mg/kg of bw (Rahman *et al.*, 2011).

**8.3 Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data:** No data available

**8.4 Special uses in North East India:** No data available

**8.5 Dosage forms used in tradition:** No data available

## **9. Phytochemical profile**

### **Major chemical constituents**

The chemical constituents of *Lagerstroemia speciosa* include corosoli acid, lageracetal, amyl alcohol, ellagic acid, gallic acid, 4- hydroxyl benzoic acid, beta sitosterol, 3,3,4-tri-O-methyl ellagic acid, 3-O-methyl-3,4-methylenedioxy ellagic acid, Asiatic acid, alphitolic acid, 3,3-di-O- methyl ellagic acid, 3,4,3,4- tetra-Omethylflavellagic acid, 3,4-di-O-methyl-3,4-methylenedioxy flavellagic acid, 3-O-methyl ellagic acid, 6,7-dihydroxy coumarin, alanine, isoleucine, alpha amino butyric acid, ellagitannin and methionine and also consists of metals like Iron, Magnesium, and Zinc (Koduru *et al.*, 2017).

## **10. Pharmacological Studies**

**Anti-viral activity:** When tested for anti-human rhinovirus (HRV) activity in Hela cells; orobol 7-O-D-glucoside (O7G) isolated from leaves showed broad-spectrum anti-HRV activity towards HRV of groups A and B. Anti-HRV activity of O7G using a cytopathic effect (CPE) reduction method exhibited broad-spectrum anti-HRVs activity with a 50% inhibitory concentration ( $IC_{50}$ ) ranging from 0.58 to 8.80  $\mu\text{g ml}^{-1}$ .

The 50% cytotoxicity concentration ( $CC_{50}$ ) of O7G is  $>100$   $\mu\text{g}/\text{ml}$ , and the derived therapeutic indices are more than 12. (Choi *et al.*, 2010).

The inhibitory concentration ( $IC_{50}$ ) of orobol 7-O-D-glucoside (O7G) ranged from 0.58–8.80  $\mu\text{g}/\text{ml}$  and the cytotoxic concentration ( $CC_{50}$ ) was found higher than 100  $\mu\text{g}/\text{ml}$ . The compound has great potential to be developed into a potent anti-human rhinovirus agent (Wei *et al.*, 2014).

#### Anti-diabetic properties

The anti-diabetic activity of a standardized leaf extract of (Glucosol<sup>TM</sup>) with 1% corosolic acid was demonstrated in a randomized clinical trial involving Type II diabetics (Judy *et al.*, 2003). Doses of 32 mg and 48 mg of Glucosol<sup>TM</sup> were given daily for 2 weeks and showed a significant reduction in the blood glucose levels. It was recorded that the extract in the form of soft gel capsules had better bioavailability than that in hard gelatin capsules with declines of 30% and 20% of blood glucose levels, respectively. The hypoglycemic activities of irradiated and non-irradiated ethanol leaf extracts are tested on alloxan-treated diabetic mice. Extract at 25% and 50% had hypoglycemic effects comparable to that of insulin and the decline in blood glucose levels was evident 1.5 hours after administration (Deocaris *et al.*, 2005).

#### 10.1. Clinical pharmacology: NA

#### 11. Toxicity and safety

The crude ethanol extract is non-toxic in rats; it was well tolerated at a concentration of 500, 1000, 2000, and 3000 mg/kg. No biochemical and histological changes were recorded (Mahaboob *et al.*, 2013).

In acute toxicity study, there were no records of mortality or toxic reaction in rats after administration of the methanolic crude extract roots (200, 400, 800, 1600 and 3200 mg/kg,) when given orally (Hussain *et al.*, 2014).

#### 12. Clinical studies: No data available

#### 13. Contraindications: No data available

#### 14. Precautions: No data available

#### 15. Adverse reactions: No data available

#### 16. Marketed formulation, if any: No data available

## 17. References

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1. Botanical Name: **Leea indica** (Burm.f.) Merr.

2. Synonym: *Staphylea indica* Burm. f.

3. Family: Vitaceae

4. Common Names

Assamese:	Ahina
Bengali:	Kurkur, Achilagach
English:	Bandicoot Berry
Hindi:	Hastipalash, Kikurjihwa
Kannada:	Andilu
Khasi:	Riu-khonglieng
Malayalam:	Erattayani, Maniperandi
Manipuri:	Koknal
Marath:	Dino, Karkani
Oriya:	Bonotulasi
Sanskrit:	Chhatri
Tamil:	Nalava, Nyekki, Ottanali
Telugu:	Ankadosa

5. Description: A shrubs or small tree. Leaves 2 or 3-pinnate, leaflets oblong or elliptic-lanceolate, apex caudate-acuminate, serrate-dentate; lateral nerves 12-15 pairs, intercostae parallel, curved; stipules obovate-obtuse. Young leaves bright-red. Cymes to 6 x 8 cm, peduncles 3-4 cm long, paired, axillary. Flowers greenish-white. Staminal tube shortly lobed at apex, anthers combined. Fruit a berry purple. Seeds densely red-glandular.

6. Distribution: Indo-Malaysia, China and Australia. Distributed throughout India.

7. Part Used: Whole Plant.



*Leea indica* Merr.

## 8. Medicinal / Therapeutic Uses

### 8.1. Uses described in pharmacopoeias and in traditional systems of medicine:

It is widely used in diarrhea, dysentery, colic, ulcers, skin diseases, vertigo, and headache. The leaves and roots are known to treat diabetes, cardiac diseases, and various ailments such as fever, headache, dizziness, soreness, eczema, sprain, leprosy, bone fracture, body pain, muscle spasm, diarrhea, and dysentery. It is also used as an ingredient in the preparation to treat leucorrhea, intestinal cancer, and uterus cancer. The leaf decoction is given to women during pregnancy and delivery for birth control or to treat obstetric diseases and body pain. (Bais, 2013; Prashith et al., 2018).

### 8.2. Uses supported by clinical data: No data available

### 8.3. Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data:

Headache, dizziness, soreness, eczema, sprain, leprosy, bone fracture, body pain, muscle spasm.

### 8.4. Special uses in North East India

In Assam, the stem bark paste is used for the treatment of hydrocele (Sonowal, 2013) and the root extract with honey is used as expectorant to relieve cough (Jain et al., 1980).

In Tripura, decoction of roots is used for the treatment of stomachache and diarrhea (Sen *et al.*, 2011).

8.5. Dosage forms used in tradition: No data available

## 9. Phytochemical profile

Major chemical constituents

Root, Leaves:  $\beta$ -Sitosterol, Lupeol, Gallic acid

Root-Di-*n*-octyl phthalate,  $\beta$ -Amyrin, Quercitrin, Dibutyl phthalate,  $\alpha$ -Tocopherol

Flowers: Di-isobutyl phthalate, Di-*n*-butyl phthalate, *N*-butyliso-butyl phthalate

Whole plant: Mollic acid arabinoside, Mollic acid xyloside

Leaves: Phthalic acid, Palmitic acid, Eicosanol, Solanesol, Farnesol, Ursolic acid, N-butyl gallate (Mishra *et al.*, 2016); Alkaloids, glycosides, steroids, tannins, flavonoids, reducing sugars, and gums (Tareq *et al.*, 2017)

## 10. Pharmacological Studies

The leaves are reported to possess pharmacological activities like antitumour (Mohammed *et al.*, 2012), analgesic (Emran *et al.*, 2012), antiviral (Abdul *et al.*, 1996), sedative and anxiolytic (Mohammed *et al.*, 2011), phosphodiesterase inhibitory (Temkitthawan *et al.*, 2008) and Nitric oxide inhibitory (Saha *et al.*, 2004).

### 10.1. Experimental pharmacology

#### a. Anti-viral activity

Ethanic extract obtained from leaves shown to exhibit antiviral activity against herpes simplex virus type-1 with a MIC value of 0.05 mg/ml. The extract was ineffective against vesicular stomatitis virus (Hamidi *et al.*, 1996).

#### b. Anti-diarrheal activity

Study evaluated the methanolic extracts by castor oil-induced diarrhea in mice. During the observation period (4 hrs), the total latency periods (first diarrheal stool after the administration of castor oil) and the number of diarrheic feces excreted by the animals were recorded. Results showed both extracts reduced total number of stool in mice and increased latency period (Tareq *et al.*, 2017).

#### c. Antitumor Activity

Study evaluated a crude methanolic extract of leaves for anti-tumor and cytotoxic activity and was used against Ehrlich Ascites Carcinoma (EAC) cells in Swiss albino

mice, there was a significantly decrease in tumor weight measurement, survival time and tumor cell growth inhibition. On brine shrimp lethality assay the extract showed significant cytotoxic activity (LC<sub>50</sub> less than 25 µg/ml) (Raihan *et al.*, 2011).

d. Antiulcer activity

Methanolic extract was evaluated on gastric ulcer in pylorus ligating-induced and aspirin-induced models. 400 mg/kg dose of methanol extract significantly ( $p<0.01$ ) reduced gastric ulcer index in both models. Antiulcer activity was confirmed by histopathological studies and was attributed to secondary metabolites such as flavonoids, tannins, and saponins (Dalu, 2018).

e. Thrombolysis

An *in vitro* thrombolytic model was used to check the clotlysis by using streptokinase as a positive and water as a negative control and was found that *Leea indica* showed a significant percentage of  $39.30 \pm 0.96\%$  clot lysis and thus, the plant possessed an effective thrombolytic properties which can used for patients suffering from atherothrombotic diseases (Rahman *et al.*, 2013).

f. Hepatoprotective Activity

Extraction of ethanol from the stem bark indicates hepatoprotective activity against liver injury induced by paracetamol in rats. The treatment of animals with the extract at two doses, namely, 200 and 400 mg/kg body weight resulted in significant decrease in elevated level of serum marker enzymes, bilirubin, and triglycerides as compared to positive control group of rats (Mishra *et al.*, 2014).

g. Sedative Activity

The sedative property assessed from methanolic extract of leaves by whole cross, open field, and thiopental sodium-induced sleeping time tests and found that the leaf extract showed a dose-dependent suppression of motor activity, exploratory behavior, and prolongation of thiopental induced sleeping time in mice in a dose-dependent manner(Raihan *et al.*, 2011).

h. Anxiolytic Activity

An elevated plus maze (EPM) test was performed to evaluate anxiolytic potential of crude methanol extract of leaves. The methanol extract at the dose of 400 mg/kg body weight, significantly increased the entries of mice into the open arms, and the time spent in the open arms of the EPM(Raihan *et al.* 2011).

i. Wound Healing Activity

Ethanolic extract disclose a wound healingpotential in NIH 3T3 mouse fibroblast cells and RAW 264.7 mouse macrophage cells by scratch assay. It was observed that the

extract treatment triggered migration of cells at the site of the gap (the wound) created by scratching the area of cells (0.5 mm width) indicating the potential of *Leea indica* to heal the wound(Azizi *et al.*, 2016).

#### j. Hypolipidemic Activity

The administration of alcoholic and hydroalcoholic extracts of leaves in rats showed a significant decrease in the level of triglycerides, total cholesterol, LDL, and VLDL and increased HDL indicating hypolipidemic activity of leaf extract (Dalu *et al.*, 2014).

#### k. Analgesic Activity

An acetic acid writhing test and formalin-induced licking response test was done to investigate the analgesic activity of leaf extract and it was found to significantly inhibit the writhing response induced by acetic acid. The oral administration of extract also suppressed the formalin-induced pain response in mice(Emran *et al.*, 2012).

#### l. Antimicrobial Activity

The antibacterial and antifungal activity from essential oil of flower is due to the higher percentage of phthalates (95%) in it. Guaiacol, anethole and 3 H pyrazole are reported to have antibacterial, antifungal activities. Tested showed moderate antibacterial and antifungal activity (Srinivasan *et al.*, 2009).

#### m. Central Nervous System Activities

Raihan *et al.*,(2011) reported the crude methanolic extract of leaves was evaluated for its central nervous system (CNS) depressant effect using rodent behavioral models, such as hole cross, open field and thiopental sodium induced sleeping time tests for its sedative properties and an elevated plus-maze (EPM) test for its anxiolytic potential, respectively. The methanolic extract at doses of 200 mg/kg, p.o. and 400 mg/kg, p.o., showed a dose dependent suppression of motor activity, exploratory behavior (in hole cross and open field tests) and prolongation of thiopental induced sleeping time in mice; the highest CNS depressant effect was shown at a dose of 400 mg/kg, p.o. The results confirmed *in-vivo* evidence that leaves have significant sedative and anxiolytic effects. Decisively, these results may rationalize the scientific basis for use of this plant in traditional medicine for treatment of anxiety and related disorders(Raihan *et al.*, 2011).

#### n. Anti-Cancer / Apoptosis / Cervical Cancer Cell Line

Leaf extract and its fractions are evaluated for cytotoxicity on various cell lines (Ca Ski, MCF-7, MDA-MB-435, KB, HEP G2, WRL 68 and Vero) by MTT assay. The ethyl acetate fraction showed the greatest cytotoxic effect against Ca Ski cervical cancer cells via induction of growth suppression and apoptosis effects. It presents a potential as an anticancer drug (Wong *et al.*, 2011).

o. Antimalarial Activity

The study done by AbdRazak et al., (2014) indicate the ineffectiveness of solvent extracts of leaf to exhibit antiplasmodial activity against *Plasmodiumfalciparum* K1 by HRP2-based assay.

In another study, Sulistyaningsih et al., (2017) investigated antimalarial activity of leaf extract in male Balb/c mice. It significantly decreases the parasitemia level by  $3.50 \pm 1.26\%$  on the 4th day and yielded  $24.85 \pm 1.28\%$  of suppression.

11. Toxicity and safety: NA

12. Clinical studies: NA

13. Contraindications: NA

14. Precautions: NA

15. Adverse reactions: NA

16. Marketed formulation, if any: NA

17. References

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1. Botanical Name: ***Maesa indica* (Roxb.) A. DC.**

2. Synonym: *Baeobotrys indica* Roxb.

3. Family: Myrsinaceae

4. Common Names

Assamese:	Sesu, Awa pat, Machpora, Awuapat
Bengali:	Ramjani
Bodo:	Sirkhi
English:	Wild berry
Garo:	Samnakhatok
Hindi:	Kramighnaphal
Kannada:	Guddehargi
Khasi:	Dieng sohjala-tyrkai
Malayalam:	Kirithi
Marathi:	Atki

5. Description: A large shrubs or small tree with glandular branchlets. Leaves alternate, elliptic, elliptic-lanceolate or elliptic-oblong, ovate, acute at apex, rounded and cuneate at base, serrate, glandular, membranous, with many glandular lines; nerves 10 pairs, regular; petiole 1.5-3 cm long. Flowers white and scented in axillary branched racemes; bracteoles 2, opposite, inserted, below the calyx; calyx tube adnate to the ovary, lobes 5, orbicular. Stamens 5; anthers orbicular; ovary 1-celled, ovules many, immersed in globose placenta, stigma capitate. Fruits are small a fleshy berry, pinkish-white. Seeds few, angular, black.

6. Distribution: Indo-Malaysia, Pakistan and Sri Lanka; in India (lower Himalayas), and found almost all the states.

7. Part Used: Whole plant



*Maesa indica* (Roxb.) A .DC

## 8. Medicinal /Therapeutic Uses

### 8.1 Uses described in pharmacopoeias and in traditional systems of medicine

The plant has been reported to be used against white dot condition of the eye, in some parts of Maharashtra. The compound quercetin is also reported to have antibacterial activity, aiding in defense against eye infections (Natarajan& Paulsen, 2002). The roots of the plant are used to treat pain in the joints and overall body pain, in Mangalore, Karnataka (Shiddamallayya *et al.*, 2010). Ayurveda utilizes this plant as a blood purifier as it is known to have anthelmintic and anti- syphilitic (Gaitonde, 1988). Triterpenoid, saponins extracted from plant sources like *Maesa lanceolata*; *M.chisia* and *M.indica* have been reported to have shown virucidal activity against Newcastle disease virus, vaccinia virus and herpes simplex virus (Jassim & Naji, 2003).

### 8.2 Uses supported by clinical data

Phytochemicals quercetin, quercetin-3-rhamnoside, isolated from *M.indica*, have been reported to have the ability to inhibit aldose reductase enzymes in the eye lens. The compound quercetin is also reported to have antibacterial activity, aiding in defense against eye infections (Natarajan& Paulsen, 2002).

The plant is reported to have antibacterial activity against gram positive bacteria (*Staphylococcus aureus* and *Bacillus cereus*) and gram-negative bacteria (*Pseudomonas aeruginosa* and *Shigella flexneri*) (Kekuda *et al.*, 2014).

The methanolic extract of leaf has the capability to control the production of auto antigen and inhibits protein denaturation, membrane lysis and proteinase action in rheumatic disease. It showed moderate (79.53%) antiarthritic activity in comparison with Diclofenac-Na, as shown by inhibition of protein denaturation assay. (Itu *et al.*, 2019).

### 8.3 Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

Berry-like fruits are consumed by the local people residing in Nilgiri hills, Tamil Nadu, India (Sasi & Rajendran, 2012). Seeds and leaves are used as anthelmintic and roots are used as blood purifiers. Roots are also used to treat high blood pressure in Goa. (Gaitonde, 1988). The Chinese treat hepatitis, numbness of limbs is also by the usage of the plant. (Long & Li, 2004).

### 8.4 Special uses in North East India

In Arunachal Pradesh use the decoction from leaves to treat fever, especially by the Chakma community. (Sasi & Rajendran, 2012). Plant is mainly used as fodder in Meghalaya as it is believed to increase the milk output of cattle. (Chhetri, 2010). The Wokha district of Nagaland the Lotha tribe uses the fruits to kill and expel intestinal worms. (Jamir *et al.*, 2010) Folk medicinal system of Manipur uses young leaves boiled in water for treatment of hoarse voice and sore throat (Lokho, 2012).

### 8.5. Dosage forms used in tradition

Leaves warmed and rubbed on skin diseases, leaf extract administered orally for cold and stomachache. Root extract taken to cure dysentery and intestinal disorders. Fruits consumed raw as anthelmintic. (Sasi & Rajendran, 2012). Leaves and bark crushed and filtered, filtrate is used to cure white dot and watering of the eye. (Natarajan& Paulsen, 2000).

## 9. Phytochemical profile

The plant is reported to have tannins, phenolics, quinones, flavonoids, saponins. (Shanmugam *et al.*, 2016; Itu *et al.*, 2019).

Chemical compounds isolated from *M. indica* include (24R)-stigmast-7, 22(E)-dien-3 $\alpha$ -ol,  $\beta$ -sitosterol, n-hexadecanoic acid, 1, 12-bis (3,3 -dihydroxy-4,4 - dimethyl- 5,5 - dimethoxyphenyl) dodecane, chrysophanol, 2,3-dihydroxypropyl palmitate and 1 (9Z,12Z)-2,3- dihydroxypropyl octadeca-9,12- dioenoate (Devarajan *et al.*, 2014).

A quinone compound called Kiritiquinone was also isolated from the ethyl acetate extract of fruits (Kuruvilla *et al.*, 2010).

The petroleum ether extract of leaves yielded sitosterol and ethyl acetate extract of leaves gave quercetin-3 rhamnoside as reported (Ahmad & Zamnn, 1973). The roots were reported to contain  $\beta$ -sitosterol, stigmasterol, quercetin, and rutin. (Gaitonde, 1988).

## 10. Pharmacological Studies

It has shown to have a variety of pharmacological activities like antimicrobial, antidiabetic, antioxidant and antiarthritic effects. (Kekuda *et al.*, 2014; Patil *et al.*, 2014; Shanmugam *et al.*, 2016 & Itu *et al.*, 2019).

### Antidiabetic

The solvent extracts of stem and bark of the plant, when tested on rats, have shown significant antidiabetic (hypoglycemic) activity by the inhibition of alpha glucosidase enzyme, with increasing concentrations. (Patil *et al.*, 2014).

### Antioxidant

The methanol extract of fruit has better antioxidant property (676 mg AA equivalents/g extract). The lower antioxidant capacity was found for petroleum ether extract of fruit (131 mg AA equivalents/g extract). Acetone extract fruit shows maximum capability of ferric reducing, chelating metal ions and phosphomolybdenum reduction activities. (Shanmugam *et al.*, 2016).

10.1. Clinical pharmacology: NA

11. Toxicity and safety: NA

12. Clinical studies: NA

13. Contraindications: NA

14. Precautions: NA

15. Adverse reactions: NA

16. Marketed formulation, if any: NA

## 17. References

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1. Botanical Name: ***Meliosma simplicifolia*** (Roxb.) Walp.

2. Synonym: *Millingtonia simplicifolia* Roxb.

3. Family: Sabiaceae

4. Common names

English: Simple leaf Meliosma

Hindi: Coghsa

Khasi: Jhurlungkren, Dieng-lapia

5. Description: A small tree up to 20 feet high with reddish-pubescent young shoots. Leaves simple, oblong-lanceolate to oblanceolate-obovate, leathery, densely coppery pubescent when young, glabrous or pubescent on midrib and nerves above, coarsely to sharply serrate or subentire to entire, acuminate, cuneate at the base; petiole 1-2 cm long, pubescent. Flowers white, sessile; bracteoles 3 or more, sub-orbicular, imbricate. Sepals similar to and larger than bracteoles. Outer petals orbicular, entire, inner petals with 2 patent lobes at apex. Stamens adnate to petals. Ovary glabrous; style as long as or slightly shorter or longer than ovary. Fruit a subglobose drupe, black.

6. Distribution: Pakistan, India, Nepal, Tibet, Myanmar, China, Malaya and Indo-China. In India almost all the States.

7. Part Used: Aerial part



*Meliosma simplicifolia* (Roxb.) Walp

## 8. Medicinal /Therapeutic Uses

### 8.1. Uses described in pharmacopeias and in traditional systems of medicine:

Thai system of medicine uses the plant as an anti-diabetic medicine as it is shown to inhibit aldine reductase enzyme. (Choi *et al.*, 2014). Used as antiviral against Ranikhet disease virus (Aswal *et al.*, 1986).

### 8.2. Uses supported by clinical data

### 8.3. Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

In Tamil Nadu, the people of the Manna tribal group, mothers are given fresh tender bark of plants after delivery for the contraction of the uterus. (Augustine *et al.*, 2010). Thai medicine uses the bark of the plant by boiling it to relieve lumbago and fever; the boiled bark is administered as a bath. (Khuankaew *et al.*, 2014).

### 8.4. Special uses in North East India

Paste of fresh bark is consumed during unusual urine sensation. The powdered roots and bark are taken with leaves of *Hedyotis scandens* during asthma, in Arunachal Pradesh. (Monlai, 2013).

### 8.5. Dosage forms used in tradition

Leaves are ground to paste and consumed. Roots and bark are powdered, or consumed raw for treatment of asthma, or for gynecological purposes. (Augustine *et al.*, 2010; Monlai, 2013).

## 9. Phytochemical profile

The methanolic extracts of stem contained phenolics ( $39.83\pm3.62$ g GAE/100g). Flavonoids ( $21.78\pm0.14$ g/ 100g extract) and tannins ( $4.47\pm2.49$ /100g extract) were extracted from the stem (Pavithr & Sekar, 2020).

The methanolic extract of stem of the plant contained phytochemicals like penol, 3,5-bis(1,1-dimethylethyl)- 3,4-dihydroxymandelic acid, 3-lospropoxy-1,1,1,3,5,7,7,7-octamethyl-3,5- bis (trimethylsiloxy) tetrasiloxaneheptadecanolic acid, methylester 1,1,1,3,5,7,7,7-octamethyl-3,5-bis-trimethylsiloxyane elcosanoic acid, methyl esterheptasiloxane, hexadecamethyl-octasiloxane,1,1,3,3,5,5,7,7,9,9,11,11,13,13,15,15-hexadecamethyl-hexasiloxane, tetradecamethyl- cyclononasiloxane, actadecamethyl- - silcone oil, purin-6-amine, (2-fluorophenyl)methyl) (Pavithr & Sekar, 2020).

## 10. Pharmacological Studies

### Anti-inflammatory activity

The stem extracts tested orally for anti-inflammatory activity (250mg/kg) showed a decrease in paw edema, in Wistar albino rats after six hours. As compared to the standard, ( $5.16 \pm 0.98$ ) significant ( $p>0.05$ ) decrease in edema was observed when a high dose (200mg/kg) of the extract was administered, ( $3.63 \pm 0.04$ ). (Pavithr & Sekar, 2020).

10.1. Clinical pharmacology: NA

11. Toxicity and safety: NA

12. Clinical studies: NA

13. Contraindications: NA

14. Precautions: NA

15. Adverse reactions: NA

16. Marketed formulation, if any: NA

### 17. References

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1. Botanical Name: ***Memecylon umbellatum*** Burm.f.

2. Synonym: NA

3. Family: Melastomataceae

4. Common names

Assam:	Lali-dimabophang, Theihadum
English:	Iron-wood tree
Hindi:	Anjan
Kannada:	Archeti, Harchari lakhonde
Malalayam:	Anakkayavu, Kanalei kannavu, Kashavu
Marathi:	Anjani kurpa, Limba
Oriya:	Nirassa bonohorono
Sanskrit:	Anjani
Tamil:	Alli, Anjani, Kaya
Telugu:	Alli, Kikkalli, Uddalalli.

5. Description: A medium-size trees up to 8-25 feet high. Bark pale brown, fissured, thinly flaky when old; blaze yellowish brown. Branchlets terete, glabrous. Leaves simple, opposite, decussate; canaliculate, glabrous; elliptic to elliptic-ovate, apex acuminate, sometimes acute, base acute to sub-attenuate, margin entire, coriaceous, glabrous, drying brown; midrib canaliculate; secondary nerves obscure; tertiary nerves obscure. Inflorescence clusters of distinctly peduncled dense cymose umbels, axillary or on lateral tubercles. Flowers deep blue. Fruit a globose, berry, yellow. Seed single.

6. Distribution: Sri Lanka, Malay Peninsula, Malay Archipelago, Sylhet, Tenasserim, Kolli hills of Eastern Ghats, Khasi hills-Nongpoh.

7. Part Used: Whole Plant



*Memecylon umbellatum* Burm.f.

## 8. Medicinal /Therapeutic Uses

### 8.1 Uses described in pharmacopeias and in traditional systems of medicine:

The leaf powder is used as hypoglycemic, useful for diabetes (Karuppusamy, 2007). The seeds are used to relieve from cough; the bark is known for its use as a treatment for bruises. (Nadkarni, 1976).The leaves are reported to possess antiviral activity. (Kirthikar & Basu, 1991; Sastri, 1962; Dhar *et al.*, 1968).The leaves were also used in snakebite (Sastri, 1962). In Ayurveda and other traditional medicine systems the decoction prepared from its leaves is used in the treatment of menorrhagia and excessive menstrual discharge. (Nadkarni, 1976; Chopra *et al.*, 1956). In Dakshin Kannada District traditionally the decoction of the root is used as spasmolytic and given to small children. (Joshi *et al.*, 2011).

### 8.2 Uses supported by clinical data

Obese mice when orally administered with methanolic extract for a duration of 8 weeks showed a significant reduction in fasting glucose levels, body weight and triglycerides. Reduction in serum IL6 and serumoxidized LDL along with data from histological sections of liver and subcutaneous adipose suggest that the extract helps in the improvement of insulin resistance in treated mice (Sunil *et al.*, 2017).

The alcoholic extract of leaf was examined for wound healing potential in the form of ointment (0.5, 1.0 and 2% w/w), the excision and the incision wound model in rats. The extract induced a significant response in both the wound models as compared to the standard drug nitrofurazone ointment (0.2%w/w) (Puratchikody & Nagalakshmi, 2007).

The paste of leaves is used in the treatment of herpes (Maruthiet *et al.*, 2000). The plant was also found active against Ranikhet virus. (Dhar *et al.*, 1968). The triterpenes present in the plants have anti-inflammation, anti-viral infections, anti-cancer and anti-diabetes activity (Joshi and Joshi *et al.*, 2009; Wang *et al.*, 2011; Kunkel *et al.*, 2012). Lipids in the plants showed pharmacological activity against HIV, rheumatoid arthritis, (Woyengo *et al.*, 2009; Joshi and Joshi *et al.*, 2009).

### 8.3 Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

Seeds are used as a sedative. Leaves are used to treat bone fractures. Leaf juice is applied externally on herpes. Leaf paste applied on pimples for a cure (Karuppusamy, 2007). The paste of the leaf and its powder is used in snake bite. A root decoction is used for abnormal menstrual periods (Savinaya *et al.*, 2016). The leaves are used as a cooling astringent and applied on the face; it is extensively used by the people of Paliyan tribes to cure skin ailments like pimples. (Joshi *et al.*, 2011). It's also used in the treatment of conjunctivitis. (Kirthikaret *et al.*, 1991, Sastri, 1962).

### 8.4. Special uses in North East India:NA

### 8.5. Dosage forms used in tradition

The leaf of the plant is ground into a paste and applied onto the skin to treat pimples. (Joshi *et al.*, 2011). Leaf juice is applied externally on the herpes affected part with cow's urine, daily twice, till cure. (Karuppusamy, 2007). Young leaves are crushed with black gram (*Vigna mungo*) and taken orally with egg albumin and butter, daily twice for 3 weeks for bone fracture (Rajakumar & Shivanna, 2009).

One teaspoon of shade-dried leaf powder mixed with a cup of water and boiled rice (kept overnight) is taken early in the morning for forty days or until cure, for control of blood sugar levels (Ayyanar *et al.*, 2008). A decoction made from the leaves is used in the treatment of menorrhagia and menstrual discharge (Nadkarni, 1976; Chopra *et al.*, 1956)

### 9. Phytochemical profile

Phytochemical groups such as phytosterols, terpenoids, glycosides, tannins and flavonoids amino acids, carbohydrates, gum, resins, proteins and other phenolic groups are found in *M. umbellatum*. (Bharthi *et al.*, 2016).

The phyto constituents present in the plant include umbellactone,  $\beta$ -amyrine, oleanolic acid, ursolic acid, sitosterol, octacosanoic acid, cerotic acid, ethyl palmitate, palmitic acid and butyric acid. (Bharthi *et al.*, 2016).

Octocosanoic acid, Cerotic acid, Ethyl palmitate was found to be present in the root extract of the plant. (Joshi *et al.*, 2009).

### 10. Pharmacological Studies

The plant showed potent antioxidant, radical scavenging, antibacterial, antimutagen, and anticarcinogenic activity. (Joshi and Joshi *et al.*, 2009; Murugesan *et al.*, 2011).

#### Antimicrobial activity

The leaf extracts of the plant have shown significant antimicrobial activity against a range of human pathogens. The petroleum ether, chloroform and ethanol leaf extracts showed significant activity against *Streptococcus pneumoniae* causing brain abscesses, pneumonia and septic arthritis, *Proteus vulgaris*, *Pseudomonas aeruginosa* causing urinary tract infections and septicaemia, *Salmonella typhi* causing typhoid fever, *Vibrio* species causing diarrhoeal infections and the fungus *Candida albicans*. The antimicrobial activity of the petroleum ether, chloroform and ethanolic leaf extract showed concentration-dependent activity against all the tested bacteria with the zone of inhibition at various concentrations. (Murugesan *et al.*, 2011).

#### Analgesic and anti inflammatory activity

The aqueous and acetone extracts of the roots screened for analgesic and anti-inflammatory activities in mice and rats. The two extracts exhibited significant analgesic activity as compared with the control (saline, 10ml/kg) as evidenced by a significant increase( $p<0.01$ ) in reaction time. The analgesic activity was higher in acetone extracts as compared to pentazocine (5mg/kg, p.o). The extracts progressively reduced rat paw oedema induced by subplantar injection of carrageenan. (Killedar & More, 2009).

#### Antipyretic activity

The ethanolic extract was evaluated for antipyretic activity in yeast induced pyrexia model in rats. A dose dependent reduction in yeast induced hyperpyrexia was observed in rats when compared to the standard drug paracetamol. (Joshi *et al.*, 2009).

#### Antigenotoxic activity

The alcoholic and aqueous extracts of leaf when administered to mice, prevented genotoxicity of cyclophosphamide which induced chromosomal aberration and micronucleus formation. The frequency of occurrence of chromosomal aberration and micronucleus were reported to be time and dose dependent. A slight depression in the mitotic index compared to negative controls was observed. (Shetty *et al.*, 2010).

#### Anthelmintic and anti-insect activity

The root extracts were screened for anthelmintic effect using *Pheretima posthuma* (Indian earthworms) and anti-insect effect using *Tribolium castaneum* (Herbst) (red flour beetle). The acetone and methanolic extracts of the roots showed significant ( $p<0.01$ ) activity as compared to control. Albendazole and Piperazine citrate, used as

an anthelmintic activity standard. Neem extract, Celphos (Aluminium phosphide) and citronellal were used as standards for anti-insect activity. The acetone extract at 20mg/ml showed anthelmintic activity compared to Albendazole and insecticidal activity at 10mg concentration comparable to celphos at 5%. (Killedar & More, 2010).

#### Anticancer

The methanolic extract of leaf showed significant dose-dependent cytotoxicity against colon carcinoma cells (HCT-116) with an IC<sub>50</sub> of 276.63 ±11.75 g/mL. The extract also exhibited varying cytotoxic selectivity towards cancer cells as compared to normal cells. Apoptosis was the preferred mode of cell death for anticancer agents in HCT-116 by acridine orange/ethidium bromide (AO/EB) staining. The cell growth inhibition was tested by sulforhodamine assay in both cancer and normal cells. (Chaudhary *et al.*, 2017).

#### Antioxidant

The leaf extract exhibited dose-dependent antioxidant activity. DPPH and ABTS assays conducted using methanolic and chloroform leaf extracts of the plant showed antioxidant activity equivalent to standard BHA. The methanolic extract of the plant exhibited a very good scavenging activity that is more than the ascorbic acid standard used, which could be due to the presence of a high amount of the flavonoids and terpenoids in the extract (Puttaswamy & Achur, 2013).

- 10.1. Clinical pharmacology:NA
11. Toxicity and safety:NA
12. Clinical studies:NA
13. Contraindications:NA
14. Precautions: NA
15. Adverse reactions: NA
16. Marketed formulation, if any: NA

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1. Botanical Name: ***Murraya paniculata* (L.) Jack**
2. Synonyms: *Murraya exotica* L.
3. Family: Rutaceae
4. Common names
  - Bengali: Kamini
  - English: Lime berry, Orange-jasmine
  - Hindi: Bisar, Kamini, Marchula
  - Kannada: Angarakanaganida, Pandry
  - Marathi: Kunti, Marchulajuti, Pandari
  - Oriya: Ban mallika, Har kankali
  - Sanskrit: Ekangi/Kashteveera
  - Tamil: Konji
  - Telugu: Karepaku, Nagagolunga.
5. Description: An evergreen shrub or small tree, up to 10 feet high. Leaves opposite, imparipinnate, 3-7-foliolate, rarely trifoliolate, glossy, usually glabrous; leaflets cuneate-obovate, ovate, elliptic or almost rhomboid, sometimes reflexed marginally, acute to acuminate, coriaceous. Inflorescences-axillary, paniculate, petals white, corymbose, fragrant. Fruits Fruit a berry, oblong or ovoid, pointed; seeds 2, red when mature.
6. Distribution: It is distributed to India, Sri Lanka, SE Asia, and Malaysia to Australia; found in India, Maharashtra, Karnataka, Kerala and Tamil Nadu.
7. Part Used: Whole plant.



*Murraya paniculata* (L.) Jack

## 8. Medicinal/therapeutic uses

Various parts of this plant have been used in traditional medicine. In Bangladesh the leaf extract is orally used to alleviate pain. In India, people sometimes used root bark of this plant as remedy for coughs, hysteria, rheumatism and diarrhoea (Saqib *et al.*, 2015; Parrotta *et al.*, 2001). Furthermore, cooked leaves and boiled twigs applied to assuage inflamed joints and stomach-ache respectively in India. Used in the treatment of toothaches, stomach pain, gout and abortion. The plant has folkloric repute to manage gastrointestinal, respiratory and cardiovascular diseases but no scientific study has been conducted so far to provide basis for its traditional use (Sukohar *et al.*, 2017; Wu *et al.*, 2016; Chowdhury *et al.*, 2008).

### 8.1. Uses described in pharmacopoeias and traditional system of medicines

Leaves of this plant are used as a stimulant, astringent and are utilized by local people to cure diarrhoea, dysentery, cough, rheumatism, thrombosis, ache stasis. (Parrotta *et al.*, 2001). It is taken as drink for the treatment of venom bite or as a scrubber on bitten limb. The root and bark is chewed and rubbed to skin to cure body aches. The crushed leaf is applied on fresh cuts, and drunk in dropsy as remedy (Alagesaboopathi *et al.*, 2013, Aziz *et al.*, 2010). It can be used in treatment of toothache, stomach-ache and gout (Faisal *et al.*, 2014, Shabir *et al.*, 1997). It has abortive function and used in treatment of venereal disease (Jiang *et al.*, 2016). The phytochemical constituents, antimicrobial and analgesic properties of this plant, has ethno medicinal uses in the Indian sub-continent for treatment of toothache. We conclude that this plant can form an effective remedy for toothache treatment and merits scientific attention towards discovery of possibly novel drugs.

### 8.2. Uses supported by clinical data

The extracts showed analgesic (Podder *et al.*, 2011), anti-giardial (Sawangiaroen *et al.*, 2005), anti-amoebic (Sawangiaroen *et al.*, 2006; Fatkenheuer *et al.*, 1997), anti-inflammatory (Wu *et al.*, 2016), anti-cancer, larvividal, vasorelaxant (Kishii *et al.*,

1992), anti-oxidant, anti-implantation, ant-nociceptive (Sharker *et al.*, 2009), oxytocic, and anti-fungal (Sundaram *et al.*, 2011), anti-diabetic (Gautam *et al.*, 2012), antispasmodic activity, anti-bacterial (Patel *et al.*, 2016), etc.

### 8.3 Traditional/folklore uses described in folk medicine and supported by experimental or clinical data

In India, the plant is widely used in folklore medicines, such as ant nociceptive, anti-inflammatory, and as an anti-oxidant (Sharkar *et al.*, 2009). It is used as a species in Pakistan. It has a diverse used for hilts and daggers (kris or kreeses) in Malaysia and Indonesia and its barks or leaf extracts is used as a traditional medicine for wide range of purpose. (Nguyen *et al.*, 2019). It is also used in breeding of root-stocks for citrus, as it contains compounds which can tolerate lime and nematodes. In Bangladesh the leaf extract is orally used to alleviate pain (Chowdhury *et al.*, 2008). In the Philippines, leaves were also used to treat diarrhoea and dysentery because of their stimulant and astringent activities. Their root bark is used as an anodyne or local anaesthetic for the treatment of gout, contusion and bone ache. The ground bark of plant is used in mixture of a drink and as antidote in snake bites and rubbed on the bitten limb. The ground bark of the root is eaten and rubbed on body to cure body ache (Kinoshita *et al.*, 2002). The powdered leaves are used as an application to fresh cuts, and decoction of the leaves is drunk in dropsy. They possess antibiotic activity against *Mycococcus pyogenes* and *Escherichia coli* (Aziz *et al.*, 2010).

### 8.4. Special uses in north east India

It is cultivated as an ornamental tree or hedge because of its hardiness, wide range of soil tolerance. Traditionally, we use leaves to cure diarrhoea and ache.

### 8.5. Dosage form used in tradition

The folk medicinal practitioners of Jessore district in Bangladesh advise boiling the leaves of the plant in water and then gargling with the water (to which a little table salt has been added) three to four times daily for three days. It is added to food and beverages by local peoples to enhance flavour and fragrance besides its various therapeutic applications in Pakistan. Its leaves are used in preparing soup, fish and meat and chicken dishes (Faisal *et al.*, 2014).

## 9. Phytochemical profile

Phytochemical analysis contains carbohydrates, proteins, amino acid, phytosterol, indole alkaloids, coumarins, phenols, exotines, terpenoids, cinnamates, flavonoids and flavone derivatives were identified. A large number of phytoconstituents have been reported from the plant, which has been reviewed (Chowdhury *et al.*, 2008; Ng *et al.*, 2012).

Leaves oil - Indole alkaloid, oxygenated flavones, sesquiterpenes (lcadinene), methylanthranilate and sesquiterpene alcohol. The oil also contains methylsalicylate,

$\alpha$ -cubebene,  $\beta$ -cubebene,  $\beta$ -cyclocitral , isogermacrene, trans-nerolidol, (-)-cubenol,  $\beta$ -caryophyllene.

Coumarins isolated from leaves include paniculatine, coumurrayin, osthol, 8-isopentenyllicettin, phebalosin, murralongin, imperatorin, murragin, isomexoticin, mupanidin, murpanicin, hainanmurpanin, isomerazin, 7-methoxy-8-(2'- methyl-2'-formylpropyl) coumarin, murrayanone, murraculatin germacrene D and bicycle-germacrene (Ng *et al.*, 2012; Sayar *et al.*, 2014; Ito *et al.*, 2005).

Roots -Indole alkaloid derivatives named paniculidines D-fand six analogs (4-9). Coumarins isolated from roots include mexoticin, murrangatin, murralongin, murrangatinepalmitate, sibiricin, omphamurin, murraol, murracarpin, murralonginolisovalerate, isomurralongialisovalerate, murrangatineisovalerate, chloculol, 6-methoxy-7-geranylloxy coumarin, umbelliferone, 8-(2'- oxo-3'-methyl) butoxy-7-methoxy coumarin, minumicrolin.( Ng *et al.*, 2012; Sayar *et al.*, 2014; Ito *et al.*, 2005).

Flowers - Scopoletine glycoside, scopoline, murralongin, merranzin hydrate, 5,7-dimethyl -8-(3'-methyl-2-ketobutyl) coumarin, murpanidine, auraptenol, 7-methoxy-8 (1'-ethoxy-2'- hydroxyl-3'-methyl-3'-burenyl) coumarin, yuehgesins A-C, braylin, omphalocarpin, (-) murracarpine, murrayacarpines A and B (Chowdhury *et al.*, 2008; Olswore *et al.*, 2005).

Stem - 7-(3-methyl-2- butenyloxy)-8-(3-butetyl-3-methyl-2-oxo) coumarin, 7-O- $\beta$ - D-glucopyranosyloxy-8-(3-butetyl-3-methyl-2-oxo) coumarin, 8-(butenyl-3'-methyl)-7-O- $\beta$ -D-galactopyranoside, 7-methoxy-8- (2'-isovaleryloxy-3-butetyl-3-methyl) coumarin, marmesin-4'- O-a-L-arabinopyranoside, 7-methoxy-8-(3-butetyl-3-methyl-2- oxo) coumarin, and 7-methoxy-8-(butenyl-3'-methyl) coumarin (Sayar *et al.*, 2014).

Fruits –scopoletine (Olswore *et al.*, 2005).

## 10. Pharmacological Studies

Some of the important pharmacological actions as follow analgesic, anti giardial, anti-amoebic, hypoglycial activity, anti-bacterial, ant- microbial, anti-cancer,etc.

**Analgesic:** In acetic acid induced writhing model in Swiss-albino mice, bark extract at a dose of 200 and 400 mg/kg body weight caused significant inhibition of writhing by 37 ( $p < 0.001$ ) and 45% ( $p < 0.001$ ) respectively (Podder *et al.*, 2011).

**Anti-giardial:** Giardia intestinal is one of the most common, universal pathogenic intestinal protozoan parasites of humans. It is becoming increasingly important among HIV/AIDS patients. The plants have potential for use as therapeutic agents against *G. intestinalis* infections (Sawangjaroen *et al.*, 2005).

**Anti- amoebic:** Amoebiasis is an increasingly important parasitic disease among patients with HIV infection regardless of whether they have AIDS. Although HIV/AIDS patients are not especially prone to infection with *Entamoeba histolytica*, it has been suggested that they are more susceptible to an invasive form of the disease than are normal patients (Fatkenheuer et al., 1977; Hung et al., 1999). Infection with *E. histolytica* has also been reported to be an important cause of acute and chronic diarrhoea in HIV patients (Waywa et al., 2001; Joshi et al., 2002; Arenas-Pinto et al., 2003). The anti-amoebic activities of chloroform extracts used by AIDS patients in southern Thailand were screened, at a concentration of 1,000 µg/ml, against *E. histolytica* strain HTH-56:MUTM and strain HM1:IMSS growing in vitro. The extracts were incubated with 2x10<sup>5</sup> *E. histolytica* trophozoites/ml of medium at 37°C under anaerobic conditions for 24 h. The cultures were examined with an inverted microscope and scored (1–4) according to the appearance and numbers of the trophozoites. The extracts that caused inhibition were selected and retested using the same conditions but with concentrations that ranged from 31.25 to 1,000 µg/ml using *E. histolytica* strain HM1:IMSS, and the IC<sub>50</sub> values for each extract were calculated. It (IC<sub>50</sub> 116.5 µg/ml) was classified as being “moderately active”. The IC<sub>50</sub> of a standard drug, metronidazole, was 1.1 µg/ml (Sawangjaroen et al., 2006; Sawangjaroen et al., 2005).

**Hypoglycaemic activity:** The effects of total flavonoids extracted from the leaves on diabetic nephropathy. Treating certain amount of extracts in rats showed significantly decreased the levels of serum blood urea nitrogen, serum creatinine, creatinine clearance, interleukin-6, urinary albumin, 24h-urinary albumin excretion rate, and fasting blood glucose in diabetic rats. It also shows the decrease in triglyceride, total and LDL cholesterol levels (Zou et al., 2014).

**Antibacterial assay:** The antibacterial activity of *M. Paniculata* (Methanolic extract) on *Xanthomonas citri* showed different results on different level of concentration (40µg/ml, 80 µg/ml, 120 µg/ml, 160 µg/ml, 200 µg/ml) but the maximum zone of inhibition was found on 200 µg/ml that is 25mm( leaves). On the same concentration the positive control Kanamycin gave 30mm zone of inhibition which indicates leaf extracts were effective against tested bacterial strains. The leaf extract revealed the presence of alkaloids, flavonoids, phenolic compounds, which are all reported to have growth inhibition against gram positive and gram negative bacteria (Patel et al., 2016).

**Antioxidant Activities:** Recently in 2011 it has been reported the antioxidant property for the first time. They detected seventy polymethoxylated flavonoids (PMFs) in the leaves extract and thirty nine PMFs in the branches extract of the plant. PMFs include a particular group of flavonoids responsible for numerous biological properties including antioxidant activity (Sayar et al., 2014, Ito et al., 2006).

**Antimicrobial Activity:** The extract has been traditionally used as an antimicrobial medication and is believed to demonstrate significant antimicrobial activities. The leaves extract has been reported to be safe in its oral effective dose as it did not indicate toxicity when tested on rodents (Sayar *et al.*, 2014, Akbar *et al.*, 2011).

**Anti-cancer:** The major compound found in oil, (E)-caryophyllene, was found to possess cytotoxic activity against MDA-MB-231, and Hs 578T human tumour cells (Sayar *et al.*, 2014).

**Anti-inflammatory:** For treatment of toothache, two modes of treatment have been reported ethno medicinally, either gargling with hot water extract of leaves or brushing teeth with stems. Therefore, relevant phytochemicals for relieving toothache must be searched among the leaves and stems. One such analgesic phyto-constituent, namely isomurrayafoline, has already been reported from leaves (Narkheda *et al.*, 2012; Sukohar *et al.*, 2017).

**Antinociceptive Activity:** Oral administration of *M. paniculata* leaves extract measure the antinociceptive activity. They injected the 0.7% of acetic acid solution to the Swiss albino mice and then oral administration of 250 and 500 mg/kg leaves extract produced significant antinociceptive activity of 26.27 and 66.67 writhing inhibitory percentage in mice in a dose dependent manner. It was reported oral administration of ethanol extract of leaves at the doses of 50, 100 and 200 mg/kg significantly inhibited the writhing at the rate of 28.84%, 54.93% and 67.91%, respectively in Swiss albino mice, which has been intraperitonally administrated with acetic acid [5]. On the basis of these results it can be suggested that bark and leaves extracts might possess antinociceptive activity (Narkheda *et al.*, 2012).

**Anti-spasmolytic:** That plant usually exhibit spasmolytic effect due to calcium channel blocking mechanism or potassium channel opening (Saqib *et al.*, 2018).

**Anti-obesity:** There is a decrease in the mean Body Mass Index (BMI) were significantly after giving kemuning leaves infusion in obese patients (Sukohar *et al.*, 2017).

### 10.1.Clinical pharmacology

The current state of research implicates great potential of the isolated bioactive compounds in treating diseases. With the advancement in medicinal chemistry and bioinformatics, the ethno medicinal usage can be scientifically explained and proved through *in vitro* or *in vivo* studies and may consequently be developed as potential plant-based drugs. It is found that found in extract has indicated significant cytotoxic activity against U251, HeLa, H460, HepG2 and MCF-7 cell lines (Sayar *et al.*, 2014)

From the studies Fatima *et al.* (2015) that it possesses anti-spasmodic, bronchodilator and vasodilator effect mediated possibly through Ca<sup>+</sup> antagonist property, which provides pharmacological basis for its folkloric use in hyperactive gastrointestinal and respiratory disorders (Fatima *et al.*, 2015). From the isolated

jejunum experiment, plant extract was checked on isolated rabbit jejunum for the presence of spasmolytic activity. Rabbit was killed at its cervical portion, jejunum portion was taken out. Isolated jejunum preparations shows rhythmic contraction spontaneously in controlled experimental conditions and allow the analysis of relaxing effect in the absence of agonist. Spasmolytic activity was observed by application of dose of extract in cumulative fashion. The relaxant effect of plant extract was taken as percentage difference in spontaneous contraction of isolated jejunum preparation noted immediately prior to adding any test material. This type of study is also used to distinguish between potassium channel openers and calcium channel blocker. It is interesting that calcium channel blockers are used in management of diarrhoea through their anti-spasmodic property (Saqib *et al.*, 2015).

Gautam *et al.* (2012) reported that antioxidants significantly increased in Sprague-Dawley rats after 14 days oral administration of ethanol extract of leaves. They found administration of 100, 200 and 400mg/kg of the leaves extract increased superoxide dismutase (SOD) from 80.43 to 109.31 U/mg protein, catalase (CAT) from 36.17 to 59.18 U/mg protein and glutathione peroxidase (GPx) from 1.51 to 2.12 U/mg protein. They mentioned antioxidant activity of leaves extract is due to presence of alkaloids, flavonoids and phenolic compounds (Sabhir *et al.*, 1997).

## 11. Toxicity and safety

- It has been reported that leaves extracts show significant cytotoxicity activity against MDA-MB-231, and Hs 578T human tumour (Sayar *et al.*, 2014; Jada *et al.*, 2007).
- It has been reported the extracts has cytotoxic effects on breast cancer, and to other cancer celllines. This cytotoxic activity may be due to presence of umbeliferone and scopolin and two coumarin found in this plant (Sayar *et al.*, 2014).
- According to Irwin *et al.*,(2015), the rats administered this plant extracts at 2000 and 5000mg/kg by the oral route, there were no abnormal toxicity sign such as pilorectin, diarrhoea, and alteration in locomotors activity or death during 14 days observation (Saqib *et al.*, 2015; Arenas-Pinto *et al.*, 2003).

## 12. Clinical studies

The leaves act as an anti-obesity, but also acts as a hepatic-protector from its content of flavonoids which acts as an anti-oxidant to liver cells. They infused the leaves with SGOT and SGPT enzymes in obese patients. They used 15 male obese patients aged 25-50years.15g of leaves were boil in leaves simplicon in 500 cc boiled water ( $70^{\circ}\text{C}$ ) for about 15 minutes or until the volume reduced by half (250 cc). Each male was given 250 $\mu\text{l}$  of the leaf's infusion treatment twice a day after meal for 15 days. The serum level of SGOT and SGPT of each male patient were recorded and compared it before and after consumption. The average value of

SGOT pretest is 35,87 U/l, SGPT 41,20 U/l, and posttest SGOT 25,47 U/l, SGPT 31,67 U/l with Paired T test bivariate analysis of SGOT p=0,011 and SGPT p=0,032. The leaves infusion could decrease SGOT and SGPT enzymes activity in obese patients (Sukohar *et al.*, 2018).

13. Contraindications: NA.

14. Precautions: NA

15. Adverse reactions: NA

16. Marketed formulation, if any: NA

17. References

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1. Botanical Name: ***Nyctanthes arbor-tristis L.***
2. Synonym: NA
3. Family: Oleaceae
4. Common names
  - Bengali: Seoli, Sephalika;
  - English: Coral jasmine, Night jasmine;
  - Gujarati: Jayaparvati;
  - Hindi: Harisinghar, Seoli;
  - Kannada: Harsing, Parijata;
  - Malayalam: Parijatakam, Pavizhamalli;
  - Marathi: Khurasli, Parijatak;
  - Oriya: Godokodiko, Gunjo seyoli, Singaroharo;
  - Sanskrit: Parijata, Sephalika;
  - Tamil: Manjhapu, Parijatham, Pavalamalli;
  - Telugu: Kapilanagadustu, Pagadamalle, Parijatamu.
5. Description: A deciduous shrub or small tree, sometimes found in forest fringe as escape. Branchlets pubescent, 4-angled. Leaves ovate, shortly acuminate, distantly toothed or entire, coriaceous, scabrid, base rounded, cuneate or acute. Flowers white, sweet scented, sessile, 3-7 together on hairy quadrangular peduncles arranged in cymose panicles. Calyx tube funnel shaped, 4-5 toothed; corolla tube cylindrical, orange red, lobes white, 5-8, contorted in bud. Anthers sub-sessile near the mouth of the corolla tube. Ovary 2-celled, style cylindric, bifid. Fruit is a compressed orbicular capsule. It is a very common ornamental species planted in many places for its fragrant flower.
6. Distribution: Indigenous to India (subtropical Himalayas); found under cultivation/planted almost in all the states.
7. Part Used: Aerial part.



*Nyctanthes arbor-tristis* L.

## 8. Medicinal /Therapeutic uses

### 8.1. Uses described in pharmacopoeias and in traditional systems of medicine:

The leaves of this plant have broad spectrum of medicinal use such as anti-bacterial, anti-inflammatory, anti-pyretic, anti-helminthic effect, antioxidant activities, anti-leishmaniasis, anti-viral, antifungal, anti-histaminic and anti-malarial activity. It is also used as laxative, in rheumatism, in piles treatment, in liver and biliary disorders, skin ailments, sciatica and as a sedative (Bhalakiya & Modi, 2019; Hiremath *et al.*, 2016; Shukla *et al.*, 2012). Seeds of this plant are used for the treatment of hair and scalp issues such as scalp scurvy, alopecia and diseases caused by helminthes (Chatterjee *et al.*, 2007; Nair *et al.*, 2005). Seeds also possess antiviral activity against Encephalomyocarditis and Semliki forest virus (Gupta *et al.*, 2005). The bark is used for the treatment of bronchitis and snakebite (Chatterjee *et al.*, 2007). In central India, various parts are used to relieve cough, hiccup, dysentery, snakebite, and sores by the tribal people. The inflorescence is used to treat scabies and other skin diseases (Jain *et al.*, 2005).

8.2. Uses supported by clinical data: Not available

8.3. Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

- Treatment of scalp diseases and improves hair growth. It is found that the natives of Bagbahera region use seeds as hair tonic to get rid from dandruff and lice. Reduce cold by chewing the bark with betel nut and leaf and used in treatment of fever and body pain. The paste of boiled stem bark with Arjuna is rubbed on the body to cure internal injury and joint broken bones (Sasmal *et al.*, 2007).
- Decoction of root is used in treatment of enlarged spleen, used as anthelmintics and barks are used to treat dysentery and diarrhea (Kirtikar & Basu, 2000; Sasmal *et al.*, 2007; Jain, 1991).

8.4. Special uses in North East India

Apart from its role in offering to god is mainly used to cure inflammatory diseases, respiratory congestion, and fever, it is also well known for its anthelmintic property (Ningthoujam *et al.*, 2013; Dolui *et al.*, 2004). The crushed leaves are used for treatment of malaria (Ningthoujam *et al.*, 2013; Dolui *et al.*, 2004).

8.5. Dosage forms used in tradition

Leaves juice (10-15 ml) to be taken orally to work as anthelmintic, 15 ml flower juice (orally) for treatment of black water fever (Dolui *et al.*, 2004). 10-20 ml of leaf juice with honey is used to treat chronic fever and with loha-bhasma (ayurvedic medicine) used in treatment of anemia, and hepato-billary diseases. Decoction (50-100 ml) of the leaves is used for obstinate sciatica. Mixture of bark oil along with rice gruel and rock salt is used in treatment of eyes diseases. For the treatment of anemia, the tender leaves with ginger juice and honey along with loha bhasma is found effective (Hiremath *et al.*, 2016).

9. Phytochemical profile

Leaves contain Mannitol, an amorphous resin, glucoside, glucose and essential oil, vitamin C, carotene,  $\beta$ -amyrin,  $\beta$ -sitosterol, hentriaccontane, benzoic acid, flavanol glycosides- Astragaline (Kaempferol 3-glucoside), Nicotiflorin (kaempferol 3-rhamnoglucoside), Triterpenoid (oleanolic acid, nyctanthic acid, friedeline, lupeol tannic acid, ascorbic acid, methyl salicylate, an amorphous glycoside), Iridoid glycosides (arborsides A, B, C), Iridoid glycoside (6,7-di-O-benzonylnyctanthoside (I), 6-O-trans-cinnamoyl-6-b-hydroxyloganin (II), 7-O-trans-cinnamoyl-6-b-hydroxyloganin), Phenylpropanoid glucoside (desrhamnosylverbascoside5), Iridoid glucoside (arborside D), Calceolarioside A, Polyacetyles and flavanol glycoside (quercetin-3,30 -dimethoxy-7-O-rhamnoglucopyranose), Octacosane, 10 -hydroxyl-30, 4-dimethyl-1,10 -bi (cyclohex-3-en)-2 one,  $\beta$ -sitosterol (Rani *et al.*, 2011; Agrawal & Pal, 2013).

Flower contains Essential oil, nyctanthin, D-mannitol, Arborside C, 6-b-hydroxyloganin, nyctanthoside, D-mannitol and flavanoids (astraglin and nicotiflorin),

Carotenoid glycoside ( $\beta$ -monogentiotioside ester of a-crocetin (or crocin-3),  $\beta$ -monogentiotioside- $\beta$ -D monoglucoside, ester of a-crocetin (crocin 2),  $\beta$ -digentiotioside ester of a-crocetin (or crocin-1) Cyclohexylethanoid rengyolone; a new iridoid glucoside (6-O-trans-cinnamoyl-7-O-acetyl-6b-hydroxyloganin), Sugars, carotenoids, aglycone (crocetin) (Rani *et al.*, 2011; Agrawal & Pal, 2013).

Seeds contain Glycerides of linoleic, oleic, lignoceric, stearic, palmitic and myristic acids, 3,4 secotriterpene acid, vitamin A, parasitosterol, sterol (nycosterol), Tetracycline terpene (nyctanthic acid) Glycerides (trisaturated, disaturated, mono, di and tri unsaturated acid, Arbortristoside A and B, 4-O- $\beta$ -D-mannopyranosyl-D-mannopyranose, O- $\beta$ -D-glucopyranosyl-(1-4)-O- $\beta$ -D-mannopyranosyl- (1-4)-O- $\beta$ -D-mannopyranose, Iridoid glycoside (Arbortristoside A) (I), nyctanthic acid, oleanic acid, friedelin,  $\beta$ -sitosterol glucoside, 6 bhydroxyloganin. Arbortristoside D and E, Melanin, Water soluble polysaccharide composed of D-glucose and D mannose Arbortristoside A and C, Phenylpropanoid glycoside (nyctoside A), stearic acid, lauric acid, linoleic acid and oleic acid. Stem contains Glycoside-naringenin-40-O- $\beta$ -glucopyranosyl-a-xylopyranoside and  $\beta$ -sitosterol (Rani *et al.*, 2011; Agrawal & Pal, 2013).

## 10. Pharmacological Studies

Anti-arthritis activity of seeds, leaves and fruit extract were tested against adjuvant induced (Freud's complete adjuvant) arthritic mice model on 0 and 10<sup>th</sup> days. On daily treatment with extracts of leaves and fruit resulted in reduced TNF  $\alpha$ , IL-1, IL-6 from 14th day. A shift in balance between pro-inflammatory and antiinflammatory cytokines was observed in adjuvant induced mice, hence supporting inflammation. The extract of leaves and fruit was found to possess anti-arthritis properties (Rathore *et al.*, 2007)

Antidiabetic activity of the ethanol extract of stem bark was performed that exhibited dose-dependent antidiabetic property. With the treatment of stem bark the levels of serum cholesterol and triglycerides were controlled in diabetic rats. This may be due to the hypolipidemic effect of ethanolic extract and significant restrain of TBARS in liver was observed. Significant reduction in lipid peroxidation, serum glutamic pyruvic transaminase, serum glutamic oxaloacetic transaminase, Alkaline Phosphatase, cholesterol and triglyceride levels were observed after administration of chloroform extracts of leaves and flower (50, 100 and 200 mg/kg) orally for 27 days on STZ diabetic rats compared to diabetic control rats. (Husain *et al.*, 2010).

Antioxidant activity of acetone-soluble fraction of the leaf extracts showed notable antioxidant activity as showed by few in vitro experiments like DPPH, hydroxyl, and superoxide radicals, as well as H<sub>2</sub>O<sub>2</sub> scavenging assays, metal chelating assays etc (Rathee *et al.*, 2007).

Antileishmanial activity was done with the methanolic extract of leaves and found that iridoid glucosides (arbortristosides A, B, C and 6- $\beta$  hydroxy-loganin) possess antileishmanial activity when tested in vitro (against amastigotes in macrophage cultures) and in vivo (in hamsters) test systems. In another study, calceolarioside A

was tested in-vitro and *in vivo* (*L. donovani* Ag83 infected golden hamster) for reduction of hepatic and splenic parasite that proved its potentiality against visceral leishmaniasis (Poddar *et al.*, 2008).

Bharti *et al.* (2011) have tested the wound healing property of leaf extract on Wistar albino rats and complete epithelization of the wound was observed in 16 days as compare to untreated rats.

Ethanol and n-butanol fraction as well as isolated compound (arboristoside A, iridoid glycoside) from ethanol extract of seeds exhibited antiviral potential against Encephalomyocarditis Virus (EMCV) and Semliki Forest Virus (SFV) (Gupta *et al.*, 2005).

#### 10.1. Clinical pharmacology

Leaf extracts was found to be a potential source to cure multiple drug resistant malaria caused by *Plasmodium falciparum*. Malarial patients treated with fresh five leave administered orally (three times a day) for 7-10 days showed relief of symptoms and signs. With this treatment, among 120 patients, ninety-two (76.7%) showed complete cure within 7 days with few exceptions that cured by 10 days. It is found that the paste was well tolerated, and no severe side effects were reported thus concluded that dose dependent treatments can significantly cure malaria (Karnik *et al.*, 2008).

#### 11. Toxicity and safety

Cytotoxic test of this plant was done with benzofuran derivative 4-hydroxyhexahydrobenzofuran-7-one that was obtained from the plant extracts and evaluated in Swiss Albino mice (20mg/kg mouse/day) and negligible cytotoxic effect was observed (Khatune *et al.*, 2003). Khatune (2001), have studied the LD<sub>50</sub> (14.80, 12.62, 12.79 respectively) of chloroform, ethyl acetate and petroleum ether extract of flower and found cytotoxic activity against *Artemia salina* (Brine shrimp). While studying the anti-inflammatory activity of leaves it was observed that a dose of 32 g/kg exhibited 75% mortality in albino rats (Saxena *et al.*, 1984). However the seeds are found to be more toxic than the leaves, LD<sub>50</sub> of arboristoside-A, a compound found in seeds exhibited 100% mortality at 1 gm/kg in mice on intra-peritoneal administration thereby suppressing the locomotory activity in mice (Das *et al.*, 2008 a, b). Iridoid glucosides found when tested for toxicity against Human embryonic kidney (HEK 293) and mouse macrophage (J774A.1) cell lines resulted that the compounds are safe for therapeutics application (Shukla *et al.*, 2012).

#### 12. Clinical Studies

Clinical study of antimalarial property was examined against malarial parasite *P. vivax* infected 21 patients selected randomly with around 61 % of patients were from age group of 20-30 years (7 females and 14 males). Improvement was observed at the end of first week of treatment by decreasing body temperature however, complete recovery from the infection was observed by the end of 2<sup>nd</sup> week of treatment (Ghiware *et al.*, 2007).

### 13. Contraindications

The flowers infusion is found to possess sedative activity with single oral treatment on healthy adult cross-bread albino males rats weighing 200–250 g and female rats weighing 200–225 g. Rearing, head dipping, cumulative time spent on head dipping, and locomotory activity in male rats were more prominent than the female rats, however, no impairment on male libido or fertility was observed (Ratnasooriya *et al.*, 2005).

### 14. Precautions: No study found.

### 15. Adverse reactions

Usage of the plant is dose base so overdose can cause diarrhea and even death under extreme medical condition. Consult an Ayurvedic doctor or traditional healer before consuming.

### 16. Marketed formulation, if any

- SBL Nyctanthes Arbor Tristis Mother Tincture Q
- Biotique Carrot 40 SPF Sunscreen for all Skin Types Lotion
- Dr Willmar Schwabe India Nyctanthes Arbortristis Dilution 1000 CH
- Bjain Nyctanthes Arbortristis Globules 30 CH
- Bio Resurge Arthosurg-G Tablet
- Allen's Arnica Plus Hair Vitalizer

All of the above-mentioned formulated products used either *N. arbor tristis* L. solely or used it as one of the key ingredients.

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1. Botanical Name: **Polyalthia suberosa** (Roxb.) Thwaites

2. Synonym: *Uvaria suberosa* Roxb.

3. Family: Annonaceae

4. Common names

English: Corky Debbar Tree

Hindi: Cham-khirni

5. Description: A medium-size tree up to 20 feet high with young branches tomentose. Leaves simple, alternate, distichous, estipulate; petiole 2-3 mm long, brown pubescent, slender; oblong, elliptic-oblong or oblong-lanceolate, base slightly narrowed, oblique or obtuse, apex obtuse or obtusely acute, margin entire, undulate, glabrous and shiny above, pubescent and pale beneath, submembranous; lateral veins 9-12 pairs, pinnate, faint; intercostae reticulate. Flowers bisexual, yellowish-green, mostly suffused with purple, solitary, rarely in pairs, extra-axillary; pedicels slender; sepals 3, spreading, ovate, acute, pubescent outside, glabrous inside, petals 6 (3+3); outer petals ovate to oblong-lanceolate, acute, slightly reflexed, thickly coriaceous, silky pubescent outside, glabrous inside; inner ones slightly longer; torus convex; stamens numerous, ca. 1 mm long, connectives slightly convex at top concealing the anther cells; carpels many, pubescent, ovule one, style oblong, stigma triangular, flat. Fruit aggregate of berries; fruitlets subglobose, purple, puberulous. Seeds 1, globose, smooth.

6. Distribution: Indo-Malaysia region, Bangladesh, China, Myanmar, Sri Lanka, Thailand, and Vietnam. In India West Bengal, Assam, Meghalaya, Orissa, Madhya Pradesh, Andhra Pradesh, Tamil Nadu and Kerala.

7. Parts Used: Stem and leaf.



*Polyalthia suberosa* (Photo by: Priyanka Ingle, BSI)

## 8. Medicinal /Therapeutic Uses

### 8.1. Uses described in pharmacopoeias and traditional systems of medicine

In Indian System of Medicine, the Genus *Polyalthia* plants are being used as bitter tonic, abortifacient, febrifuge, a cure for scorpion stings, high blood pressure, and, a respiratory stimulant. (Kitikar *et al.*, 1975). It is useful against microbial infection, inflammation in the eye. (Uddin *et al.*, 2013)

### 8.2.Uses supported by clinical data: NA

### 8.3.Traditional/ Folklore uses described in Folk medicine, not supported by experiment or clinical data

The roots are used to treat fever in Tiruchirappalli District, Tamil Nadu (Nandagoapalan *et al.*, 2014). Ripe fruits are eaten as diuretic, soporific, and sedative in Barishal, Bangladesh (Islam *et al.*, 2019). It has been traditionally used as adaptogenic drug (Mistry *et al.*, 2010).

In folk medicine, is used as abortifacient, laxative, febrifuge analgesic, filler of tooth cavities, and anti-HIV drug and for rheumatism and various skin infections (Yasmen *et al.*, 2018). In Andhra Pradesh, India, decoction of grounded root bark mixed with fruits of *Piper longum* used for puerperal fever (Sri *et al.*, 2014).

#### 8.4. Special Uses in North East India: NA

#### 8.5. Dosage forms used in tradition: NA

### 9. Phytochemical profile

The methanol extract of leaves of showed the presence of alkaloids, tannins, steroids, glycosides, saponins, xostepha-nine and lanuginosine. The leaves contain alpha-and beta-amyrin, lupeol, beta-sitosterol, stigmasterol and campes-terol (Muthuraja *et al.*, 2014).

#### 9.1. Major chemical constituents

Tetrahydro protoberberine (Tetrahydropalmatine) (Sahai *et al.*, 1996). Tripertine (Subersol) (Li *et al.*, 1993). Kalasinamide (Tuchinda *et al.*, 2000). Phenyl tetrahydrofuran-5-pyrone [23 (2-furyl) tricos-5, 7 dienoic acid, 1 (2-furyl) pentacos-16, 18 diyne] (Tuchinda *et al.*, 2001).

### 10. Pharmacological Studies

Crude extract of leaves of may possess antibacterial, analgesic, antidiarrhoeal and cytotoxic effects (Bellah *et al.*, 2012).

It contains a compound, Suberosol (Class: C-31, Lanostane Triterpene) which possesses anti HIV activity (Ito *et al.*, 1993). Two new 2 -substituted furans, 1- (2-furyl) pentacos-16, 18-diyne and 23- (2-furyl) tricos-5, 7-dienoic acid, have been isolated from stems. The structures were assigned by spectroscopic methods. The two compounds together with the previously reported kalasinamide, N-trans-feruloyltyramine and N-trans-coumaroyltyramine showed anti-HIV activities (Tuchinda *et al.*, 2001).

It yields Lantostane-type-triterpene, suberosol which suppresses anti-HIV replication activity in H9 lymphocytes *in vitro*. (Narayan *et al.*, 2013). Anti-HIV replication activity in H9 lymphocyte cells was shown by Lanostane-type triterpene, suberosol isolated from ethanolic extract of the stems and leaves (Li *et al.*, 1993). The stems and leaves contain the triterpene, suberosol, which showed anti-HIV replication activity. The stem bark contains alkaloids, xostepha-nine and lanuginosine, which exhibited antibacterial activity against several Gram-positive (+) and Gram negative (-) bacteria (Muthuraja *et al.*, 2014).

### 10.1.Experimental pharmacology

**Antibacterial Activity:** It showed moderate antibacterial activity against *Vibrio cholerae*, *Sheigella sonnei*, *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Streptococcus saprophyticus* where the zone of inhibition was 13, 11, 12, 15, and 10 mm respectively while mild activity against *Shigella dysenteriae*, *Plesiomonas*, *Hafnia* and *Streptococcus pyogenes* where the zone of inhibition was 6-8 mm (Bellah *et al.*, 2012).

**Analgesic Activity:** The effect of the MeOH extract on acetic acid-induced writhing model in mice. The extract produced about 38. 60 % and 59.07% ( $P<0.01$ ) writhing inhibition at doses of 250 and 500 mg/kg respectively, which was comparable to the standard drug diclofenac sodium where the inhibition was about 77.78 % ( $P, 0.01$ ) at the dose of 25 mg/kg (Bellah *et al.*, 2012).

**Antidiarrhoeal Activity:** The effect on castor oil induced diarrhoea in mice. The extract caused an increase in latent period (0. 60 hr) *i.e.* delayed the onset of diarrhoeal episode at the dose of 500 mg/kg as compared to the standard antidiarrhoeal agent loperamide where the mean latent period was 0. 93 min. The extract also decreased the frequency of defecation at the dose of 500 mg/kg where the mean numbers of stool at the 1st, 2nd, 3rdand 4th hour of study were 7. 4, 8, 6.6 and 3.2 respectively which was comparable to the standard drug loperamide where the mean numbers of stool were 7, 8.4, 6.2 and 3.4 respectively (Bellah *et al.*, 2012).

**Cytotoxic Activity (Brine Shrimp Lethality Bio-Assay):** In this bioassay, the extract showed lethality against the brine shrimp nauplii. The extract showed different mortality rate at different concentrations. The plot of percentage mortality versus log concentration on the graph paper produced an approximate linear correlation between them. The concentrations at which 50 and 90% mortality occurred were obtained by extrapolation (LC50: 30  $\mu\text{g}/\text{ml}$ ; LC90: 400  $\mu\text{g}/\text{ml}$ ). Brine shrimp lethality bioassay indicates cytotoxicity as well as a wide range of pharmacological activities such as antimicrobial, pesticidal, antitumor, etc. (Bellah *et al.*, 2012).

**Antioxidant, analgesic and anti-diarrhoeal activity:** Study screened hydromethanol extracts of leaves, bark and fruits for antioxidant, analgesic, and antidiarrheal activity. Bark extracts showed maximum reducing activity, higher than standard reference ascorbic acid. All parts showed analgesic activity with significant ( $p<0.05$ - $0.01$ ) inhibition of writhing reaction in a dose-dependent manner. In castor oil-induced diarrhoea, there was statistically significant ( $p<0.05$ ) inhibition of frequency of diarrhoea, the bark showing 69. 52% inhibition while the fruits showed 63. 81% inhibition at 400 mg/kg dose level. Overall, bark and fruit extracts showed strong antioxidant potential with excellent analgesic and ant diarrhealactivity (Labu *et al.*, 2013).

The stem possesses a remarkable amount of medicinally active compounds which are responsible for high bioactivity that can serve as a potential source of the drug (Akter *et al.*, 2019). The bark and leaves are parts of crude hydromethanolic extract. Which possesses remarkable cytotoxic, CNS depressant and analgesic potential (Mazumdar *et.al.*, 2016).

#### 10.2.Clinical Pharmacology: NA

#### 11. Toxicity and safety

From the acute toxicity study, sign of toxicity or mortality was not observed up to the high dose of 4000 mg/kg for PSDE as well as PSNH or control group. Tree was no change in food intake or other behaviours during 2-week observation period and was the same as prior to the experiment. This seemingly specified that the test groups did not express acute oral toxicity (Yasmen *et al.*, 2018). The extracted mucilage from leaves is non-toxic, has the potential as a suspending agent, binding agent and can be used as a pharmaceutical adjuvant (Sri *et al.*, 2014).

#### 12. Clinical studies: NA

#### 13. Contraindications: NA

#### 14. Precautions: NA

#### 15. Adverse reactions: NA

#### 16. Marketed formulation (if any): NA

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1. Botanical Name:	<b>Psidium guajava L.</b>
2. Synonym:	NA
3. Family:	Myrtaceae
4. Common names:	
Bengali:	Goaachhi, Peyara, Piyara;
English:	Common guava, Yellow guava, Lemon guava. <sup>1</sup>
Gujarathi:	Jamrud, Jamrukh, Peru;
Hindi:	Amrud, Safed safari;
Kannada:	Jama phala, Sebehannu;
Malayalam:	Koyya, Pera;
Marathi:	Jamba;
Sanskrit:	Mansala;
Tamil:	Koyya;
Telugu:	Ettajama, Goyya, Tellajama.

5. Description: A medium-size tree with smooth with peeling bark. Young stem 4-angled. Leaves elliptic-oblong, base rounded to obtuse-cuneate, apex acute-apiculate, hirsute on both sides when young, glabrous on ageing except the nerves, thin-coriaceous, lateral nerves prominent. Cymes axillary, 1-3-flowered; pedicel short. Calyx tube 4-9 mm long, ovoid, densely hirsute; lobes 4, united and closed in bud. Flowers white, broadly ovate, caducous. Stamens many. Ovary globose, many-celled; ovules numerous; style subulate. Fruit a berry, globose crowned by persistent calyx lobes. Seeds many, embedded in fleshy pulp.

6. Distribution: Originally from Tropical America; now naturalized in the tropics. In India the plant is cultivated all most all the states.

7. Parts Used: Whole plant.



*Psidium guajava* L. (Photo: Priyanka Ingle, BSI)

## 8. Medicinal /Therapeutic Uses

### 8.1. Uses described in pharmacopoeias and traditional systems of medicine

Infusion of the roots with the roots or pericarp of *Punica granatum* at 250 ml is used by the Bapedi traditional healers living in Limpopo Province, South Africa, to treat diarrhoea (Semenya & Maroyi, 2012).

### 8.2. Uses supported by clinical data

Anti-diarrhoeal activity: Anti-diarrheal activity of aqueous leaf extract (PGE) was examined on experimentally-induced diarrhoea in rodents that was traditionally used by the African folk medicine to treat plethora human ailments, such as diarrhea. The result showed that the extract (PGE, 50, 100, 200 and 400 mg/kg, p.o) could significantly delay the onset of diarrhoea, reduced the frequency of defaecation and the wetness of the faecal droppings and decreases the weight of the wet stools, indicating that h PGE possesses anti-diarrhoeal activity (Ojewole et.al., 2008).

### 8.3. Traditional/Folklore uses (described in folk medicines, not supported by clinical experiment or clinical data

Malaysia: In Tambunan and Keningau areas of Sabah, the young leaves of guava are used for the treatment of diarrhea, stomachache, dysentery and acute gastroenteritis (Ahmad & Ismail, 2003).

Bangladesh: The stem bark juice was used in dysentery and leave decoction was used for the treatment of toothache and vomiting (Rahman et al., 2008).

Leaves have antimarial, anti-inflammatory, analgesic and antipyretic activities. The leaves are also used for the treatment of fever, diarrhea and in psychiatry as a tonic.

The roots of the plant are used for cerebral affections, nephritis, epilepsy, rheumatism and vomiting (suffering from cholera) (Pullaiah, 2002).

The root and unripe fruit are used for treating diarrhea, while the leaves are used for dysentery (Sairam, 2002).

#### 8.4. Special Uses in North East India

Assam: Young branches to treat female infertility, while the plain tribes of Nagaon district use the leaf of the plant for treating metrorrhagia (Bora et al., 2016). The juice from tender twigs is taken for the treatment of blood dysentery (Purkayastha & Nath, 2006).

#### 8.5. Dosage forms used in tradition

Branch: Juice from the young branch (5-6 numbers) at 30-50ml is given orally up to the third day of menstruation, and 3-5 numbers of leaves are made into a paste and given orally till the disease is cured (Bora et al., 2016).

Leaves: Young leaves are steamed in hot water and drink to relieve from stomachache and diarrhea (Ahmad & Ismail, 2003). For the treatment of dysentery, a handful of leaves are boiled in one cup of water and the egg yolk is mixed together after the volume of water has reduced to half. Four teaspoon of this is taken thrice a day (Sairam, 2002).

Fruit: The unripe fruits are mixed with sugar and eaten, while powdered form of the root bark mixed with little honey is taken at 1/4th teaspoon for diarrhea (Sairam, 2002).

### 9. Phytochemical profile

#### 9.1. Major chemical constituents

Leaf: Phytochemical screening of leaf extract showed the presence of alkaloids, flavonoids, saponin, glycosides and reducing sugar (Chollom et al., 2012). Phytochemical analysis from dry leaf powder showed that it contains flavonoids, terpenoids, quinones and phenol constituents respectively (Gayathri & Kiruba, 2014).

Leaf, bark and root: Ethanolic and aqueous extraction from the leaf, bark and root reported the presence of tannin, polyphenol, alkaloid, saponin and oxalate constituents (Obaineh & Shadrach, 2013).

Essential oil: A total of 27 compounds were identified using Gas chromatography/mass spectroscopy (GC/MS) in the leaf essential oil of which the major compounds were  $\alpha$ -terpinyl acetate (23.57 %), trans-caryophyllene (17.65 %), nerolidol (12.16 %),  $\alpha$ -cadinol (6.71 %),  $\alpha$ -copaene (6.5 %) and minor compounds identified were  $\alpha$ -humulene (3.92 %) and (-)-caryophyllene oxide (3.66 %) (Borah et al., 2019).

## **10. Pharmacological Studies**

### **10.1. Experimental pharmacology**

Antiviral activity: In vitro study of eight Indonesian plant leaves extract viz., *Psidium guajava* (Jambubiji), *Euphorbia hirta* (Patikankerbau), *Piper bettleL.* (Sirih), *Carica papaya* (Pepaya), *Curcuma longa L.* (Kunyit/turmeric), *Phyllanthus niruri L.* (Meniran), *Andrographis paniculata* (Sambiloto), and *Cymbopogon citratus*( Serai) was done to identify their antiviral activity against dengue virus serotype-2 (DENV-2) strain NGC using Huh7it-1 cell lines. It was reported that among the 8 plant leaves extracted, Psidium guajava and Carica papaya have a potential antiviral activity against the virus as it inhibits the virus replication up to 92.6% and 89.5% respectively (Lozoya et al., 2002).

A work to elucidate the anti-influenza activity against the highly mutative influenza virus H1N1 (a clinical influenza A) from dried leaves that have resulted in the limitation effectiveness of influenza vaccines showed that the tea made from the dried leaves of guava has potential anti-influenza activity, by preventing the entry of the virus into the host's cell (Sriwilaijaroen et al.,2012).

### **10.2. Clinical pharmacology**

Determination of the antiviral potential of aqueous leaf extract against Newcastle disease virus in vivo revealed that the leaf extract at concentration of 250mg/ml and 200mg/ml could completely inhibit the growth of the virus in the embryonated egg (Chollom et al.,2012).

### **11. Toxicity and safety: Not available**

### **12. Clinical studies**

A clinical study for evaluating the phytodrug (QG-5®) developed from the leaves of guava was done to treat a group of adult patients suffering from Acute Diarrheic Disease(ADD). In the study, it was reported that the phytodrug decreases the abdominal pain of the patients (Lozoya et al.,2002).

### **13. Contraindications**

It should not be given to children, during pregnancy and lactation mothers.

### **14. Precautions: Not available**

### **15. Adverse reactions: Not available**

### **16. Marketed formulation, if any: Not available**

## 17. References

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1. Botanical Name: ***Punica granatum L.***

2. Synonym: NA

3. Family: Punicaceae

4. Common names

Bengali:	Dalim
English:	Pomegranate
Gujarati:	Dadam
Hindi:	Anar
Kannada:	Dalimba
Malayalam:	Matalam
Marathi:	Dalimba
Sanskrit:	Dadima
Tamil:	Madulai
Telugu:	Danimma

5. Description: A medium-size tree; stem smooth with pealing bark. Young stem 4-angled. Leaves elliptic-oblong, base rounded to obtuse-cuneate, apex acute-apiculate, hirsute on both sides when young, glabrous on ageing except the nerves, thin-coriaceous, lateral nerves prominent; petioles. Cymes axillary, 1-3-flowered; peduncles; pedicel short. Calyx tube 4-9 mm long, ovoid, densely hirsute; lobes 4, united and closed in bud. Petals 4, white, broadly ovate, caducous. Stamens many. Ovary globose, many-celled; ovules numerous; style subulate. Fruit a berry, globose crowned by persistent calyx lobes. Seeds many, embedded in fleshy pulp.

6. Distribution: Indigenous to Iran, Afghanistan and Baluchistan; introduced and cultivated at tropical to subtropical regions of India.

7. Parts Used: Whole plant.



*Punica granatum* L. (Photo: Priyanka Ingle, BSI)

## 8. Medicinal/Therapeutic uses

### 8.1. Uses described in pharmacopoeias and traditional systems of medicine

Northern Thailand: Decoction made from young leaf used for the treatment of diarrhoea by the Karen tribe of Thailand (Tangjitman *et al.*, 2015).

### 8.2. Uses supported by clinical data

Anti-diarrhoeal activity: Methanolic extract from the seed was evaluated for its anti-diarrhoeal activity against different experimental models of diarrhoea in rats. Results showed that seed extract showed significant inhibitory activity against castrol-oil induced diarrhoea and PGE<sub>2</sub> induced enter pooling in rats, which indicates the efficacy of seed extract as an anti- diarrhoeal agent (Das *et al.*, 1999).

### 8.3. Special uses in North East India

Jammu and Kashmir: The fruit, bark, leaves and seeds are used for treating various ailments namely dysentery, jaundice, anaemia and headache (Rao *et al.*, 2015).

North-West Pakistan: The fruit is used as a febrifuge and vermicide (Adnan *et al.*, 2014).

Tamil Nadu: Dried fruit are used for treating diarrhoea and stomachache (Duraipandita *et al.*, 2006).

Venezuelan coast: In Trinidad and Tobago, the seed of *Phyllanthus amarus* is used for treating of stomach problems (Lans, 2007).

#### 8.4. Special Uses in North East India

Assam: Leaves are used to treat diabetes and dysentery (Sharma & Sharma, 2010).

Manipur: The fruits and young twigs are used for treating chest pain, diarrhoea and dysentery (Nanda *et al.*,2013).

#### 8.5. Dosage forms used in tradition

Fruit: Dried fruits are mixed ground and mixed with water and taken internally to treat stomachache and diarrhoea (Duraipanditan *et al.*,2006).

Fruits are ground finely and applied on forehead to relief from headache. Fruits are given as a tonic to anemic persons and if taken twice a day daily are used for the treatment of dysentery. Fruits are eaten to strengthen the heart. A spoonful of the powdered bark is taken as astringent (Rao *et al.*,2015). In Thadou tribe, fruits are punctured and filled with almond oil and tied properly, heated and eaten to cure chest pain, while the young twigs have anti-diarrhoeal activity and the fruits are eaten against dysentery (Nanda *et al.*,2013). The grinded fruits are taken orally 2-3 times a day to kill intestinal germ. The juice from the fruit is mixed with sugar and opium and taken orally to reduce fever (Adnan *et al.*,2014).

Leaves: Leaf Juice is taken orally in treating diabetes or is mixed with *Aegle marmelos* and given in empty stomach to treat dysentery (Sharma & Sharma, 2010).

Seed: Ash obtained from the seeds is styptic (Rao *et al.*,2015).

### 9. Phytochemical profile

#### 9.1. Major chemical constituents

Juice, Peel and Seed: Determination of total phenol distribution from juice, peel and seed from four cultivars viz., Lefan, Katirbasi, Cekirdeksiz-IV and Asinar of *Punica granatum* using Folin-Ciocalteu colorimetric method showed that the highest level of phenolic content were obtained from peel extracts ranging from 1775.4 to 3547.8 mg gallic acid equivalent (GAE)/L among the cultivars (Gozlekci *et al.*,2011).

Whole plant: Phytochemical screening from the whole plant revealed the presence of triterpenoids, steroids, glycosides, saponins, alkaloids, flavonoids and tannins respectively (Bhandary *et al.*, 2012).

## 10. Pharmacological Studies

### 10.1 Experimental pharmacology

Antiviral activity: *In vitro* study of the leaves of *Punica granatum*, *Andrographis paniculata*, *Melia azedarach* and *Momordica charantia* as potential antiviral activity against Human Herpes Virus-3 isolated from Chickenpox and Zoster in comparison with acyclovir showed that aqueous extraction of the leaves of *Punica granatum* has potential antiviral activity against HHV-3 whose *in vitro* activity was comparable with acyclovir (Angamuthu *et al.*, 2019).

Evaluation of peel extract as anti-adenovirus activity *in vitro* by report that the peel extraction exhibited strong activity against adenovirus with a selectivity index (SI) value of 8.9 (Moradi *et al.*, 2016). Antiviral activity of 21 medicinal herbs traditionally used in Southern Mainland China were studied against Human simplex virus type 1 (HSV-1) and Human respiratory syncytial virus and the result showed that aqueous extract of *Agrimonia pilosa*, *Pithecellobium clypearia* and *Punica granatum*, respectively, showed anti-HSV-1 activity probably due to the presence of polyphenolic compounds that contributed to their antiviral activity (Li *et al.*, 2004).

A work to test the effectiveness of a purified flavonoid-rich fruit extract against influenza virus using real time PCR, plaque assay, and TCID 50% hemagglutination assay was done and it was found that PPE suppresses the replication of the virus in MDCK cells and also demonstrated that from the four components of PPE viz., ellagic acid, caffeic acid, luteolin, and punicalagin, punicalagin showed anti-influenza effect by blocking the replication of the virus RNA, inhibit the agglutination of chicken RBC's and had virucidal effects. He also found that the extract increases synergistically the anti-influenza effect of the drug oseltamivir (Haidari *et al.*, 2009).

Antibacterial activity: Aqueous and methanol extract of 26 medicinal plants having antibacterial properties used in Mexico to treat gastrointestinal disorders reports that the extract from *Caesalpinia pulcherrima*, *Chiranthodendron pentadactylon*, *Cocos nucifera*, *Geranium mexicanum* (aerial parts and roots), *Hippocratea excelsa*, and *Punica granatum* possessed strong antibacterial activity against most of the pathogens (Alanis *et al.*, 2005).

Antioxidant: Aqueous and ethyl acetate extraction of *Punica granatum* aril, juice and rind showed that it has a significant antioxidant activity (Ricci *et al.*, 2006).

### 10.2 Clinical pharmacology

Screening fruit juice in its inhibitory effects against HIV-1 IIIB using CD4 and CXCR4 as cell receptors reveal that HIV-1 entry inhibitors from pomegranate juice adsorb onto

corn starch and the resulting complex was also found to blocks the virus binding to CD4 and CXCR4/CCR5 which inhibits infection by primary virus clades A to G and group O (Neurath et al.,2005).

#### 11. Toxicity and safety

Investigation into the toxicity of the whole fruit used in Cuban medicine for the treatment of respiratory diseases showed that doses of the extract of less than 0.1 mg per embryo are not toxic. It was also found that when a dose of 0.4 and 1.2mg/kg of the extract was administered to Wistar rats, no toxic effects were found in terms of food intake, weight gain, behavioral or biochemical parameters.

#### 12. Clinical studies: Not available

#### 13. Contraindications: Not available

#### 14. Precautions: Not available

#### 15. Adverse reactions: Not available

#### 16: Marketed formulation, if any: Not available

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1. Botanical Name: ***Rhus chinensis*** Mill.

2. Synonym: NA

3. Family: Anacardiaceae

4. Common names

English: Nutgall tree, Chinese sumac

Assamese: Noga-tenga, Nagatenga, Nagatenga

Kannada: Sabma, Deing-sohma

Nepali : Bhakmilo

Manipuri: Heimang

5. Description: A medium-size tree up to 20 feet high. Leaves compound, imparipinnate; ovate-elliptic to oblong, rounded at base, acute or acuminate at apex, serrate along margins, tomentose on both sides; secondary nerves 6-8 pairs. Flowers in panicles, white, fragrant; calyx lobes ovate, persistent; petals elliptic-oblong, whitish; stamens 5, ovary conical. Fruit a drupe, obliquely oblong, black when ripe, with persistent calyx.

6. Distribution: Nepal, Bhutan, Myanmar, Thailand, Indo-China, Malaysia, China, Japan and Pakistan. In India distributed Jammu & Kashmir, Himachal Pradesh, Uttar Pradesh, West Bengal, Sikkim, Assam, Arunachal Pradesh, Nagaland, Manipur, Meghalaya and Rajasthan.

7. Parts Used: Whole plant



*Rhus chinensis*

## 8. Medicinal /Therapeutic Uses

### 8.1 Uses described in pharmacopoeias and in traditional systems of medicine

The leaves and the root are used as depuratives, stimulating blood circulation. Its decoction is used in the treatment of hemoptysis, inflammations, laryngitis, snakebite, stomachache, and traumatic fractures (Duke & Ayensu, 1985; Djakpo & Yao, 2010). The ripe fruits of this plant have long been used in Asia to treat dysentery and diarrhea, as well as other gastro-intestinal disorders (Kala, 2005; Pradhan & Badola, 2008; Bose *et al.*, 2008). The fruit produces a sour juice when boiled with water. This juice, when diluted with water or/and mixed with raw eggs, treats diarrhea and dysentery (Pradhan & Badola, 2008). It is used as a food preservative (Pradhan & Badola, 2008). The seed is used in the treatment of cough, dysentery, fever, jaundice, malaria, and rheumatism (Duke & Ayensu, 1985; Abbasi *et al.*, 2009). It is a frequent ingredient in polyhedral prescriptions for diabetes mellitus (Duke & Ayensu, 1985). It has hemostatic effects, often used to promote clotting following traumatic injuries and to treat burns. It is also used to treat rectal and intestinal cancer, prolapse of the rectum, seminal enuresis and hemor-rhoids (Djakpo & Yao, 2010).

8.2 Uses supported by clinical data: anticaries, antioxidant, antibacterial, antiviral, antifungal, anticholesterol, antimutagenicity, hepatoprotective (Heirangkhongjam and Ngaseppam, 2018).

8.3 Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

Traditionally, different parts of the plant such as leaves, stem, flower, fruit, root, seed and gall (abnormal outgrowths of the plant caused by aphids infestation) are used in the treatment of gastrointestinal problems, urinary complaints and many other health issues (Singh *et al.*, 2003). Different parts of the plant was reported for its usage in traditional medicine, in the treatment and prevention of diarrhoea, dysentery, colic, hepatitis, jaundice, kidney and urinary complaints due to stone, coughs, jaundice, malaria, diabetes mellitus, antiseptic, astringent, haemostatic, persistent cough with blood, spontaneous sweating, and skin infections (Khumbongmayum *et al.*, 2005; Singh & Singh, 2009).

#### 8.4 Special uses in North East India

##### Sikkim

Local processing involves drying up of fruits initially and cleaning them appropriately. Individual fruits/seeds are separated from their pedicels. Fruits are then soaked in lukewarm water for around half an hour. Then it is hand rubbed in lukewarm water and squeezed to separate extract, again soaked, hand rubbed and squeezed. The process is repeated for 3–4 times on the same batch, same process can be repeated for a new batch. The extract is then filtered through a sieve. The filtrate is boiled for 6 h in a khadkudo (a traditionally designed copper vessel). During boiling, a piece of iron is put in the extract; scientific reason for this is unknown. Boiling completes when thick dark black colour bhakmilo juice (chuk) is developed. Final chuk obtained can cool completely. It is stored in bottles or airtight containers and can be used for 4–5 years, consumed at home or sold in the market. The residual fruit peel is also stored for making pickles or used as veterinary medicine for livestock (Sharma *et al.*, 2019).

Bhakmilochuk is traditionally used for treating blood stool, indigestion and for ethno-veterinary use for treating namle (worm infestation) in cattle. Further, the fruit peels are grounded into powder and is used as dry pickle. Traditionally, only fruit is used; however, the most important part i.e. gallnut, which has wide applicability in tannin, dye, ink industry and also in pharmaceutical hold promise for its use in human health in the future, as a food supplement or as a medicine (Sharma *et al.*, 2019).

The formulations used by Traditional Practitioners of Sikkim East and Sikkim South Districts: It is popularly known as Bhakmilo are used to treat Diarrhoea, dysentery

and stomach disorders. The decoction of fruit is taken. The fruit powder is taken with water to treat dysentery, gastritis, and food poisoning.

## Manipur

Leaves when orally taken are found to be effective as it is Depurative, stimulates blood circulation, effective against laryngitis, stomach ache, traumatic fractures, spermatorrhea, snake bite, diarrhea. Fruits of this tree are effective against Diarrhoea, dysentery, colic, hepatitis, jaundice, kidney and urinary complaints due to stone. Seeds are used orally for Coughs, dysentery, fever, jaundice, hepatitis, malaria, and rheumatism. Roots when taken orally are effective against Diarrhoea, spermatorrhea, malaria, jaundice, and snake bite. Galls of this tree are effective against Diarrhoea, diabetes mellitus, antiseptic, astringent, haemostatic, persistent cough with blood, spontaneous sweating, fever, malaria, and skin infections (Khumbongmayum *et al.*, 2005; Singh & Singh, 2009).

## 8.5 Dosage forms used in tradition: liquid extracts, powders

## 9. Phytochemical profile

Major constituents reported are phenolics, flavanoids, and tannins (Sharma *et al.*, 2015; Devi & Singh, 2018). The main organic compositions were gallic acid (71%) and its isomers (Devi & Singh, 2018). The leaves contain a high level of gallotannins along with phenolic compounds, gallic acid, and methyl gallate (Wu-Yuan *et al.*, 1988). The level of Unsaturated Fatty Acid (UFA) is about 65-80% of which the degree of oleic acid, linoleic acid, and linolenic acid is 62.6- 71.8%, 58-75% and 2% respectively (Devi & Singh, 2018). New benzofuran lactone, rhuscholide A has been isolated from the stems along with six known compounds: (1) 5-hydroxy-7-(3,7,11,15-tetramethylhexadeca-2,6,10,11-tetraenyl)-2(3H)-enzofuranone;(2) betalin; (3) betulonic acid; (4) moronic acid; (5) 3-oxo-6 beta-hydroxyolean-12-en-28-oic acid and (6) 3-oxo-6 beta-hydroxyolean-18-en-28-oic acid. the structure of rhuscholide A was found to be 5-hydroxy-3-(propan-2-ylidene)-7-(3,7,11,15-tetramethylhexadeca-2,6,10,11-tetraenyl)-2 (3 H)-benzofuranone (Gu *et al.*, 2007). Another compound dimethylcaffic acid has also been isolated from stems (Wang *et al.*, 2008).

## 10. Pharmacological activities (as per available literature)

### 10.1. Experimental pharmacology

The newly isolated compound, rhuscholide A, a benzofuran lactone from the stems possesses significant anti-HIV-1 activity with an EC<sub>50</sub> value of 1.62 μM and a therapeutic index (TI) of 42.40. Other compounds such as 5-hydroxy-7-(3,7,11,15-tetramethylhexadeca-2,6,10,11-tetraenyl)-2(3H)-benzofuranone;betulonicacid moronic acid & 3-oxo-6 beta-hydroxyolean-18-en-28-oic acid also possessed anti-HIV-1 activities with EC<sub>50</sub> values of 3.70, 5.81, 7.49 and 13.11 μM, respectively (Gu *et al.*, 2007). Compound, dimethylcaffic acid from the stem inhibited HIV-1 replication with EC<sub>50</sub> of 7.16 g/ml and targets at/before integration step. The compound,

rhuscholide A targets late-steps of HIV-1 life cycle (Wang *et al.*, 2008). Moronic acid and Betulonic acid from *R.Javanica* exhibited novel anti-HSV activity. Moronic acid was found to be more efficient than Betulonic acid against wild type 1 (HSV-1) with 3.9 and 2.6 µg/ml of 50% plaque reduction, respectively. The methanolic extract of fruit of *R. javanica* or *Rhus semialata* has a significant anti-diarrhoeal effect and substantiated its use in the treatment of diarrhoea in traditional medicine (Devi & Singh, 2018). *R. javanica* possessed antimicrobial activity the leaves have high potential for inhibiting MRSA which is linked to the presence of phenolics (Wu-Yuan *et al.*, 1988).

Four different treatments were done on bovine enamel blocks and were subjected to a pH-cycling regime for 12 times, where each cycle included 5 minutes of the following treatments – 4 g/L of *R. chinensis* gall extract, 4 g/L of Gallic acid, 1 g/L of sodium fluoride solution (positive control) and deionized water (negative control). It was reported that the main organic composition were gallic acid (71%) and its isomers. In pH cycling, gallic acid was found to have similar effects to that of gall extract in inhibiting enamel demineralization. It could be a promising component for the development of anti-caries agents (Huang *et al.*, 2012). It was reported that the leaf extract protected the plasmid DNA injury from ROS produced by SnCl<sub>2</sub>. Therefore, phenolics content in extracts could be a useful antioxidant compound and can be used in pharmacological applications (Qiu *et al.*, 2014). It was reported that the 80% methanolic extract is exhibited significant antioxidative and hACAT activities in rats. Two compounds namely hydroxyl dammarenone and semialactone were isolated through MS and NMR spectroscopic analysis, respectively. Results suggested that the extracts may have an adequate capacity to prevent and treat hypercholesterolemia or atherosclerosis via an inhibitory effect on hACAT (Kim *et al.*, 2010).

The aqueous extract from the gall was examined for its inhibitory effect on alpha-glucosidase activity. It was further confirmed by *in-vivo* experiment in five groups of rats at graded doses of 250-1000 mg/kg of AEGRC and Acarbose (2.5 mg/kg) as standard. Thus, AEGRC have antidiabetic effect thereby suppressing carbohydrate absorption from the intestine and ultimately reducing the postprandial increase of blood glucose (Shim *et al.*, 2003).

10.2. Clinical pharmacology: Clinical studies have not been reported till date.

## 11. Toxicity and safety

Gallnuts contain large amounts (50-70%) of gallotannin. Long-term medicinal intake of high doses of hydrolyzable tannins may cause negative health effects. Large amounts of tannins lead to an excessive astringent effect on mucous membranes, and oral administration may cause irritation of the gastric mucosa, nausea, and vomiting (Schulz *et al.*, 2004).

12. Clinical studies: Clinical studies have not been reported till date.

### 13. Contraindications

Generally safe for most healthy adults, though toxic side effects have been reported in animal studies when taken in high doses for long periods of time.

### 14. Precautions

Pregnant women or nursing are encouraged to avoid taking Gallachinensis powder (used in dental health, digestive aid) without the approval of a doctor.

### 15. Adverse reactions

Gallnuts contain large amounts (50-70%) of gallotannin. High doses of tannic acid can be cytotoxic. Tannic acid can cause fatal liver damage if used on burns or as an ingredient of enemas. Tannins are metal ion chelators and inhibit absorption of minerals such as iron; therefore, they can cause anemia in cases of long-term usage. Chronic intake of tannins inhibits digestive enzymes, particularly membrane-bound enzymes of the small intestinal mucosa (Mills & Bone, 2000). Hence, the use of gallnuts over a long period at high doses, either orally or topically, is not recommended.

### 16. Marketed formulation, if any

Chinese gall extract (Part Used: Seed, Appearance: Brown yellow fine powder to white powder, Specification: 5:1, 10:1, 20%-90% Tannins) Gallnuts Extract Tannic Acid for treating chronic diarrhea and dysentery; eliminating irritability, diuretic, cooling blood and detoxification; enhance immunity. This product is manufactured by Hunan Huakang Biotech Inc.

Hei-mang (*Rhus chinensis*) Red Tea: Manufactured by Dweller Pvt.Ltd. The *Rhus chinensis* fruits soaked overnight for energizing sips the next day. Traditional herbal healers of Manipur believe that Hei-mang fruits are antioxidant, antiviral, antibacterial, anti-diarrhea, digestive.

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1. Botanical Name: ***Scoparia dulcis* L.**
2. Synonym: NA
3. Family: Scrophulariaceae
4. Common names
  - Assamese: Bon-dhonia, Modhu-mehari, Bon chini
  - Bengali: Bon Dhonya
  - English: Sweet broom weed
  - Hindi: Mithi Patti, GhodaTulsi
  - Kannada: Mruganmhi Gida
  - Malayalam: Karakanjavu, Kallurukki, Meenanganni
  - Marathi: Dulas
  - Sanskrit: Asmaghni, Peshanabheda
  - Tamil: Sarakkothini
5. Description: A small erect annual herb with semi-woody stem. Leaves opposite or alternately whorled, rhomboid or elliptic, serrate, acute, cuneate, punctate, sessile, Flower minute with longer pedicel, axillary, white. Fruit a capsule small, globose, green, red when ripe.
6. Distribution: Native of Tropical America; now Pan Tropical. In India widely distributed all most all the states.
7. Parts Used: Whole plant



*Scoparia dulcis*

## 8. Medicinal /Therapeutic Uses

It is often considered as one of the source plants of Pashanabhesha (*Bergenia ligulata*) of Ayurveda is widely used in Indian folk and Ayurvedic medicine for the treatment of diabetes mellitus (Md Zulfiker *et al.*, 2011). Fresh or dried plants have been traditionally used as remedies for various ailments such as stomach problems that is, peptic ulcer (Babincova *et al.*, 2008), hyperlipidemia (Pari & Latha, 2006), hypertension (Esum *et al.*, 2011). It has various biologically active secondary metabolites such as carbohydrates, coumarins, phenols, saponins, glycosides, tannins, amino acids, flavonoids, terpenoids, catecholamine, noradrenaline, and adrenaline (Okhale *et al.*, 2010). The main chemical constituents such as scoparic acid A-C, scopadulcic acid A and B, scopadulciol, scopadulin and ammeline have been shown to contribute to the observed medicinal effect of the plant. Some aspects of the several speculated pharmacological properties have been validated by scientific research, which includes the presence of hypoglycaemic and antitumour promoting compound and also has antimicrobial and antifungal effects as well as antihyperlipidemic action (Mishra *et al.*, 2011).

### 8.1 Uses described in pharmacopoeias and in traditional systems of medicine

Whole plant is used for treating snakebites and as an antidote for cassava intoxication, also ground with the bark of *Sindora sumatrana* and alum taken as a remedy for infections of the urinary tract. A decoction of plant is consumed during

menstruation as a contraceptive and abortifacient. Plant paste is used to apply on eczema, and on forehead to cure headache, the juice is used to detect pregnancy as the juice is mixed with the urine of a woman, further the change in color suggests that the woman is pregnant. Ariel part of the plant is boiled and the brew is applied to gums to treat cutting teeth of children and also used as analgesic, antimalarial, emetic, diuretic, antipyretic, antiviral, febrifuge, vermifuge, astringent, gastric disorders, diarrhea/ dysentery, cough, bronchitis, hypertension, hemorrhoids and insect bites. Decoction of Stems and leaves used as febrifuge to cure fever and work as antidiabetic. Roots decoction is consumed to relief stomachache, diarrhea, malaria, and the paste of roots is applied on skin infections; mastitis and also used as Veterinary medicine, to treat wounds and ulcers with maggots. Dried roots used as contact therapy, to improve and to cure stomach troubles by tying the roots on the arm. Leaves chewed to treat cough, pounded leaves given in spermatorrhea and the paste of leaves applied to treat skin diseases. Of these, the leaves are used by the Deori and Rabha tribes for alleviation of diabetes, jaundice, stomach problems, skin disease, and piles (Bhuyan & Baishya, 2013). In Trinidad and Tobago, juice is used for reproductive problems in both men and women (Lans, 2007). An ethnobotanical survey in the Nossa Senhora Aparecida do Chumbo District (NSACD) located in Pocone, Mato Grosso, Brazil and found that *S. dulcis* was used for several disease categories with diabetes being one of them. (Bieski *et al.*, 2012) Some regions of South Indian State of Tamil Nadu, a survey of the phytotherapeutic agents used by the Nadars revealed that the juice was taken orally to treat fever and kidney stones (Jeeva & Femila, 2012).

## 8.2 Uses supported by clinical data

The aqueous extracts have antihyperglycemic (Attanayake *et al.*, 2015) antidiabetic and antihyperlipidemic effects (Senadheera *et al.*, 2015). Flavonoids from the methanol extract of the aerial parts impart an antihyperglycemic activity the antidiabetic activities as well as its antioxidant and anti-inflammatory properties in relation to the diabetes and its complications. Evidence has been demonstrated through scientific studies as to the antidiabetic effects of crude extracts as well as its bioactive constituents. The primary mechanisms of action of antidiabetic activity of the plant and its bioactive constituents are through  $\alpha$ -glucosidase inhibition, curbing of PPAR- $\gamma$  and increased secretion of insulin. Scoparic acid A, scoparic acid D, scutellarein, apigenin, luteolin, coixol, and glutinol are some of the compounds which have been identified as responsible for these mechanisms of action. It has also been shown to exhibit analgesic, antimalarial, hepatoprotective, sedative, hypnotic, antiulcer, antisickling, and antimicrobial activities and as an alternative and complementary therapy for diabetes (Pamunuwa *et al.*, 2016). The plant juice 2 teaspoon thrice a day is given to treat fever and applied on forehead to cure headache. The juice of leaves is taken orally for kidney stone (Jeeva & Femila, 2012).

### 8.3 Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

It is a common weed throughout the tropics and been widely taken up as a medicinal herb wherever it goes with a very wide range of uses in tropical America like treating pulmonary complaints, fevers, skin disorders, diabetes, herpes, coughs and colds, fevers, nausea, dizziness, and as an antidote for snakebites and cassava intoxication. In low doses, often in milk, it is used to relieve vomiting in infants, whilst in larger does it is used to induce vomiting to clear out the digestive system. The whole plant is used for treating a wide range of disorders including diabetes, herpes, coughs and colds, fevers, nausea, dizziness, and as an antidote for snakebites and cassava intoxication. In low doses, often in milk, it is used to relieve vomiting in infants, whilst in larger does it is used to induce vomiting to clear out the digestive system (De Filipps et al. 2004). Indigenous people in Ecuador consume tea of the entire plant to reduce swellings, aches and pains. The 'Tikuna' Indian women drink the plant decoction for three days each month during menstruation as a contraceptive and/or to induce abortions. The indigenous tribes in Nicaragua use a hot water infusion and/or decoction of the leaves (or the whole plant) for stomach pain, for menstrual disorders, as an aid in childbirth, as a blood purifier, for insect bites, fevers, heart problems, liver and stomach disorders, malaria, sexually transmitted diseases, and as a general tonic (Taylor, 2005).

### 8.4 Special uses in North East India

Bodo, Karbi, Ahom, Deori, Rabha, Mising, and Sonowal Kachari tribes of Assam used different plant part for alleviation of diabetes, jaundice, stomach problems, skin disease, and piles (Bhuyan & Baishya, 2013). Darlong and Halam tribes of Tripura used decoction of leaves and twigs as anthelmintic for infants of age 6 months to 1 year and  $\frac{1}{2}$  glass of extract is taken once daily for 3 - 4 days in empty stomach to cure jaundice (Das, 2012; Chandra De, 2016).

### 8.5. Dosage forms used in tradition

Oral preparations are used for anemia, during childbirth, bronchitis, cough, fever, as an emetic, hyperglycemia, retinitis, as a refrigerant, venereal, for stone, ketonuria, cicatrizant, diarrhea, diabetes, dysentery, as a diuretic, for albuminuria, insect/animal bite, snake bite, as an aphrodisiac, for leprosy, kidney stones, as a purgative, for menstrual disorders, toothache and for vermifuge (Taylor, 2005).

Medicinal Parts	Dosage
S. dulcis Leaves	2–3 g twice daily Infusion 1 cup (150 ml) boiling water poured over approximately 2 grams of dried leaf, Steep, covered, for 5–10 minutes and drink.
S. dulcis Whole plant	Infusion (Tea) of powder 1 cup dosages 1 or 2 times daily.

## 9. Phytochemical profile

Phytochemical analysis of the extract revealed the presence of tannins, saponins, alkaloids, flavonoids, terpenoids, phenols, steroids and carbohydrates (Nahannu *et al.*, 2018)

The main phyto-constitutens include scopadulcic acids A and B, scopadiol, scopadulciol, scopadulin, scoparic acids A-C and betulinic acid. Other chemicals include: acacetin, amyrin, apigenin, benzoxazin, benzoxazolin, benzoxazolinone, cirsimarin, cirsitakaoside, coixol, coumaric acid, cynaroside, daucosterol, dulcinol, dulcioic acid, friedelin, gentisic acid, glutinol, hymenoxin, ifflaionic acid, linarin, luteolin, mannitol, scoparinol, scutellarein, scutellarin, sitosterol, stigmasterol, taraxerol, vicenin, vitexin

## 10. Pharmacological Studies

It is widely reported to have antiurolethic and antidiabetic pharmacological uses, in addition some other pharmacological properties have also been evaluated and those include antiproliferative, anticancer, antitumor, antibacterial, antifungal, antiviral, antiinflammatory and antioxidant effects (Valsalakumari & Narayanan, 2017; Hayashi, 2008). The chemical constituents are Scoparic acid A, scoparic acid D, scutellarein, apigenin, luteolin, coixol, and glutinol are some of the compounds which have been identified as responsible for the primary mechanisms of action for the antidiabetic activity of plant and its bioactive constituents through  $\alpha$ -glucosidase inhibition, curbing of PPAR- $\gamma$  and increased secretion of insulin. It has also been shown to exhibit analgesic, antimalarial, hepatoprotective, sedative, hypnotic, antiulcer, antisickling, and antimicrobial activities (Pamunuwa *et al.*, 2016). Alcohol and water extract aerial parts possesses marked nephroprotective activity with minimal toxicity (Dhondiram, 2014). The fruit part in combination with *Aervalanata* is endowed with higher antiurolithiatic activity (Lakshmi *et al.*, 2015) Pharmacological screening of hydro alcoholic extract possesses extra pancreatic effects which justifies the use of the plant in the folklore diabetic treatments (Reddy *et al.*, 2012) and the crude extract also presents therapeutic potential for the treatment of osteoarthritis due to its anti-inflammatory and anti-nociceptive action (lima *et al.*, 2019).The methanolic and aqueous leaf extracts against clinically important human pathogens *S. aureus*, *P. mirabilis*, *S. typhi*, *V. cholerae* and *B. subtilis* showed promising antimicrobial activity (Jose & Shina 2017).

### 10.1 Experimental pharmacology

Anticancer effect of SDC was evaluated in herpes simplex virus thymidine kinase (HSV-TK) expressing (TK+) cancer cells bearing TK+ tumors In vitro enzyme assay performed using TK+ cells resulted the synergistic effect of SDC with drug combination (acyclovir and ganciclovir) provided benefit to HSV-TK/pro drug gene therapy (Hayashi *et al.*, 2006).Antiviral activity of five diterpenoids isolated and examined *in vitro* against herpes simplex virus type 1 in hamster test model. Among these compounds, only scopadulcic acid B was found to inhibit the viral replication by interfering with considerably early events of virus growth as indicated by single-

cycle replication experiments. Scopadulcic acid B, when applied orally or intraperitoneally immediately following virus inoculation effectively prolonged both the appearance of herpetic lesions and the survival time at the dose of 100 and 200 mg/kg per day (Hayashi *et al.*, 1988). Another study reported that active as an antiviral against (HSV) herpes simplex virus type 1 (Murti *et al.*, 2012). *In-vitro* analysis was performed with Huh7it cells and HCV JFH1 (genotype 2a) by determining inhibition concentration 50 ( $IC_{50}$ ). The toxicity (Cytotoxicity Concentration 50,  $CC_{50}$ ) test was performed by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and mechanism of action were analyzed using time addition experiment. The  $IC_{50}$  test result of 80% EE and DCMF showed anti-HCV activity with a value of  $12.7 \pm 4.8$   $\mu\text{g}/\text{ml}$  and  $5.8 \pm 0.69$   $\mu\text{g}/\text{ml}$ , while EAF, BF, and AF respectively resulted in  $IC_{50}$  value of  $>100$   $\mu\text{g}/\text{ml}$  that suggested there was no inhibition effect on HCV JFH1. The DCMF was the most active fraction but toxic to the cell with  $CC_{50}$  value  $>23$   $\mu\text{g}/\text{ml}$  and selectivity index (SI)  $>3.9$  (Widyawaruyant *et al.*, 2020). The *in-vitro* antiurolithiatic study of the whole plant through titrimetric and turbidity method has showed extremely significant action on urinary calculi (Sasidharan *et al.*, 2017). The extracts of ariel part showed the maximum reduction in blood glucose concentration and hypoglycemic effect in healthy rats. Further a highly significant dose dependent antihyperglycemic effect was shown by all selected plant extracts at and above the therapeutic dose in streptozotocin induced diabetic rats. The results confirm that the optimum effective dose was found to be approximately equal to the traditional therapeutic dose of each extract (Attanayake *et al.*, 2014). Alcohol and water extracts of aerial parts possesses marked nephro protective activity with minimal toxicity on healthy female albino mice (Jeda *et al.*, 2014). Methanolic extract was performed on streptozotocin-induced diabetes mellitus showed significant inhibition of blood glucose level as compared to control and like that of standard glibenclamide. The overall data potentiates the traditional value as an antidiabetic drug (Mishra *et al.*, 2013). The aqueous methanol extract of the plant confirmed the traditional use of the plant for having antisickling activity. Evaluation of the antisickling activity involved the inhibition of sodium metabisulphite-induced sickling of the HbSS red blood cells obtained from confirmed sickle cell patients who were not in crises. Concentrations of the crude extract and its fractions were tested with normal saline and p-hydroxybenzoic acid serving as controls. Results confirmed that the effect in the management of Sickle cell disorders (Abere *et al.*, 2015). Jose & Sinha studied phytochemical and antimicrobial details of the methanolic and aqueous leaf extracts against clinically important human pathogens viz. *Staphylococcus aureus*, *Proteus mirabilis*, *Salmonella typhi*, *Vibrio cholerae* and *Bacillus subtilis*. The methanolic and aqueous extract showed toxicity against all the bacteria, *V. Cholerae* and *P.mirabilis* being highly susceptible with a zone of inhibition of 4 mm at 10mg/ml and 2 mm at 10mg/ml respectively in agar diffusion method. The broth dilution method showed more pronounced antimicrobial activity through 100% inhibition for all the pathogens in the range of 1-32mg/mL concentration (Jose & Sinha, 2017).

## 10.2. Clinical pharmacology

In their study investigated the influence of scopadulcic acid B on the course of the primary corneal Herpes Simplex Virus by means of a hamster test model. When the treatment was initiated immediately after virus inoculation, scopadulcic acid B, when applied orally or intraperitoneally, effectively prolonged both the appearance of herpetic lesions and the survival time at the dose of 100 and 200 mg/kg per day(Hayashi *et al.*, 1998). Study conducted by Pari and Venkateswaran (2002) in experimental diabetic rats with an Oral administration of 0.15, 0.30 and 0.45 g/kg body weight of the aqueous extract of leaves (SLEt) for 45 days resulted in a significant reduction in blood glucose, glycosylated haemoglobin and an increase in total haemoglobin but in the case of 0.45 g/kg body weight the effect was highly significant. The aqueous extract also prevented a decrease in the body weight. An oral glucose tolerance test was also performed in experimental diabetic rats, in which there was a significant improvement in glucose tolerance in animals treated with SLEt and the effect was comparable to that of glibenclamide (Pari & Venkateswaran, 2002). Lima *et al.*, (2019) evaluate the analgesic and anti-inflammatory effect of the crude extract in an experimental model of osteoarthritis. The results showed that a 15-day treatment with crude extract reduced edema, spontaneous pain, peripheral nociceptive activity, and proinflammatory cytokines in the synovial fluid. The highest inhibition of cyclooxygenase 2 in the crude extract occurred at 50 µg/mL. The crude extracts present therapeutic potential for the treatment of osteoarthritis due to its anti-inflammatory and anti-nociceptive action (Lima *et al.*, 2019).

## 11. Toxicity and safety

The aqueous extract of *S. dulcis* did not produce any mortality up to the oral dose level of 8 g/kg body weight in mice. There were no changes in behaviour, posture, nature and frequency of stooling, mood and motor activity. The animals did not convulse, exhibit writhing or die. Daily administration of the extract for 30 days did not produce gross toxicological symptoms or deaths. Histopathology of the heart and liver showed mild vascular and portal congestions respectively. There was no degeneration of tissues in the lungs and testis at both doses except for mild interstitial congestions. Since, toxicological evaluation showed no adverse effect or degeneration of tissue, *S.dulcis* is regarded relatively safe (Abere *et al.*, 2015).

## 12. Clinical studies

Senadheera *et al.*, (2015) studied the anti-diabetic effects of commercially produced Porridge made with leaf extract decreased Fasting Blood Glucose (FBG) and HbA1c ( $p >0.05$ ) of type 2 diabetic patients. The porridge had no effect on cholesterol measurements and no toxicity was observed at the dose tested. Therefore, the SDC porridge can be recommended as a suitable meal for diabetic patients (Senadheera *et al.*, 2015). Orhue and Nwanze (2006) investigated the effect of oral administration of the herb, on *Trypanosoma brucei* induced changes in plasma lipid profile in rabbits over a period of twenty-eight days. The results showed that infection with *T. brucei* resulted in significant increases in plasma total cholesterol, triacylglycerol, and

low-density lipoprotein (LDL)-cholesterol, while the level of high-density lipoprotein (HDL)-cholesterol was also significantly reduced. Further comparative analysis of data revealed that these lesions were significantly less severe.

### 13. Contraindications

The plant extract demonstrated hypoglycaemic activity in experimental rats, as such is contraindicated in people with hypoglycaemia (Taylor, 2005).

### 14. Precautions

It is advisable to avoid taking this plant during pregnancy as traditionally it has been used as an abortive and /or childbirth aid (Taylor, 2005).

### 15. Adverse reactions: None reported so far.

### 16. Marketed formulation, if any

1. Raintree Vassourinha (*S.dulcis*) Powder (1lb) (<https://www.raintree.com/vassourinha-powder>).
2. Amazon Therapeutic Vassourinha (NP) Organic Extract Liquid(<https://www.walmart.com/ip/Amazon-Therapeutic-Vassourinha-Np-Organic-Extract-Liquid-1-Oz/102277603?wmlspartner=wipa&selectedSellerId=961>).
3. Diasulin- Antidiabetic herbal product marketed in India. Made from the mixture of *Cassia auriculata*, *Coccinia indica*, *Momordica charantia*, *Syzygium cumini*, *Emblica officinalis*, *Trigonella foenum graecum*, *Curcuma longa*, *Gymnema sylvestre*, *Tinospora cordifolia*, *Scoparia dulcis* (Jonnalagadd & Selka, 2013).

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1. Botanical Name: ***Siegesbeckia orientalis* L.**

2. Synonym: NA

3. Family: Asteraceae

4. Common names

Assam:	Bahalgani, Gawal;
Bihar:	Latlatia;
English:	Siegesbeckia;
Gujarati:	Pilibadkadi;
Hindi:	Gobariya
Tamil:	Kadambu, Katampam;
Telugu:	Kadembu, Katampam.

5. Description: An erect herb up to 90 cm high. Leaves ovate, acute at apex, cuneate and decurrent at base, pubescent, dentate along the margins; petiole 1-5 cm long. Heads 8 x 4 mm, solitary, terminal, on slender, densely hairy peduncles; bracts biseriate, outer bracts spathulate, 8 mm long, viscid hairy; inner ovate, short. Flowers: outer row ligulate, female, inner bracts rows bisexual, tubular; limb of ligulate corolla 2 mm long, 3-lobed, yellow. Disc florets 2 mm long; anthers bases obtuse. Fruit anachenes, curved, truncate at apex, 4-angled; black; pappus absent.

6. Distribution: Native of Mauritius; found throughout the India as a garden escape; 800-1800 m altitude ranges.

7. Parts Used: Whole plant



*Sigesbeckia orientalis*

## 8. Medicinal /Therapeutic Uses

It is often used as part of a formula with other plants in decoctions in modern traditional Chinese medicine to treat various forms of arthritis, rheumatic pain, back ache, sciatica. In 2015, the extract of the aerial parts approved for use in dietary supplements for promoting healthy joints in USA. It is also used in cosmetics and personal care products due to its anti-inflammatory activity. Modern scientific research has shown that the molecules have a number of pharmacological actions. It has been shown to be an anti-inflammatory and analgesic, supporting its use in musculoskeletal diseases. It has been shown to modulate cellular immunity, humoral immunity, and nonspecific immunity, as well as adjusting cytokine production in the body's immune function which could be beneficial for auto-immune arthritic conditions, such as rheumatoid arthritis

### 8.1.Uses described in pharmacopoeias and in traditional systems of medicine

The aerial parts have been used as the traditional Chinese medicine in the treatment of rheumatic arthritis, hypertension, malaria, neurasthenia, and snakebite. The whole plant has been commonly used for the treatment of acute arthritis, rheumatism, and gout in Vietnam. A tincture of the (whole) plant with glycerine is used for the treatment of ringworm and other skin disease, ulcers, and sores; as a diaphoretic and cardiotonic; also for renal colic and rheumatism in China. The whole plant is used for arthritis, a bad back, boils, dermatitis, hemiplegia, hypertension, leg ache, rheumatism, side ache, sciatica, and weak knees. It is ground and taken alone or with other plants for convulsions, paralytic stroke, and rheumatoid arthritis. It is also used for insect, dog, tiger bites and ulcers. Additionally, it is decocted for malignant tumors, malaria, and

numbness. The root is used externally for abscesses. The plant has a hypoglycemic property. The root contains an essential oil, a substance suggesting salicylic acid, and a bitter glycoside (rutoside). Also, extracts are said to have antiviral, hypoglycemic, and insecticidal properties.

#### 8.2. Uses supported by clinical data

Hung *et al.*, (2017) have used an *in vitro* approach to assess the potential of four extracts and key enzymes relevant to metabolic syndrome, such as Type 2 diabetes-associated hyperglycemia, obesity and hypertension in connection with their phenolic contents, antioxidant activities and advanced glycated end products formation. Hence ethanol extract has the potential to be a therapeutic agent for the prevention or treatment of metabolic syndrome (Hung *et al.*, 2017). Previous literature has reported that ethanolic extract had immunosuppressive activity on ovalbumin in mice (Sun *et al.*, 2006). The ethyl acetate extracts could inhibit the proliferation of human cervical cancer HeLa cells (Wang *et al.*, 2009).

#### 8.3. Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

The first record of use in China in 7th century AD, where the plant, under its Chinese name *Xi Xian Cao*, was recorded to treat backache, joint pain, sciatica, rheumatic pain, and muscular pains. It has also been widely used across Europe since at least the 1980s as a treatment for backache, joint and muscle pains, although it was referenced as a medicinal plant in Europe as far back as 1907 in Potter's Cyclopaedia of Botanical Drugs and Preparations where it is referenced as a remedy for syphilis, venereal diseases and leprosy. The aerial parts have been used traditionally to treat rheumatic conditions such as arthritis, pain in the joints and muscles, sciatica, as well as to treat hypertension and some forms of paralysis. In traditional Chinese medicine, when used traditionally, patients would be given the dried herb to brew into a decoction, either on its own or in combination with herbs such as *Prunella vulgaris* (commonly known as heal-all) or *Clematis chinensis* (Chinese Clematis), herbs that have complimentary activity. Honey pill made from the extract weighing 20-30g and containing 9gm of the extract is used to "dispel wind-dampness and strengthening the sinews: for wind-heat-damp painful obstructions.

#### 8.4. Special uses in North East India

Tribes of Meghalaya used crushed leaves to apply for injuries and wounds (Neogi *et al.*, 1989)

#### 8.5. Dosage forms used in tradition

A tincture of the (whole) plant with glycerine is used for ringworm and other skin disease, ulcers, and sores; as a diaphoretic and cardiotonic; also for renal colic and rheumatism. The juice of fresh herb is used as a dressing for wounds, and decoction of leaves and young shoots is used as a lotion for ulcers and parasite skin disease. In China, it was often prescribed on its own as a large honey pill (*Xi Xian Cao*). To make this honey pill, the dried plant was decocted twice with water, each time for two hours. The decoctions (liquid extract) were then concentrated. Further dried plant was then infused with rice wine and heated until the wine was completely absorbed. The

concentrated decoction and the wine infused material was dried, pulverized and mixed with honey to make large honey pills, with each honey pill weighing 20-30g and containing 9g of the extract is used to “dispel wind-dampness and strengthening the sinews: for wind-heat-damp painful obstructions. Aqueous extract, in syrup, sometimes combined with potassium iodide, used as alterative, sudorific, and antisyphilitic In Europe, mixture of equal parts of a tincture and glycerine used externally for ringworm and other parasitic eruptions.

As antiseptic, fresh plant applied to unhealthy ulcers. Decoction of leaves and young shoots used as lotion for ulcers and parasitic skin diseases. In India, powdered dried roots made into a paste with water, mixed with cooked vegetables, and used to cure eczema, mouth, throat, and other skin diseases (Kaur *et al.*, 2017).

## 9. Phytochemical profile

More than hundreds of compounds have been isolated and identified from this species including pimarane and kaurane types of diterpenes and their glycosides, and melampolide and germacranoide types of sesquiterpenoids. Among the diterpenoids, kirenol, darutigenol and ent-16 $\beta$ ,17- dihydroxykauran-19-oic acid is the commonly existing chemical compounds of this herb (Guixin & Zhihong, 2015).

The major phytochemicals are diterpenes, sesquiterpenes, and flavonoids. Chemical constituents of the aerial parts of were investigated and two new compounds, namely  $\beta$ -D-glucopyranosyl-ent-2-oxo-15,16-dihydroxy-pimar-8(14)-en-19-oic-late (compound 1) and [1(10)E,4Z]-8 $\beta$ -angeloyloxy-9 $\alpha$ -methoxy-6 $\alpha$ ,15-dihydroxy-14-oxogermacra-1(10),4,11(13)-trien-12-oic acid 12,6-lactone (compound 2), as well as five known ent-pimaranediterpenes (compounds 3–7) were observed(Yang *et al.*, 2016).

## 10. Pharmacological Studies

The whole plant has been commonly used for the treatment of acute arthritis, rheumatism, and gout in Vietnam (Nguyen *et al.*, 2017).A tincture of the (whole) plant with glycerine is used for the treatment of ringworm and other skin disease, ulcers, and sores; as a diaphoretic and cardiotonic; also for renal colic and rheumatism (De Filips *et al.*, 2018), aerial parts of the plant have been used as the traditional Chinese medicine in the treatment of rheumatic arthritis, hypertension, malaria, neurasthenia, and snakebite (Wang & Hu, 2006). It has been reported to exhibit anti-allergic, anti-infertility, anti-inflammatory, antirheumatic, immunosuppressive (Kim *et al.*, 2019), antioxidant (Pradhan *et al.*, 2018) and anti-metastatic activities (Chang *et al.*, 2016).

### 10.1 Experimental pharmacology

Antiviral activity was observed in 242 samples belonging to 96 families among them the plant extract of *S. orientalis* tested for having antiviral activity against Ranikhet disease virus, by interferon induction activity. Chang *et al.*, (2016), demonstrates that the ethanol extract (SOE) significantly inhibited the proliferation of RL95-2 human endometrial cancer cells. Treating RL95-2 cells with SOE caused cell arrest in the G2/M phase and induced apoptosis of RL95-2 cells by up-regulating Bad, Bak and Bax protein expression and down-regulation of Bcl-2 and Bcl-xL protein expression. Treatment with SOE increased protein expression of caspase-3, -8 and -9 dose-dependently, indicating that apoptosis was through the intrinsic and extrinsic apoptotic

pathways. Moreover, SOE was also effective against A549 (lung cancer), Hep G2 (hepatoma), FaDu (pharynx squamous cancer), MDA-MB-231 (breast cancer), and especially on LNCaP (prostate cancer) cell lines. In total, 10 constituents of SOE were identified by Gas chromatography-mass analysis. Caryophyllene oxide and caryophyllene are largely responsible for most cytotoxic activity of SOE against RL95-2 cells. Overall, this study suggested that SOE is a promising anticancer agent for treating endometrial cancer (Chang *et al.*, 2016). Another study of inhibitory effects of ethanol extract (SOE) on the migration and invasion of endometrial cancer cells, which were stimulated by transforming growth factor  $\beta$  (TGF $\beta$ ) were evaluated by determining wound healing and performing the Boyden chamber assay reveals that SOE can inhibit TGF $\beta$ 1-induced cell wound healing, cell migration, and cell invasion in a dose-dependent manner, overall SOE is a potential anti-metastatic agent against human endometrial tumors (Chang *et al.*, 2016). Similarly Type II endometrial carcinoma typically exhibits aggressive metastasis and has a poor prognosis. Study investigated the inhibitory effects of ethanol extract on migration and invasion of endometrial cancer cells, which were stimulated by transforming growth factor  $\beta$  (TGF $\beta$ ). SOE showed potential anti-metastatic activity as evidenced by inhibition of TGF $\beta$ -induced cell wound healing, cell migration, and cell invasion in a dose dependent manner in RL95-2 and HEC-1A endometrial cancer cells, along with reversal of TGF $\beta$ -induced epithelial-mesenchymal transition (Yang *et al.*, 2016). Guo *et al.*, (2018) investigated the involvement of toll-like receptor 4 (TLR4) signalling cascades in the effects of an ethanolic extracts on inflammatory mediators in murine macrophages reveals the pharmacological basis for clinical application in the treatment of inflammatory disorders (Yu *et al.*, 2018, Guo *et al.*, 2018), also a comparative study on the anti-inflammatory effects of three species found more in *S.orientalis* L. and *S. glabrescens* Makino than *S. pubescens* Makino (Linghu *et al.*, 2020). An experiment on Hairy root cultures were initiated by inoculation of leaf discs to investigate the antimicrobial activities of kirenol, hairy root. It was found that high level of kirenol contents was obtained from hairy roots which were effective against gram-positive bacteria. Interestingly, the extract from hairy roots showed a diverse antimicrobial effect from that of kirenol (Wang *et al.*, 2012). Kim *et al.*, (2019) reported the significant effect of standardized SOE on running distance and time, by stimulating mitochondrial regulatory genes and effectively upregulating the AMP-activated protein kinase (AMPK)/sirtuin 1 (SIRT1)/ PGC-1a/peroxisome proliferator-activated receptor delta (PPARd) signaling pathway in the skeletal muscles of normal diet (ND) and high-fat diet (HFD) mice. Furthermore, kirenol, a major bioactive constituent increased ATP production and mitochondrial activity by upregulating the expression of biomarkers of mitochondrial biogenesis and by activating the AMPK/SIRT1/PGC-1a/PPARd signaling pathway in L6 myotubes. These results suggest that SOE and kirenol can be potentially effective nutraceutical candidates for enhancing exercise capacity (Kim *et al.*, 2019).

## 10.2 Clinical pharmacology

The study on Postoperative Cognitive Dysfunction (PODC), Systemic Inflammation, and Neuroinflammation observed three-month-old male mice which were fed different doses extract for 14 days. The results showed that animals with extract pretreatment

demonstrated memory improvement in a dose-dependent manner compared with control, with neuroprotective effect of *S. orientalis* in postoperative animals, indicating a therapeutic potential of *S. orientalis* in minimizing POCD and the possibility of utilizing this traditional Chinese medicine perioperatively. Aerial part and the crude ethanol extract (CEE) and its n-butanol-soluble fraction (BuOHfr.) was prepared from the plant materials. Their study suggested that anti-hyperuricemic and anti-inflammatory mechanism is related to xanthine oxidase XO inhibitory effect of the phenolic components. Our findings support the use of this plant as the treatment of gout and other inflammatory diseases (Nguyen *et al.*, 2017). Kim *et al.*, (2019) studied the stimulatory effects of this plant extract (SOE) on exercise capacity in mice using a treadmill to measure the running distance and time of mice with different diets with (SOE) treatment and they found out that the mice treated with SOE effectively enhances exercise endurance capacity by activating skeletal muscle mitochondrial biogenesis (Kim *et al.*, 2019).

11. Toxicity and safety: Not Reported

12. Clinical studies: Not Reported

13. Contraindications: Not Reported

14. Precautions

Compassionate use of antimalarial drug artesunate (ART) and Chinese herbs is not recommended during standard radio chemotherapy with temozolomide TMZ for (GBM) glioblastoma multiforme (Efferth *et al.*, 2016).

15. Adverse reactions: Not Reported

16. Marketed formulation, if any

1. Phynova Joint and Muscle Relief Tablets containing 500mg *Sigesbeckia*.
2. Cosmetics containing *Sigesbeckia* extract.
3. ([https://www.ewg.org/skindeep/browse/ingredients/723546-SIGESBECKIA\\_ORIENTALIS\\_EXTRACT/](https://www.ewg.org/skindeep/browse/ingredients/723546-SIGESBECKIA_ORIENTALIS_EXTRACT/))

17. References

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1. Botanical Name: ***Solanum virginianum* L.**

2. Synonym: NA

3. Family: Solanaceae

4. Common names

Bengali: Kantkari

English: Yellow berried Nightshade, Wild Eggplant.

Gujarati: Bhoyerangani

Hindi: Katai

Marathi: Dorallringani

Oriya: Bheji begun, Ankranti

Sanskrit: Kantakari, Ksudra, Dhavani, Nidigdha, Agnidamini.

Tamil: Kandan- kattiri

Telugu: Callamulaga, Nella molunga

5. Description: An erect branched diffuse herbs with glandular hairy stem prickles 2 cm long, spine scent, gradually or not broaden towards the base, present on all parts except berries. Leaves alternate-distichous, ovate or elliptic, acute, leaf base attenuate, leaf margin lacerate, membranous; petioles to 8 cm long. Peduncle absent. Flowers 2-4 together, axillary; pedicel 2 cm long, stout; corolla 18 mm across, sparsely hispid. A globose berry, green with white stripes, ripening yellow; seeds many. Fruiting throughout the year. Seeds flat not pitted.

6. Distribution: Africa, Asia, Thailand, Vietnam, and Pacific Islands. It is common weed in wasteland and roadside

7. Parts Used: Whole plant



*Solanum virginianum* L.

## 8. Medicinal /Therapeutic Uses

It is used in the preparation of a variety of medicines. It is employed in the treatment of epilepsy, pain relieving, headache, hair falls, bronchial asthma, skin problems, cough, and other diseases (Tekuriet *et al.*, 2019). The effect of the plant for bronchial asthma attributes to the depletion of histamine as reported by Khareet *et al.*, (2007). The seed extract showed the antioxidant and anticancer activities against Dalton's Ascites Lymphoma (DAL) cells (Gnanavel *et al.*, 2015). The whole plant extract showed antibacterial activity, natural antifungal against and seed-borne fungi and fungal diseases of plants. It also revealed the plant can be used as natural antioxidant having effectiveness in the prevention and control of oxidative damage caused by free radicals. In suitable form, the plant can be used as a natural insecticide to control insect vectors that transmit arboviral diseases such as dengue and others (Kekuda *et al.*, 2017). The plant possesses anti-urolithiatic and natriuretic activities, tumoricidal properties, anti-allergic and anti-cancerous effects. Nasal administration of this herb is useful in reducing migraine and headache. The fumigation of the plant is helpful in piles. The decoction of the plant used in the treatment of gonorrhoea (Poojari & Bhalerao, 2018).

### 8.1. Uses described in pharmacopoeias and in traditional systems of medicine.

In ancient Ayurveda, it is described as pungent, bitter, digestive, alternate astringent. Its root is an expectorant, used in Dashmularista, an ayurvedic tonic for lactating mothers and severely used in rural areas as a successive preventive of smallpox and measles (Datta *et al.*, 2011). The fruits are edible and known for several medicinal uses like anthelmintic, antipyretic, laxative, anti-inflammatory, anti-asthmatic and aphrodisiac activities (Rane *et al.*, 2014). A decoction of the fruits of the plant is used by Kondh tribe of Dhekanal district, Orrisa for the treatment of

diabetes. (Tekuri *et al.*, 2019). The plant is credited with diuretic property and is used to cure dropsy. The stem, flowers and fruits are prescribed for relief in burning sensation in the feet accompanied by vesicular eruptions. The antispasmodic, antitumor, cardiotonic, hypotensive, antianaphylactic and cytotoxic activities are also reported (Parmer *et al.*, 2010). The Mukundaratribals of Rajasthan use the paste of the roots in hernia. Leaves are applied during muscular pain and juice mixed with black pepper to treat rheumatism. The paste applied on painful joints in arthritis, reduces pain and swelling. In Sri Lanka and Thailand, roots are used in cough and fever (Arora *et al.*, 2019). The powered decoction of plant extract issued by the local people of Gallies, North Pakistan as folk medicines in treating throat infections and other inflammatory problems (Kayani *et al.*, 2014).

#### 8.2. Uses supported by clinical data

The Ayurvedic use of extract for curing throat infection and inflammatory problems is well supported clinically for its antiasmatic effect. It has been reported to exert anti-histaminic effect and mast cell stabilizer (Vadnere *et al.*, 2008). The seed known to possess antimicrobial, antiradical and insecticidal effect (Kekuda *et al.*, 2017). Ameliorative property of the whole plant extract which effect the haematological parameters (Pichaimani *et al.*, 2017). The preliminary antimalarial study was also conducted (Mohan *et al.*, 2007). It posses nephroprotective activity (Hussain *et al.*, 2012) and antiurolithiatic property (Patel *et al.*, 2010).

#### 8.3. Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

It is traditionally used for throat infection, asthma, cold and cough. It promotes comfortable breathing by helping in secretion of mucous. The root of the plant helps to maintain body temperature and reduces muscle and joint pain when taken with black pepper. It is also known for reducing the sugar level in case of diabetics. Tonics made from the plants are used to ease constipation and flatulences by releasing gas from the body by increasing the digestive fire. Antihelmentic property of the plant extract to kill worms in intestine. The paste of the plant is applied on the feet, to comfort the burning sensation. It is also used to reduce fertility and blocks spermatogenesis. The fresh juice is applied on hair to prevent hair loss and dandruff removal. Dropsy is cured and the roots are used to treat piles. It is also used to treat skin diseases.

#### 8.4 Special uses in North East India

It is used for the treatment of fever, muscle pain, asthma, appetizer, stomachache, piles, etc. Seeds are used as diuretic. Juice of berries is used for sore throat in Manipur (Subharani, 2015).

## 8.5 Dosage forms used in tradition:

In Ayurveda, Siddha and Unani to treat variety of diseases. It is useful in treating worms, cough, hoarseness of voice, fever, painful urination, enlargement of the liver, muscular pain, and stone in the urinary bladder.

Medicinal Part	Dosage	Remedy
Whole plant extract	2-3gm in 50ml water	Cough
Whole plant paste	Applied tropically	Arthritis
Fresh leaf juice	2 drops	Epilepsy

The dosage is given in intervals, per day based on the condition of the patient and diseases. The fresh plants are crushed, and the juice is tropically applied on hair to relieve dandruff and promote hair growth. It is a home remedy for cough and haemorrhage. (<https://www.bimbima.com/ayurveda/kantakari-solanum-xanthocarpum-details-benefits-and-medicinal-uses/1585/>)

## 9. Phytochemical profile

The bark, leaves, roots, and fruits are extensively used in traditional medicine due to the presences of several phytoconstituents like alkaloids, terpenoids, saponins, steroids and flavonoids.

The major bioactive components of the plant are as glycoalkaloid (solanosine), steroidal compound (carpesterol) and steroidal alkloids (caffeic acid, coumarins, and triterpinoids) (Tekuri *et al.*, 2019). Solasodine have been reported as anticancer, insecticidal and antiaccelerator cardiac activities (Roshy *et al.*, 2012).

The other effective bioactive compounds which include polyphenol (caffeic acid), coumarins (esculetin and aesculin), steroids (carpesterol, campesterol, daucosterol, stigmasterol, cycloortanol and cholesterol), triterpinins and sapogenin (lupeol and diosgenine) have also been reported (Tekuri *et al.*, 2019). The fruit volatiles were dominated by benzyl benzoate and (E,E)-geranyl linalool; heptacosane was the major component of the leaf oil; the stem oil was dominated by palmitic acid, heptacosane and linoleic acid, while solavetivone, palmitic acid and linoleic acid were the major components of the root essential oil (Satyal *et al.*, 2015).

## 10. Pharmacological Studies

Pharmacologically, the plant has been reported for its anti-inflammatory, antiasthmatic, antioxidant and hepatoprotective activities. Solasodine is a glycoalkaloid present in the plant and has been reported as a potential neuroprotective, cholinergic, antinociceptive, analgesic and anticonvulsant agent (Verma *et al.*, 2020). The berries are the main source of solasodine and diosgenin. The compound diosgenin was found to possess remarkable anti-inflammatory efficiency (Parmer *et al.*, 2010). The ethanolic extract of whole plant showed potent

antimicrobial activity when tested against human pathogens (Devi *et al.*, 2016). In suitable form, the plant methanolic extract can be used as a natural insecticide to control the insect vector, *A. aegypti* that causes the dengue viruses. (Kekuda *et al.*, 2017). The fruit extract of the plant showed nephroprotective potential against gentamicine induced nephrotoxicity and renal dysfunction (Hussain *et al.*, 2012). The antiviral activity of the plant has been reported but the study shows slow inhibitory activity against HIV-RT, which might be improved by isolation and purification of the active ingredient from potential extract to enhance the activity. (Kumar & Pandey, 2014).

### 10.1. Experimental pharmacology

The medical efficacy of fruit as antioxidant, anticancer and anti-HIV was estimated. The fruit extracts displayed potent DPPH radical scavenging activity. The hexane fraction provided 55% lipoprotection in rat kidney homogenate. Non-polar extracts exhibited appreciable cytotoxic activity (70-91%) against leukemia (THP-1) and lung cancer (HOP-62) cell lines. Lower inhibitory activity was observed in extracts against HIV Reverse Transcriptase enzyme (Kumar and Pandey, 2014). Similarly, *in vitro* study of seed extract also showed promising antioxidant and anticancer activity in swiss albino mice against Dalton Ascites Lymphoma (DAL). Tumor was induced in mice by intraperitoneal inoculation of Dalton Ascites Lymphoma cells ( $1 \times 10^5$  cells / mouse). Probably, the presence of flavonoids and phenolic compounds showed significant antioxidant activity and this activity may be responsible for its anticancer activity (Garnavel *et al.*, 2015).

Study was conducted to determine antimicrobial, antiradical, and insecticidal activity of methanolic extract of the whole plant. The extract exhibited inhibitory activity against all bacteria. Gram-positive bacteria showed greater susceptibility to extract when compared to Gram-negative bacteria. The extract was effective in inhibiting the mycelial growth of all test fungi with marked activity against *Curvularia* sp. and *Alternaria* sp. The extract scavenged DPPH and ABTS radicals dose dependently and showed concentration-dependent larvicidal activity with high lethal activity observed against 2nd instar larvae (Kekuda *et al.*, 2017)

### 10.2. Clinical pharmacology

It is used for the management of fever, bronchial asthma and cough for thousands of years. The clinical efficacy of dried whole plant shown significant improvement in some respiratory diseases like bronchial asthma. Pilot study performed by Vadnere *et al.*, (2008) aimed at investigating the anti-asthmatic property of petroleum ether, ethanol, water extract of flowers. The result suggest that the plant extract possess antihistaminic, mast cell stabilizing and decreased capillary permeability effect and hence has potential role in the treatment of asthma and allergic disorders (Vadnere *et al.*, 2008). Further, *in vivo* investigation on the citric-acid induced cough efforts in guinea pigs shows that the antitussive activity of the orally administered pectic arabinogalactan is greater than codeine phosphate, supporting it use in traditional

medicine (Raja *et al.*, 2014). The ethanol extract of plant influenced the haematological parameters in the freshwater fish *Cyprinus carpio* when assessed against heavy metals such as lead acetate (Pichaimani *et al.*, 2017). Further, the leaf extract exhibited anti-diabetic property when intraperitoneal injection administered to diabetic rats(100 mg/kg b.w.) for a period of 45 days. It lowered the levels of blood glucose and a significant increase in plasma insulin (Sridevi *et al.*, 2011).  $\beta$ -Sitosterol, a phytosterol also reported to possess anti-diabetic properties (Tekuri *et al.*, 2019). Report suggest the role of solasodine as a major biomarker, which inactivated Cav 2.2 and Cav 2.3 channels by acting as a competitor of Ca<sup>2+</sup>/Nlobe and reversed peripheral neuropathic pain in model animals (Verma *et al.*, 2020).

#### 11. Toxicity and safety

Studies suggest that plant extracts are non-toxic in nature, even at higher doses 2,000 mg/kg. Intake of steroid glycosides (Solanaceae) led to acute intoxication and severe cases cause death, but no adverse effect reported so far (Tekuri *et al.*, 2019).

#### 12. Clinical studies

A pilot study was undertaken to investigate the clinical efficacy and safety of a single dose in mild to moderate bronchial asthma. The study groups comprised of both males and females in the age group ranging from 18 to 50 years. The respiratory functions (FVC, FEV, PEFR and FEF%) were assessed by using a spirometer prior to and 2 h after oral administration of drug. The patients were randomly allotted to the following treatment groups and received a single dose of the medicaments. *trilobatum* 300 mg; *S. xanthocarpum* 300 mg and standard bronchodilator drug: Salbutamol 4 mg and Deriphylline 200 mg, used for comparison. Treatment with either *S. xanthocarpum* or *S. trilobatum* significantly improved the various parameters of pulmonary function in asthmatic subjects. However, the effect was less when compared to that of deriphylline or salbutamol (Govindan *et al.*, 1999).

Patients reporting with pain to the department of conservative dentistry and endodontics, SRM dental college and diagnosed with symptomatic irreversible pulpitis were selected for this study. The intensity of pain was recorded using Heft Parker Visual Analogue Scale (HP-VAS). Patient was asked to rinse the experimental solution for 3 minutes. Coloured distilled water served as control. The intensity of pain was again recorded using HP-VAS scale. The result showed 68% reduction of pulpal pain in the experimental group. Thus, it can be concluded that oral rinse showed considerable analgesic activity immediately after its usage. It can be thus safely used as an alternative emergency drug to relieve pulpal pain in symptomatic patients. (Srinivasan *et al.*, 2015)

#### 13. Contraindications:No data available

#### 14. Precautions: No data available

#### 15. Adverse reactions:No side effect recorded so far.

16. Marketed formulation, if any: COF-15 Syrup

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1. Botanical Name: ***Solanum surattense*** Burm. f.
2. Synonyms: *S. xanthocarpum* Schrader & Wendl.
3. Family: Solanaceae
4. Common names
  - Assamese: Birkuli-tita
  - Bengali: Kantakari
  - Bihari: Bhatkhataya, Rengnie;
  - English: Yellow berried nightshade
  - Gujarathi: BethiBhoyRingani, Bhoyaringani;
  - Hindi: Kateri, Kattay, Ringani;
  - Kannada: Nelagulla
  - Khasi: Sohngang
  - Malayalam: Kandankathiri
  - Marathi: Bhuringani;
  - Oriya: Ankranti, Bheji-begun; RenginiBhejiri
  - Sanskrit: Kantkari, Nidigdhika
  - Tamil: Kandangattiri;
  - Telugu: Nelamulaka, Pinnamulaka, Vankuda.
5. Description: An erect, armed perennial shrub; prickles on branches and leaves. Both stem and leaves have sharp straight pickles also pubescent. Leaves simple, opposite, pinnatifid, lacerate, acute, leaf base attenuate. Flowers distinct and deep blue in few flowered raceme. Calyx lobes recurved. Fruit a berry, globose, variegated green, ripening yellow. Seeds many, smooth, circular. Fruiting throughout the year.
5. Distribution: Native of India (Himalayas) SE Asia, Malaysia, Australia and Polynesia; found in India almost all the states in tropical regions.
6. Parts Used: Fruit.



*Solanum surattense*

## 7. Medicinal /Therapeutic Uses

### 8.1 Uses described in pharmacopoeias and in traditional systems of medicine

As a traditional medicine, the Kondh tribes of Dhenkanal district of Orissa, India use the hot aqueous extract of the matured fruits for the treatment of diabetes mellitus (Parmar *et al.*, 2010).

The root paste is used for the treatment of hernia by the Mukunda tribes of Rajasthan, India (Pandey *et al.*, 2018).

### 8.2 Uses supported by clinical data:NA

### 8.3 Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data:

In Manipur, India, the fruits are used as a traditional medicine to treat inflammatory problems as well as a throat infection. According to folklore, the entire plant is used for treating leprosy, dropsy, and cough (Verma *et al.*, 2014).

Root poultice used to treat the piles is practicing as a traditional medicine in many villages of South India. Seeds along with mustard oil fumigation used as an excellent remedy for the treatment of dental caries, teeth pain, and pus formation and associated swelling of gums (Pandey, 2004).

The Stem, flowers, and fruits are used to soothe and provide relief burning sensation in feet (Pingale, 2013).

Seeds also used as a remedy for cough and asthma (Rahman *et al.*, 2003).

#### 8.4. Special uses in North East India

In Assam the juice of the leaf is mixed with black pepper and consumed to treat rheumatic pain. In Arunachal Pradesh, the fumes of the burned dry seeds are used to treat cavity. The dried seeds are wrapped with a clean cloth, which is then burned and the fumes are released into the mouth which gives relief to toothache from teeth cavity (Saiyed & Kanga, 1936).

In Manipur the fruit is used to treat headaches and toothaches (Yuhlung & Bhattacharyya, 2016).

#### 8.5. Dosage forms used in tradition

For treating bronchitis, the fruit is boiled or soaked in water and consumed. The leaf part is made into a paste and mixed in salty water and is used for diabetes while the stem part for the dental analgesic (Sen & Chakraborty, 2019).

The fruit is crushed and mixed with two spoonful of honey and consumed to treat headache and toothache (Yuhlung & Bhattacharyya, 2016).

### 8. Phytochemical profile

Saiyed & Kanga, (1936) conducted chemical examinations on the berries which led to the isolation of glycoalkaloid (solasonine), steroidal compound (carpesterol) and steroidalkaloids (caffeic acid, coumarins, and triterpinoids).

Berries which were collected in autumn (September–October) yielded the alkaloids solasonine and solamorgine while another alkaloid solasonine was identified in the fruits collected in summer (May–June) (Parmar *et al.*, 2010).

The fruits also contain steroidal alkaloids like solanocarpine, solamorgine, and solanocarpidine (Murugan & Jayakumar, 2015).

Two other types of phenolic substances, identified as caffeic acid and methyl caffeoate were obtained from the non-alkaloid part (Siddiqui *et al.*, 1983).

The presence of  $\beta$ -sitosterol and diosgenin was found from the callus tissues.  $\beta$ -sitosterol and the diosgenin from callus tissues were found to be much higher than that of naturally grown plants (Hebleet *et al.*, 1971).

The roots contain Alkaloids, Flavonoids, Triterpenoids, Tannins, Saponins, Glycosides, and steroids (Shivani & Joshi, 2014) (Sahle Okbatinsae, 2017).

It was found that the dry seeds yielded greenish-yellow oil rich in fatty acids: linoleic acid, oleic acid, palmitic, steric and arachidonic acid (Heble *et al.*, 1971).

## 9. Pharmacological activities(as per available literature)

### 1. Experimental pharmacology

Anti-viral activity: Study on *in vitro* bioassay and anti-viral activities on Peste des Petits Ruminants (PPR) virus and Reo virus from the individual ingredients viz., *Aegle marmelos*, *Oroxylum indicum*, *Stereospermum suaveolens*, *Premna integrifolia*, *Gmelina arborea*, *Solanum xanthocarpum*, *Solanum indicum*, *Desmodium gangeticum*, *Uraria lagopoides*, *Tribulus terrestris* present in Dashamularishta, an ayurvedic tonic revealed that it is one of the ingredient in Dashamularishta has the potential to inhibit 75% of the growth of the Reo virus (Jabbaret *et al.*, 2004).

Anti-HIV: An activity carried out by Kumar & Pandey (2014) reported that the fruit extract possesses anti-reverse transcriptase (RT) activity. To evaluate the anti-RT activity, non-polar extracts (hexane, benzene, chloroform, ethyl acetate, and acetone) and aqueous extracts at dose 0.6 and 6.0 µg/ml were tested which revealed that nonpolar extracts showed that dose-dependent inhibitory activity. The highest percentage of RT inhibition at 20% was exhibited by benzene and acetone extracts at 0.6 µg/ml concentration. It was revealed that in extracts at 6 µg/ml concentration, the highest percentage of RT inhibition was exhibited by benzene at 25%, which was followed by hexane at 20% and chloroform at 15%. However, the fruit extracts (non-polar) with reference to the standard drug Nevirapine exhibited lower percentages of RT inhibition.

Antibacterial property: Studies have reported antibacterial activity of leaves against five bacterial strains such as *P. aeruginosa*, *S. typhi*, *S. aureus*, *E. coli*, and *Corynebacterium diphtheriae* (Nithya *et al.*, 2018). Ethyl acetate extracts exhibit moderate and broad spectrum activity against *P. aeruginosa* ( $8 \pm 1.2$  mm) and *S. aureus* ( $7 \pm 1.0$  mm), respectively, and does not show inhibitory activity for *S. typhi*. Solvent extractions, such as chloroform, hexane and acetone exhibit least antibacterial activity against *S. aureus*, *P. aeruginosa*, and *C. diphtheriae*.

Antinociceptive activity: A study made on the antinociceptive activity experimental animal models showed that methanol extracts of *S. xanthocarpum* significantly suppressed the frequency of acetic acid induced abdominal constrictions in the animal models. A dose of 500 mg/kg reduced the frequency of worthiness and showed inhibition of 73.08%. The antinociceptive efficiency is dose-dependent(Rahman *et al.*, 2003).

Analgesic property: The methanolic extract of aerial parts significantly and dose-dependently suppressed the frequency of acetic acid-induced abdominal constrictions in mice showing the analgesic property (Rahman *et al.*, 2003).

10.2. Clinical pharmacology: NA

#### 10. Toxicity and safety

The extracts of the herb are found to be non-toxic in nature, even at a higher dose of 2,000 mg/kg as revealed in an Acute toxicity studies on the leaf and fruits extracts (Gupta *et al.*, 2011; Ahmed *et al.*, 2016; Pingale, 2013).

#### 11. Clinical studies

A study on the clinical efficacy of *S. xanthocarpum* and *S. trilobatum* in mild to moderate bronchial asthma was undertaken by giving a dose of 300 mg tds to asthmatic individual for 3 days to determine the effect of these herbs in the treatment of bronchial asthma. It was found that both drugs produced an improvement of the peak expiratory flow rate (PEFR) within the period of study. The effect on the asthmatic individuals was progressive. It showed a decrease in cough, breathlessness, sputum production, edema, and secretions in the airways lumen which indicates bronchodilator effect (Govindan *et al.*, 1999).

12. Contraindications: NA

13. Precautions: NA

14. Adverse reactions: A

15. Marketed formulation, if any: NA

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1. Botanical Name: ***Solanum anguivi*** Lam.

2. Synonym: NA

3. Family: Solanaceae

4. Common names

Assam:	Tidbhagnri
Bengali:	Byakura, Gurkamai
English:	Poison-berry
Hindi:	Barhanta, Birhatta
Malayalam:	Cheru-chunda, Cheruvaz-hudhena
Marathi:	Dorli, Inotiringni, Ringani
Punjabi:	Katang-kari
Sanskrit:	Bhantaki, Vrihati
Tamil:	Karimulli, Mulli, Pappara-mulli
Telugu:	Kakamunchi, Tella-mulaka.

5. Description: A shrub up to 3–15 feet high; stem often prickly, bearing small, sessile stellate hairs with 4–8 arms. Leaves alternate, simple; stipules absent; densely stellate-hairy; blade elliptical-ovate, sinuate to distinctly lobed, with 2–4 pairs of lobes, base oblique, cuneate or occasionally truncate or subcordate, apex acute to obtuse, on both surfaces with more or less sessile stellate hairs having 6–10 more or less equal arms. Flowers usually bisexual, occasionally the distal flowers with short styles and functionally male, regular, usually 5-merous; calyx densely hairy, corolla white, occasionally with pale purple veins on the outer surface, stellate hairy outside, more or less glabrous inside; stamens alternate with corolla lobes, filaments short and thick, anthers connivent, yellow, opening by terminal pores; ovary superior, 2–6-celled, style about as long as stamens, stigma small. Fruit a subglobose berry, smooth, green, or white when young, red when ripe, in clusters of up to 20 fruits. Seeds subreniform, cotyledons thin, leafy.

6. Distribution: It is native to Africa, widely distributed on the African continent and its neighbouring islands and Arabia. Malay Peninsula, Phillipines, Taiwan, China, Africa, Arabia, Madagascar, America. In India, it is found almost throughout along roadsides, and in moist deciduous and semi evergreen forests.

7. Parts Used: Whole plant.



*Solanum anguivi* Lam.

8. Medicinal /Therapeutic Uses

8.1 Uses described in pharmacopoeias and in traditional systems of medicine

Fruits are used fresh or dried and ground as medicine against high blood pressure. The roots are carminative and expectorant useful in coughs, catarrhal affections, dysuria, colic, nasal ulcers, ingredient of dasamula, asthma, difficult parturition, tooth ache, cardiac disorder, worm complaints, spinal guard disorder, nervous disorder and fever. The leaves and fruits mixed with sugar are used as application for itch. Fruit is a ready source of vegetable commonly consumed in Nigeria and other African countries because of the traditional belief that it reduces the risk of diabetes and arteriosclerosis. (Elekofehinti et al., (2013).

8.2 Uses supported by clinical data

The fruits and seeds of the plant with its cholesterol lowering property and hypolipidemic property is used in the treatment of high blood pressure, hypertension and also for treating type 2 diabetes. The ability of the aqueous extract of flesh and seed of fruit to treat diabetes and hypertension to inhibit Fe 2+ and SNP induced lipid peroxidation in rats' brain in vitro was determined. The total phenol, total flavonoid, vitamin C content, ferric reducing antioxidant property as well as Fe 2+ chelating ability were also determined. The results of this study revealed that aqueous extract of fruit (flesh and seed) cause a significant decrease ( $P<0.05$ ) in the MDA production in rats' brain when compared with control. The inhibitory effect of both flesh and seeds on lipid peroxidation could be attributed to the phenol (flesh,  $7.13 \pm 0.73$ mg/g GAE, seed  $8.20 \pm 0.32$  mg/g

GAE), total flavonoid (flesh  $3.53 \pm 0.49$ mg/g QE, seed  $1.62 \pm 0.61$ mg/g QE) and vitamin C content (flesh  $12.85 \pm 0.20$ mg/g, seed  $14.92 \pm 0.11$  mg/g), as well as ferric reducing antioxidant property and Fe  $2+$  - chelating ability. Hence, fruit could be used in the management of type 2 diabetes complication due to its antioxidant ability, a property that play a major role in ameliorating complications resulting from oxidative damage in diabetes.(Elekofehinti et al., 2013).

### 8.3 Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

The domesticated species are consumed as leafy and/or fruit vegetables that are rich in essential minerals and vitamins and are recommended as a dietary staple or supplements for nursing mothers, the young, the aged, and anaemic patients. The plant is used as therapeutic agent for various diseases. The roots are carminative and expectorant useful in coughs, cultarrhal affections, dysuria, colic, nasal ulcers, ingredient of dasamula, asthma, difficult parturition, tooth ache, cardiac disorder, worm complaints, spinal guard disorder, nervous disorder, and fever. The leaves and fruits rubbed up with sugar are used as external application for itch. The fruit is a ready source of vegetable commonly consumed in Nigeria and other African countries because of the traditional believe that it reduces the risk of diabetes and artherosclerosis. (Elekofehinti et al.,2013)

### 8.4 Special uses in North East India

In Assam, the roots are used for treatment against asthma and whooping cough. In Manipur, the fruits and seeds are used for the treatment of high blood pressure and other related ailments. In Arunachal Pradesh, the roots are used as carminative and expectorant for asthma, gout, and toothache relief. In Mizoram and Sikkim, they are also eaten in various ways and used for treatment of hypertension and other related problems. (Perme et al., 2016).

### 8.5 Dosage forms used in tradition

- 5-6 gram of Brihati is used to prepare decoction. Boil dried coarse powder in one glass water till water reduces to half cup. The decoction is ready, filter this and drink. The root Powder and fruit powder is taken in a dose of 1-2 grams.

Other than this, the dose must be administered depending on the age group and conditions of the patients and otherwise it could prove to have other adverse fatal effects. Also, extra care must be taken when administering to pregnant and lactating women.(Brihati (*Solanum indicum* syn *Solanum anguivi* Lam.) Information, Medicinal Uses and More, [www.bimbima.com](http://www.bimbima.com))

## 9. Phytochemical profile

Qualitative phytochemical screening of fruits indicate the moderate presence of saponins, alkaloids, flavonoids, tannins, phenols, steroids and trace amount of triterpenoids.

Quantitative phytochemical screening of fruits is as follows: Saponins ( $1.29 \pm 0.11\%$ ), alkaloids ( $0.05 \pm 0.01\%$ ), flavonoids ( $0.46 \pm 0.02\%$ ), tannins ( $0.17 \pm 0.07\%$ ), phenols ( $1.52 \pm 0.04\%$ ), steroids ( $1.68 \pm 0.06\%$ ), triterpenoids ( $0.35 \pm 0.07\%$ ).

Proximate Composition (%) of fruits include moisture content ( $4.58 \pm 0.11\%$ ), ash content ( $8.89 \pm 0.02\%$ ), crude fat ( $5.68 \pm 0.05\%$ ), crude protein ( $36.35 \pm 1.63\%$ ), crude fiber ( $15.50 \pm 0.71\%$ ), carbohydrate ( $28.98 \pm 0.7\%$ ).

Mineral composition of fruits includes Calcium, Sodium Potassium, Iron, Magnesium, Manganese, Zinc, Copper and Phosphorus (Oyeyemi *et al.*, 2016).

## 10. Pharmacological Studies

### 10.1. Experimental pharmacology

Various studies on have clearly demonstrated the efficacy of extract in free radical scavenging, ferric reducing power, metal iron chelating that was associated with inhibition of lipid peroxidation in rat liver and brain homogenates. Also, SAG extract inhibited  $\text{Ca}^{2+}$ -induced mitochondrial swelling and did not have any effect on mitochondrial membrane potential nor mitochondrial permeability transition pore (MPTP). Although the compounds responsible for the observed activity have not yet been isolated by further studies, it is speculated that it may be related to the bioactive polyphenolic compounds found in the composition of this plant. SAG is a functional food that can be amazingly effective in the treatment of various disease and this is consistent with the traditional use of this plant in folk medicine. These effects could be attributed to the bioactive polyphenolic compounds present in the extract.

Also, Saponins from fruits exhibit free radical scavenging activities and possess reducing power and iron chelating ability making it an excellent candidate in the treatment of diseases in which reactive oxygen species (ROS) has been implicated. It also exhibited antioxidant activities in alloxan-induced diabetes by increasing the level of superoxide dismutase and catalase activities LPO (liquid peroxidation level) level both in heart and kidney. Consequently, it has an ability to prevent diabetic

complications. Hence, the above findings have given scientific evidence to saponins, a class of phytochemical from fruit as potent antioxidant that can be employed in the management of diabetes.

Thus, fruit extract is a potential source of natural antioxidants that may be used not only in pharmaceutical and food industry but also in the treatment of diseases associated with oxidative stress (Elekofehinti *et al.*, 2013).

## 10.2. Clinical pharmacology

The berries have high nutritional and pharmacological values. These potentialities depend on the stage of maturation of berries. It allowed showing the more or less important variations of the chemical composition of the berries during the various stages of ripening. Indeed, the rates of dry matter, phenolic compounds, ashes, vitamin C, magnesium, iron, and manganese of the green berries are higher compared with those of the red berries. On the other hand, the rates of sugars, proteins, lipids, cellulose, calcium, sodium, potassium, and zinc of red berries are superior to those of the green berries. The rates of phosphorus and copper in berries do not vary regardless of the stage of ripening. Besides, the loss of 40 % of vitamin C initial content stays the most important finding. Thin layer chromatography revealed ribose, arabinose, xylose, and fructose. The ribose and the xylose are replaced by the arabinose in red berries. Sterols, polyterpens, flavonoids, saponins and coumarins seem to increase during the ripening contrary to polyphenols, catechic tannins and quinons. Furthermore, the absence of alkaloids in berries indicates that the consumption of this food is not hazardous. The findings permit guidance on the choice of the berries according to their maturation stage for the prevention or the treatment of malnutrition and some public health diseases (Ghislaine *et al.*, 2014).

## 11. Toxicity and safety

Efficacy of traditional medicine was determined using the in-vitro antioxidant activity of the plant extract. Toxicological codicil of the drug was performed following OECD guidelines 423 with slight modifications. The extract administered to the rats by oral gavage at 500, 1000, 1500 & 2000 mg/kg body weight daily up to 28 days to male and female Sprague Dawley rats. Oral toxicity studies substantiate, no treatment-related death or toxic indicia were observed. It revealed that the extract could be well tolerated up to the dose 2000 mg/kg body weight and could be classified as Category 5 drug.). In conclusion, the DRE was well tolerated, lack of mortality and neither produced overt signs of clinical toxicity (loss of hair, behavioral changes, impairments in feed intake and

body weight gain. Further studies in repeated doses (subacute and chronic) must be performed to prove its safety (Saxena *et al.*, 2019).

## 12. Clinical studies

- The extract is a potential source of natural antioxidants that may be used not only in pharmaceutical and food industry but also in the treatment of diseases associated with oxidative stress. African eggplant fruit with bioactive polyphenolic compounds exerts in vitro antioxidant properties and inhibits  $\text{Ca}^{2+}$ -induced mitochondrial swelling. (Elekofehinti *et al.*, 2013)
- The fruit saponin has antidiabetic property via interference with cellular energy metabolism and inhibition of reactive oxygen species (ROS) generation. In the current study, brain specific in vitro antioxidant role of saponin was investigated in the P2 synaptosomal fraction of rat brain. Using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide reduction assay, saponin concentration- dependently (10-200  $\mu\text{g}/\text{ml}$ ) reversed  $\text{Fe}^{2+}$  and sodium nitroprusside- induced decrease in mitochondrial activity via inhibition of ROS production, ROS-induced oxidation of protein and non-protein thiol-containing molecules and lipid peroxidation as measured by thiobarbituric acid reactive substances levels. Conclusively, the fruit saponin represents a class of natural compounds with the ability to reverse synaptosomal disruption, loss of mitochondrial integrity and function often associated with the progression of Huntington's disease, Alzheimer disease, Parkinson disease and amyotrophic lateral sclerosis diseases. (Elekofehinti *et al.*, 2015)
- According to a study conducted on rats (*Rattus norvegicus*), saponins extracted from *Solanum anguivi* Lam. plants inhibit basal erythropoiesis in rats.(Elekofehinti *et al.*,2012).
- Saponin has the potential to prevent lipid peroxidation by inhibition of the lipid peroxidation process and that it has antioxidant and antiperoxidative properties. Effects of Saponin from fruit on Heart and Kidney Superoxide Dismutase, Catalase and Malondialdehyde in Rat (Elekofehinti *et al.*,2012).

## 13. Contraindications

- Even though various studies indicate the various benefits and medicinal properties of the plant, there are also some contraindications found in ayurvedic texts which indicate otherwise. Infusions of the plant, after transient stimulation depress the central nervous system and reflexes of the spinal cord. Small doses increase and large doses decrease cardiac activity. In the isolated rabbit ear, vasodilatation has been observed. Extracts of the plant affect the rate and amplitude of respiration, they also influence the isolated ileum of guinea pig. Also, the leaves when used in overdose in the treatment of scrofulous affections produce diaphoresis, nausea, purging and nervous disturbances. The juice of the fresh leaves is reported to produce dilation of the pupil.

- 14. Precautions

As the saying 'Too much of anything is not good for health' goes, (Bruhati) extracts when taken in large quantities or large doses is not good for health and it may lead to other adverse effects in the body. Dried fruits along with several other ingredients are pasted to coarse powder and preserved in airtight glass bottle. Fresh decoction is administered immediately after normal delivery twice a day up to the completion of sootikaakaala. It protects the person from pain, cough, fever, tremors, headache, excessive thirst, burning sensation, diarrhea, and emesis, etc related to anti natal problems. Care must be taken and ayurvedic healers must be consulted while administering the daily dose of 10-20ml daily otherwise it could prove to have other adverse fatal effects (Khare,2004).

### 15. Adverse reactions

No toxic effect or adverse reaction is reported with recommended dose and it can be used safely for 3-4 months. Also, it is advised to not use it at a high dose or long periods of time. Some of the adverse effects is that it is diuretic and increases dryness in the body. The seeds cause uterine contraction. It is hot in potency. Avoid in blisters, dryness and persistent bitter taste in the mouth, red eyes, hot and watery face, inflammation of the body, inflammations of the intestines and high pitta. Also, care must be taken when they are taken along with other multivitamin tablets (Khare,2004).

### 16. Marketed formulation, if any

Marketed ayurvedic products in which it is used as an ingredient:

Nalikerasavam: used in premature ejaculation

AjamamsaRasayanam: used in neurological disorder

Manasamitravatakam: used in psychological disorder

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1. Botanical Name: ***Strobilanthus cusia* (Nees) Kuntze**

2. Synonyms: *Goldfussia cusia* Nees

3. Family: Acanthaceae

4. Common names

English: Assam indigo, Chinese rain bell

Khasi: U Sybu

Assamese: Raspat

Manipuri: Khuma

Karbi: Sibu

Mizo: Ting

5. Description: An erect herb or under shrub up to 6 feet high. Leaves elliptic to ovate, both surfaces glabrous or abaxially minutely puberulent along veins, abaxially paler green, adaxially dark green, secondary veins 7-9 on each side of midvein, base attenuate, margin serrate, apex acute. Inflorescences terminal or axillary, bracteatespikes, 1-6 cm, often aggregated to form a leafy branched panicle; bracts leaflike, petiolate, oblanceolate, obovate, or spatulate, basally usually sterile; bracteoles linear-oblanceolate, deciduous before bracts. Flowers blue, straight to slightly bent, outside glabrous; tube basally cylindric, then slightly curved and gradually widened; lobes oblong, subequal. Stamens 4, included; filaments glabrous, anther thecae oblong. Ovary oblong, apex puberulent with few gland-tipped trichomes; style ca. 3.2 cm, glabrous. Fruit a capsule, glabrous, 4-seeded. Seeds ovate in outline, covered with appressed trichomes; areola small.

6. Distribution: China, India, Myanmar and Thailand. In India it is found in Assam, Nagaland, Meghalaya, and Manipur. In Meghalaya it is found in Khasi hills.

7. Parts Used: Whole Plant



*Strobilanthes cusia*( Nees) Kuntze, Borthakur and Teron, 2012

## 8. Medicinal /Therapeutic Uses

### 8.1. Uses described in pharmacopoeias and in traditional systems of medicine

It is known as Da-Ching-Yehor Quing Dai or Nan-Ban-Lan-Gen in Chinese is being used to treat the diseases of fever, inflammatory, and sore throat. It is a frequently used Chinese herbal medicine for anti-viral treatment, it was recorded in “People’s Republic of China Pharmacopoeia (2015). It has been also listed as one of the 8 major anti-severe acute respiratory syndrome (SARS) medicines during the outbreak of SARS in 2003 (Quin *et al.*, 2020).

### 8.2 Uses supported by clinical data

Anti-inflammatory: Xiao *et al.*, (2015), investigated the effects and potential mechanism of Quing Dai powder (QDP) on dextran sulfate sodium (DSS)-induced acute colitis in mice and examine the regulatory effects of QDP on macrophages. Oral administration of QDP at dosages of 1.54 and 3.08 g/kg significantly reduced the disease activity index on day 12. QDP treatment (1.54 and 3.08 g/kg) significantly decreased DSS-induced infiltration of macrophages, and production of TNF- $\alpha$ . The methanolic leaf extract are influenced on carrageenan-induced paw edema in wistar rats (Hu *et al.*, 2003).

Anti- viral: Wei *et al.*, (2015) isolated Strobilanthes A, a novel isocoumarin with an unusual tetrahydro-4 H-pyran-4-one moiety fused isocoumarin core skeleton, together with a known compound (2). Its chemical structures were elucidated by 2D NMR spectroscopy, mass spectrometry and single-crystal X-ray diffraction analysis. The biosynthetic pathway of 1 could be supposed to be originally derived from 3-methylisocoumarin, a product of AA-MA pathway. Both of two compounds displayed anti-influenza virus activity *in vitro*.

Tsai *et al.*, (2020), investigated the Anti-Human coronavirus NL63 (HCoV-NL63) activity of the methanol extract leaf and its major components. The methanol extract of leaf effectively inhibited the cytopathic effect (CPE) and virus yield ( $IC_{50} = 0.64 \mu\text{g/mL}$ ) in HCoV-NL63-infected cells. Moreover, this extract potently inhibited the HCoV-NL63 infection in a concentration-dependent manner. The components identified in the methanol extract of leaf are tryptanthrin and indigodole B (5aRethyltryptanthrin) which exhibit potent antiviral activity in reducing the CPE and progeny virus production. This study identified tryptanthrin as the key active component of leaf methanol extract that acted against HCoV-NL63 in a cell-type independent manner.

**Ant nociceptive and Antipyretic:** The methanolic extract of leaf inhibited the writhing responses of mice and decreased the licking time on both the early and late phases of the formalin test in a dose-dependent manner and also it significantly attenuated pyrexia induced by lipopolysaccharide (Ho *et al.*, 2003)

### 8.3 Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

The leaf is popularly known as Da-Ching-Yeh, in Traditional Chinese medicine is used for influenza, epidemic cerebrospinal meningitis, encephalitis B and mumps (Ho *et al.*, 2003).The dye produce from this plant is dark blue in color and is used by the Dong Community in China for clearing heat and relieve toxicity, cool blood and relieve sore throat and can kill pathogenic microorganism and improve immunity (Liu *et al.*,2014).In Vietnam the leaves extract is used internally to treat irregular menstruation, bleeding after abortion, fever, vomiting, tonsillitis and hemoptysis, and externally against eczema, impetigo, haemorrhagic gingivitis, and snake and insect bites.

### 8.4. Special uses in North East India: In Assam, Manipur and Nagaland it is used as a natural Dye (Ningombam *et al.*, 2012).

### 8.5. Dosage forms used in tradition: NA

## 9. Phytochemical profile

The Chemical constituents are alkaloids, glycosides, sterols, pentacyclic triterpenoids, flavanoids, organic acids, anthraquinones, and polysaccharide (Qin *et al.*, 2020).

**Alkaloids:** Indirubin, indigotin, trptanthrin, 4(3H)-quinazolinone, 2, 4,(1H,3H)-benzoyleneurea, 2-methyl-4(H)-quinazolinone, indican, 1H-indole-3-carboxylic acid, 10 9 3- (2'-methyl-butrylic acid methyl ester)-1H-indole, 2-benzoxazolinone, 2-hydroxy-1 4-benzoxazin-3-one, (2R)-2-O- $\beta$ -D-glucopyranosyl-2H-1, 4- benzoxazin-3(4H)-one, (2R)-2-O- $\beta$ -D-glucopyranosyl -4- hydroxy-2H-1, 4-benzoxazin-3(4H)-one , baphicacanthin A, baphicacanthin B, (2R) -2-O- $\beta$ -D- glucopyranosyl- 5- hydroxy-2-1, 4- benzoxazin-3(4H)-

one, 7- chloro -(2R) -2 -O- $\beta$ -D-glucopyranosyl-2H-1, 4-benzoxazin-3(4H)- one (Feng et al., 2016, Qin et al., 2020) and indigoidoles A, C (Lee et al., 2019).

Glycosides: Many phenylpropanoid glycosides, lignans, and their glycoside derivatives were found. Many of those extracts, such as akoside, isoakoside, carrageenin, and (+)-clove-o- $\beta$ -d glucoside, have good antioxidant property (Tanaka et al., 2004).

Sterols: Several sterols were found in the roots, leaves and fruits and they were reported having many physiological effects such as antioxidants, immune regulation, cholesterol reduction on humans. Wu et al., (2005) had extracted Stigmasterol-5, 22 diene-3  $\beta$ , 7  $\beta$ -diol and Stigmasterol-5, 22 diene-3  $\beta$ , 7  $\alpha$ -diol and with petroleum ether, and found that they have some anti-tumor activity

## 10. Pharmacological Studies

### 10.1. Experimental pharmacology

Anti-microbial activity: Shahni and Handique (2013), study the anti-microbial activity. Leaf extracts in various solvents namely ethanol, methanol, acetone and petroleum ether was tested against five bacterial pathogens. The maximum antimicrobial activity was found in the methanol extract against *Staphylococcus aureus* followed by *Bacillus subtilis*, *Enterobacter aerogenes*, *Escherichia coli* and *Klebsiella pneumonia*.

Anti-tumor activity: Cuong et al. (2016) prepared Indirubin-3'-oxime (IOX) from an indirubin-rich powder of leaves through an eco-friendly procedure. IOX obtained was evaluated for the anticancer activity both *in vitro* and *in vivo*. IOX showed anti-cancer activity against various human cell lines (KB, HepG2, MCF-7, LU-1 and LLC); in particular IOX significantly reduced the survival rate of human oral epidermoid (KB) and human lung cancer (LU-1) cells with IC<sub>50</sub> values of 2.51 and 3.52 g/ml, respectively. IOX antitumor activity *in vivo* was assessed by using Lewis lung carcinoma (LLC) cells transplanted subcutaneously in the mice flank. Mice receiving for 40 days IOX at a daily oral dose of 200 mg/kg b.w. had their life span significantly prolonged by 50% while the tumor mass was significantly ( $P<0.05$ ) decreased by about 30% as compared to control animals.

Anti-interleukin- Lee et al.,(2019) isolated the novel indole alkaloid derivatives, indigoidoles A-C were isolated from a traditional Chinese medicine, Qing Dai that was prepared from the aerial parts as a topical agent in moderate psoriasis via interleukin-17 (IL-17) targeting mechanism. The studies indicate that indigoidoles A, C, tryptanthrin, and indirubin could contribute to anti-IL 17 properties of Qing Dai.

### 10.2. Clinical pharmacology: NA

### 11. Toxicity and safety: NA

### 12. Clinical studies: NA

13. Contraindications: NA

14. Precautions: NA

15. Adverse reactions: NA

16. Marketed formulation, if any: NA

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1. Botanical Name: ***Swertia chirayita*** (Roxb. ex Fleming) H. Karst.

2. Synonyms : ***Swertia charade*** (Wall.) C. B. Clarke

3. Family: Gentianaceae

4. Common names

English: Hairy Bergenia, Stone breaker, Rock foil,

Hindi: Chirayata, Charaita, Chirata

Kannada: Nelabevu

Marathi: Charayatah, Chirayita

Sanskrit: Amabhedak, Kiratatikta, Bhunimba, Chiratika

Tamil: Nilavembu, Shirattakuchi,

Malayalam: Kiriayatta, Kiriayattu, Nilaveppa, Uttarakiriyattu

Telugu: Nelavemu

Urdu: Chiraita shireen

5. Description: An erect annual or biennial herb up to 90 cm. high with hollow stem. Leaves sessile, ovate or elliptic, amplexicaul or clasping, margin entire, apex acute. Inflorescence panicles of cymes. Flowers 4-merous, bracts elliptic-ovate. Calyx greenish yellow, lobes linear lanceolate. Corolla greenish yellow, lobes ovate, glands 2 per corolla lobe, oval or oblong, fimbriate. Stamens 4, haplostemonous. Carpel 3-5 mm; stigma lobe capitate. Fruit a capsule.

6. Distribution: Nepal (CE, 1500-2500 m), Himalaya (Kashmir to Bhutan), NE India.

7. Parts Used: Whole plant



*Swertia chirayita*

## **8. Medicinal /Therapeutic Uses**

### **8.1. Uses described in pharmacopoeias and in traditional systems of medicine**

In Ayurveda, the plant has the following uses: Pittasranut- useful in bleeding disorders such as heavy periods, nasal bleeding etc., Shophahara-useful in inflammatory conditions, Kasahara-relieves cough, cold, Trushna-excessive thirst, Jvarahara-useful in fever, Maladhwamsi-decreases bulk of stool, useful in easing bowel movement, Krumighni-useful in pediatric complaints like recurrent fever, Nidrapha-reduces sleep, Mehopaha-useful in urinary tract disorders, diabetes, Shwashara-useful in asthma and wheezing, Dahahara-useful to relieve burning sensation, Kushtahara-useful in skin diseases, Vranahara- induces quick wound healing. The plant's water decoction (kashayam) is used in washing wounds, to relieve infection. In Haritha samhitha it is used in the treatment of scorpion bite with other herbs. Whole plant is used in the treatment of High blood pressure and Diabetes (Sajem *et al.*, 2008).

### **8.2. Uses supported by clinical data**

Antibacterial, antifungal, antiviral, anticancer, anti-inflammatory, and other antidiabetic, and antioxidant activities (Verma *et al.*, 2008; Alam *et al.*, 2009; Chen *et al.*, 2011; Laxmi *et al.*, 2011).

### **8.3. Traditional/Folklore Uses described in folk medicine, not supported by experimental or clinical data**

It possesses digestive, hepatic (conditions pertaining to the liver) and tonic properties. This bitter plant promotes digestion, particularly of fats, and aid in regulating blood sugar levels. At the same time, the herb is an effective medication for leishmaniasis - a parasitic disease usually found in tropical regions. Chirata is especially beneficial for certain health conditions, including diabetes and nausea. The astringent flavor of chirata sets off an impulsive response that promotes the production of saliva and gastric enzymes. This reflex reaction owing to the use of the herb not only stops nausea (queasiness), but also helps to cure indigestion, bloating and hiccups. In addition, chirata also encourages the secretion of bile that promotes digestion as well as improves appetite (Kumar *et al.*, 2010).

### **8.4. Special uses in North East India**

Whole plant is used in the treatment of high blood pressure and diabetes in Assam, while in Sikkim and Arunachal Pradesh the seeds are used also sometimes the whole plant is used to make a bitter tonic and used as a laxative in fever, malaria, jaundice (Perme *et al.*, 2015; Shankar & Rawat, 2013).

### **8.5. Dosage forms used in tradition**

An infusion of the herb is generally employed. It is also given as tincture. The root is taken in doses of 5 to 30 grains with honey. This herb is used as part of many compound remedies.

## **9. Phytochemical profile**

The Plants contains Amarogentin, Swertiamarin, Mangiferin, Swerchirin, Sweroside, Amarooswerin, Gentianine, Oleanolic acid, Ursolic acid, Swertanone, Syringaresinol, Belidifolin, 1-Hydroxy-3,5,8-trimethoxyxanthone, 1-Hydroxy-3,7,8-trimethoxyxanthone, 1,5,8-trihydroxy-3-methoxyxanthone,  $\beta$ -Amyrin and Chiratol (Kumar & Staden, 2016).

## **10. Pharmacological Studies**

### **10.1. Experimental pharmacology**

Ethanol extract of whole plants shown Anti-viral effect against hepatitis B virus (Kumar & Staden, 2016). Basic experiments conducted such as, plaque reduction assay and time kinetics of HSV-1 antigen expression showed that *Swertia* plant product has a potential to have antiviral activity as compared to acyclovir drug treated virus control. Similarly, non-amplification of *Swertia* drug treated HSV-1 infected cells by PCR further complemented and strengthened the antiviral activity (Verma *et al.*, 2008). Petroleum ether extract of aerial parts and ethanolic extract of root have shown anti-inflammatory effect, ethanolic extract of leaves and whole plants exhibited hypoglycemic as well as anti-diabetic effect, water extract of roots shown antipyretic effect, ethanolic extract of root and leaves/stem shown analgesic effect, ethanolic extract of aerial parts shewn hepatoprotective effect, hexane extract of whole plants and isolated compound Amarogentin shown anticancer potential and ethanolic extract of whole plant shown CNS activity (Kumar & Staden, 2016). The aqueous extract at a dose of 200 mg/kg body weight, has exhibited antidiabetic activity in streptozotocin induced diabetes in rats. These extracts exhibited less marked antidiabetic activity when compared to standard drug glibenclamide in streptozotocin induced diabetes in rats (Kavitha & Dattatri, 2013).

### **10.2. Clinical pharmacology:** Clinical studies have not been reported till date.

## **11. Toxicity and safety**

The plant should be avoided by people with gastric or duodenal ulcers. Chirata might lower blood sugar levels in some people.

## **12. Clinical studies:** Clinical studies have not been reported till date

## **13. Contraindications**

The appropriate dose of chirata for use as treatment depends on several factors such as the user's age, health, and several other conditions.

## **14. Precautions**

The plant lowers blood sugar level and is not recommended before surgery and should be taken only if prescribed by a doctor for diabetic patients.

## **15. Adverse reactions:** It worsens gastric ulcers.

## 16. Marketed formulation, if any

Ayurvedic Kadu Kirayata Powder – by Herbal Hills  
Chirata Dry Extract (Swertia Chirata) – Herbal creation

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1. Botanical Name: ***Swertia macrosperma*** (C.B. Clarke) C.B. Clarke

2. Synonym: ***Ophelia macrosperma*** C.B.Clarke

3. Family: Gentianaceae

4. Common Names

English: Chiraita

5. Description: An erect annual herb up to 3 feet high with narrowly winged on angles, branched from middle. Leaves sessile, lanceolate, oblong, ovate, or rarely obovate, base obtuse, apex acute, veins 3-5. Inflorescences panicles of cymes, many flowered, spreading branched. Flowers 5 or rarely 4merous. Pedicel erect, slender. Calyx tube lobes ovate-elliptic, apex acute, midvein distinct. Corolla white or pale blue; lobes elliptic, apex obtuse. Nectaries 2 per corolla lobe, cupular, with a narrow scale and few long fimbriae. Anthers ellipsoid. Style indistinct; stigma lobes capitate. Fruit a capsules ovoid. Seeds 3-4 per capsule, brown, ellipsoid to subglobose. Seed coat smooth.
6. Distribution: Distributed in Bhutan, India, Myanmar, Nepal, Vietnam, China, Taiwan. In India Himalayas.
7. Part Used: Whole plant.



*Swertia macrosperma* C.B. Clarke

## 8. Medicinal /Therapeutic Uses

8.1 Uses described in pharmacopoeias and in traditional systems of medicine NA

8.2 Uses supported by clinical data NA

8.3 Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

It is widely used as a folk medicine for its anti- hepatitis, antipyretic and antidotal effects as “Dida” or “Zangyinchen” in Tibet, Guizhou, and Yunnan provinces of China (Wanget al., 2013a).

### 8.4 Special uses in North East India

The whole plant is used in the treatment of fever, stomachache, digestive troubles, appetizer, gastritis, laxative, hypertension, tuberculosis, malaria, skin diseases & asthma (Jasha & Chase, 2016).

### 8.5 Dosage forms used in tradition NA

## 9. Phytochemical profile (as per literature review)

### 9.1 Major chemical constituents

The chemical compounds found in this species are characterized as norbellidifolin, 1-hydroxy-3,7,8-trimethoxy-xanthone, norswertianolin, swertianolin, 1,3,7,8-tetrahydroxyxanthone-8-O-beta-D-glucopyranoside, swertiamatin, decentapicrin, conifer aldehyde, sinapaldehyde, balanophonin, together with beta-sitosterol, daucosterol, and oleanolic acid (Wang *et al.*, 2010).

An investigation of the whole plant led to the isolation of swertiabisxanthone-1 (Zhou *et al.*, 1989).

## 10. Pharmacological studies

### 10.1 Experimental pharmacology

Anti-HBV: Structural elucidation of three new compounds viz., Swermacrolactone-A, Swermacrolactone-B, Swermacrolactone-C along with the structure of the compounds presence in *S. macrosperma* against Hep G 2.2.15 cell line *in vitro* using Anti-HBV assay reported that among the compound present, luteolin is the most active compound that inhibited the secretion of hepatitis B virus surface antigen (HBsAg) and hepatitis B virus e antigen (HBeAg) with IC<sub>50</sub> values of 0.02 and 0.02 mM, respectively (Wang *et al.*, 2013b).

Anti-Diabetic: Investigation on the antidiabetics effects from the whole plant in diabetic rats was done using Ethanolic and n-Butanol extraction *in vitro* and *in vivo*. The result showed that both the extraction had excellent effects on controlling the hyperglycemia and hyperlipidemia effects (wang *et al.*, 2013a).

Anti-Microbial and Anti-Oxidant: (Jia & Xiong, 2016) investigated the anti-microbial and anti-oxidant effects of xanthones extract from whole plant. Extracts from the whole plant was utilized and partitioned by petroleum ether, ethyl acetate and n-butanol. Anti-microbial and anti-oxidant activities were detected among different fractions. In order to separate and purify the elutions, high-performance liquid chromatography was performed. The compounds were elucidated by <sup>1</sup>H, <sup>13</sup>C NMR and LCMS. The ethyl acetate extract showed maximum inhibitory activity in fungal organisms and Gram-

positive bacteria. The ethyl extract also had the highest antioxidant capacity. Eight xanthones were isolated in ethyl acetate fraction. Also, compounds IV–VI and VIII were isolated from the plant for the first time out of which compound VII had the strongest anti-oxidant effect.

#### 10.2. Clinical pharmacology: NA

#### 11. Toxicity and safety

Wang *et al.*,(2013a), reported ethanol extract of the whole plant didn't show any acute toxicity when orally administered to kunming mice. Lethal dose 50 ( $LD_{50}$ ) extract was found to be  $>10$  g/kg b.w. (per os).

The trace elements analysis concentration in the leaf was higher in the leaf samples over the roots samples. However, the heavy metals and trace elements present in the analyzed medicinal plants are reported to be within permissible limits of FAO & WHO (Jasha & Chase, 2016).

#### 12. Clinical studies: NA

#### 13. Contraindications: NA

#### 14. Precautions: NA

#### 15. Adverse reactions: NA

#### 16. Marketed formulation, if any: NA

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1. Botanical Name: **Syzygium jambos** (L.) Alston

2. Synonyms : *Eugenia jambos* L.

3. Family: Myrtaceae

4. Common Name

Assamese: Jamu, kala jamu

Bengali: Gulabjamb, Jamrul;

English: Rose-apple;

Hindi: Gulabjaman;

Kannada: Pannerrale;

Malayalam: Jambavam, Malakkachampa;

Marathi: Gulabjaman;

Oriya: Golabjamli;

Tamil: Panneerkoyya, Peru naval, Sambunaval;

Telugu: Jambuneereedu.

5. Description: A medium size tree up to 30 feet high. Leaves simple, opposite; petioles, canaliculate; lanceolate or oblong-lanceolate, cuneate at base, acuminate at apex, entire, thin-coriaceous, glabrous; secondary nerves 15-20 pairs. Cymes terminal, racemose; Flowers white or dull-white; calyx lobes turbinate; lobes ovate-orbicular, subequal, obconic; petals 4, rounded; concave; stamens many, unequal; ovary bi-celled. Fruit a berries across, globose or pyriform, yellowish-white to pink tinged, crowned by the inflexed calyx lobes, yellow or white when ripe. Seeds 1-2, grey.

6. Distribution: It is native to Asia; in India Assam, Kerala, Karnataka, Bihar, Andhra Pradesh, Tamil Nadu, West Bengal, coastal areas of Maharashtra and Gujarat.

7. Plant Part: Whole plant



*Syzygium jambosa*

## 8. Medicinal /Therapeutic Uses

In the Chinese system of traditional medicine, the fruit and root bark are believed to be of use as a blood coolant. The fruit peel is said to warm the stomach, to strengthen the spleen, and to be effective in the treatment of deep ulcers and tumours (Leonard, 2008). The fruit has been used as a diuretic and as a tonic for better health of the brain and liver. The flowers are believed to have antipyretic effects, while the seeds are believed to be effective in the treatment of diarrhoea, dysentery, and catarrh. The bark of the rose apple is also useful in the treatment of asthma, bronchitis, and hoarseness. Reports also suggest that traditional Cuban healers used its root in the treatment of epilepsy (Morton, 1987). The fruit is used in treatment of liver complaints and the bark is used for the treatment of antidiarrhoeal, astringent and antidysentric (Kharshnadi *et al.*, 2015).

### 8.1 Uses described in pharmacopoeias and in traditional systems of medicine

It has a long history of use in Indian traditional medicine for the treatment of numerous ailments. The fruit has been used as a tonic for the brain and liver and as a diuretic. The flowers are believed to reduce fever, and the seeds were used to treat diarrhoea, dysentery and catarrh. In South American cultures, the seeds have additionally been used as an anaesthetic, (Morton, 1987) and recent studies a similar analgesic efficacy to morphine in rats. According to (Avila-Pena *et al.*, 2007) Leaf decoctions were also used traditionally in the treatment of diabetes, (Morton, 1987)

although some studies have shown leaf extracts to be ineffective as antihyperglycemic agents (Teixeira *et al.*, 2004).

In Indian traditional medicinal systems the leaves were also used as a diuretic, an expectorant in the treatment of rheumatism; to treat sore eyes; and as a febrifuge. Bark of tree is used to treat asthma, bronchitis and hoarseness (Morton, 1987). Cuban healers have also used the root to treat epilepsy, leaf extracts have also been shown to possess antiviral activity towards herpes simplex type 1 and type 2 and towards vesicular somatitis virus (Athikomkulchai *et al.*, 2008; Abad *et al.*, 1997). The leaves are often used to manage diabetes mellitus, a disease for which the involvement of lipid peroxidation is well known (Giugliano *et al.*, 1996).

## 8.2 Uses supported by clinical data

### Analgesic

The analgesic potential of leaf hydro-alcoholic extracts was assessed in rats. The extract had an analgesic effect on inflammatory cutaneous pain with an efficacy higher than that of diclofenac, a known anti-inflammatory drug. The extract did not alter muscle nociception in normal conditions but it markedly reduced muscle hyperalgesia seen under inflammation of the muscle. These analgesic effects of extract on both cutaneous and deep muscle pain were not mediated by opioid receptors since they were abolished by the selective blockade of opioid receptors with the antagonist naloxone (Pena *et al.*, 2007).

## 8.3 Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

Medicinal properties this plant has some traditional use such as to treat fever, diarrhoea, dysentery, rheumatism, sore eyes, asthma, bronchitis, hoarseness (Warrier *et al.*, 1996), epilepsy, diabetes (Morton, 1987) herpes simplex type 1 and type 2, vesicular somatitis virus (Teixeira *et al.*, 2004, Athikomkulchai *et al.*, 2008). Toothache, mouth sores, cough, wound dressing, (Abad *et al.*, 1997) respiratory disorders, eczema, malaria, and infectious diseases. Other study claimed anaesthetic, diuretic febrifuge activity, (Mohanty *et al.*, 2010 and Cowan, 1999) of the plant.

Ripe fruit is used as a tonic for brain and liver and as a diuretic; seeds for treatment of diarrhoea, dysentery, and catarrh (Morton, 1987). It is also used as a tonic to reduce fever, diarrhoea, dysentery, diabetics, anaesthetic property and catarrh. The leaf decoction is applied to eyes sore, emetic and cathartic, relieve asthma, bronchitis and hoarseness, remedy for epilepsy (Varsha *et al.*, 2012). The leaves have used as a diuretic, in the treatment of rheumatism, as a febrifuge and present antiviral, anti-inflammatory and digestive properties (Morton, 1987; Slowing *et al.*, 1994a; Slowing *et.al.*, 1996).

#### 8.4 Special uses in North East India

Ripe fruits are edible and the peels made into pickles. Fresh fruit juice contains alanine, aspartic acid, cystine or cysteine, glutamine, threonine and tyrosine. Fruit used to treat liver complaints. Bark as astringent, antidiarrhoeal and antidysenteric (Laloo *et al.*, 2002).

#### 8.5 Dosage forms used in tradition: Not Available

### 9. Phytochemical profile

Both leaves and bark extracts contained polyphenols, anthraquinones, tannins, and steroids whilst alkaloids and favonoids were absent. Triterpenes and saponins were found only in the bark extract.

(Ayyanare *et al.*, 2012; Sagrawat *et al.*, 2006; Adams *et al.*, 2009; Shafi *et al.*, 2002).

Seeds Jambosine, Gallic acid, Ellagic acid, Corilagin, 3,6-hexahydroxydiphenoylglucose, 1-galloylglucose, 3-galloylglucose, Quercetin,  $\beta$ sitosterol, 4,6 hexahydroxydiphenyl glucose.

Flowers Oleanolic acid, Ellagic acids, Isoquercetin, Quercetin, Kampferol and MyricetinLeaves  $\beta$ -sitosterol, Betulinic acid, Mycaminoose, Crategolic (maslinic) acid,n-hepatcosane, n-nonacosane, n-hentriacontane, Noctacosanol, ntriacontanol, n-dotricontanol, Quercetin, Myricetin, Myricitrin and the flavonol glycosides myricetin 3-O-(4"-acetyl)- $\alpha$ -Lrhamnopyranosides.

Stembark– reported to be rich in alkaloid jambosine, and the ellagitannin spedunculagin, casuarinin, tellimagrandin I, strictinin, casuarictin, 2,3-HHDP glucose, and traces of tellimagrandin II (Morton, 1987; Okuda *et al.*, 1982). Friedelin, Friedelan-3- $\alpha$ -ol, Betulinic acid,  $\beta$ -sitosterol, Kaempferol,  $\beta$ -sitosterol-Dglucoside, Gallic acid, Ellagic acid, Gallotannin, Ellagitannin and Myricetine.

Fruitpulp- contains linalool and its oxides (Lee *et al.*, 1975), flavonoids myricetin and quercetin 3-O $\beta$ -D-xylopyranosyl (1 → 2)  $\alpha$ -L-rhamnopyranosides (Slowing *et al.*, 1994b, 1996) and ellagic acid derivatives (Chakravarty *et al.*, 1998), anthocyanins, Delphinidin, Petunidin, Malvidin-diglucosides/ The essential oils  $\alpha$ -terpineol, Myrtenol, Eucarvone, Murolol,  $\alpha$ -myrtenal, 1, 8-cineole, Geranyl acetone,  $\alpha$ -cadinol and Pinocarvone.

### 10. Pharmacological Studies

The extract of the plant is reported to have anti oxidant ,anti inflammatory, anti diabetic, anticancer, anti-ulcer, anti-pyretic, cardio vascular diseases, anti hyperlipidimic and neurological disorders like alzheimer's, anti parkinsonism (Ramirez *et al.*, 2003), Analgesic effects (Avila –Pina *et al.*, 2007). Antibacterial activity potential (against sensitive strains of *Staphylococcus aureus*, *Bacillus subtilis*,

*Enterococcus gallinarum*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Enterococcus faecium*, *Salmonella typhi*, and *Vibrio cholera*) (Katiyar et al., 2016).

### 10.1. Experimental pharmacology

#### Antiviral

Different studies have indicated that the ingestion of the jambolan presents health beneficial effects due to the pronounced pharmacological effects of extracts obtained from the fruit. Antiviral activities (Bhanuprakash et al., 2008), antioxidants (Veigas et al., 2007), gastroprotective (Chaturvedi et al., 2007), hepatoprotective (Veigas et al., 2008), and anticancer (Barh & Viswanathan, 2008) effects are reported in the literature on the different extracts obtained from jambolan fruit, however, an emphasis has been given to the antidiabetic action of this fruit, which leads to the development of different studies (Grover et al., 2000; Arayneet al., 2007). These and other biological properties reported to jambolan are related to the various phytochemicals present in its constitution such as anthocyanins and other polyphenols (Baliga et al., 2011).

Ethanol extract of the leaves showed antiviral activity on type I herpes simplex and replication inhibition of vesicular stomatitis virus (Abad et al., 1997). Several flavonoid compounds have been isolated among which quercetin 3-O-*b*-d-xylopyranosyl (1-2) *a*-l-rhamnopyranosides and myricetin are considered significant (Lim TK, 2012). It was recently revealed that the methanol fraction of the leaves contained ellagic acid derivatives like 3, 3, 4 %-tri-O-methylellagic acid and 3, 3, 4 %-tri-O-methylellagic acid-4-O- $\beta$ -d-glucopyranoside (Chakravarty et al., 1998). Moreover, several ellagitannins like casuarinin, pedunculagin, strictinin, tellimagrandin I, casuarictin and tellimagrandin II have also been reported (Okuda et al., 1982).

The hexane, dichloromethane and methanol were extracted from the leaves and investigated for anti-herpes simplex virus type 1 and type 2 (HSV-1 and HSV-2) using plaque reduction assay. Hexane and dichloromethane extracts presented the anti- HSV-1 and HSV-2 activities with more than 50% inhibition of plaque formation at the concentration of 100  $\mu$ g/ml. The IC50 values of each extract and acyclovir were determined. The cytotoxicity of the extracts to Vero cells was also evaluated. Among all extracts, the dichloromethane extract exhibited the highest activity against HSV-1 and HSV-2 with the IC50 value of 75  $\mu$ g/ml while it showed the cytotoxicity in Vero cells at the CC50 value of 150  $\mu$ g/ml. The hexane and methanol also showed the activities against HSV-1 and HSV-2 with the IC50 values of 100 and 300  $\mu$ g/ml, respectively. The cytotoxicity in Vero cells of hexane and methanol was observed with the CC50 values of 150 and 600  $\mu$ g/ml, respectively (Athikomkulchai et al., 2008).

With the changing environment, new viral diseases are being identified, so there is a demand for a safer, non-toxic remedy. The cold and hot aqueous extracts of leaves and barks were evaluated for their antiviral potential against H5N1 (avian influenza virus which causes a highly contagious disease of birds) using CPE reduction assay to establish virucidal, pre-exposure and post-exposure potential of these extracts. With hot and cold aqueous bark extracts and hot aqueous leaf extracts, 100% inhibition of the virus was observed in virus yield reduction assay and in egg based in ovo assay. CC<sub>50</sub>/EC<sub>50</sub> (selective index) for cold aqueous extract (43.5) and hot aqueous extract (248) of bark exhibited their potency against H5N1 virus (Sood *et al.*, 2012).

#### Antidiabetic

A combination of extract obtained from the seeds, fruits of *Momordica charantia*, and leaves of *Azadirachta indica* (200 mg/kg) showed ahypoglycemic effect in rabbits. Treatment of diabetes with plant extracts was started at 8 days after alloxan injection. The antidiabetic effect was produced after 72 h in many of the rabbit's groups. This effect may be due to enhanced endogenous insulin production, possibly through pancreatic β-cell regeneration or repair caused by higher insulin levels in the serum. (Khan *et al.*, 2011).

#### Anti-microbial activity

Djipa *et al.*, (2000) tested acetone and aqueous extracts of rose apple bark for antimicrobial activity against many strains of gram negative and gram-positive bacteria *in vitro* by the agar dilution method in petri dishes. Both extracts showed activity against the tested micro-organisms and proved to be effective on *Staphylococcus aureus*, *Yersinia enterocolitica* and coagulase negative *Staphylococcus hominis*, *S.cohnii* and *S.warneri*. An extract prepared from the leaves is also reported to be useful against *Aeromonas. faecalis*, *A. hydrophilia*, *Bacillus cereus*, and *Staphylococcus aureus* (Mohanty *et al.*, 2010).

#### Anti – inflammatory and antioxidant

Experiments studies on imply that it has anti-inflammatory and antioxidant properties. There have been studies that show the usage of the leaf extract to study the Protein disulfide isomerise (PDI) activity where the inhibition of the PDI activity has been cited to have therapeutic abilities to better the chances of reducing the vascular as well as haematological complications of Sickle Cell Disease (SCD). Studies also show how effective is endothelin-1 (ET-1) in stimulating the PDI activity in human endothelial cells. It is noted that the increase of PDI activity and the ET-1 stimulated *ex vivo* human polymorphic nucleated (PMN) leukocyte migration toward the endothelial cells are both dose-dependently blocked by both of which suggest that may present itself as a novel plant in the pharmacological treatment of complications of SCD (Analaura *et al.*, 2017).

### **Anticancer activity**

Studies on the human leukaemia cell line (HL-60) showed that the plant extract exhibits strong cytotoxic effects and the two hydrolyzable tannins, 1-Ogalloyl castalagin, casuarinin which was isolated from the extract, were observed to possess cytotoxic effects. Both these compounds exhibit a cytotoxic dose dependency in HL-60 cells with an IC<sub>50</sub> of 10.8 and 12.5 µM, respectively. DNA fragmentation assay and microscopic observation of the cells showed a concentration-dependent apoptosis in the cell line (Yang *et al.*, 2000).

### **Hepatoprotective activity**

Preclinical studies indicated that the leaves possess beneficial effects against carbon-tetrachloride-induced liver damage. It was found that carbon tetrachloride significantly altered serum marker enzymes, total bilirubin, total protein, and liver weight, and that the treatment with leaf extract reversed their levels, comparable to that caused by the standard drug silymarin (Islam *et al.*, 2012).

## **10.2. Clinical pharmacology: Not available**

## **11. Toxicity and safety**

The seeds are said to be poisonous. An unknown amount of hydrocyanic acid has been reported in the roots, stems and leaves. An alkaloid, jambosine, has been found in the bark of the tree and of the roots, and the roots are considered poisonous (Morton, 1987)

## **12. Clinical studies- Not Available**

## **13. Contraindications- Not Available**

## **14. Precautions - Not Available**

## **15. Adverse reactions**

May cause intestinal irritation and harmful to lungs in excessive which may lead to Silicosis disease (Parveen *et al.*, 2017).

## **16. Marketed formulation, if any - Not available**

## **17. Reference**

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1. Botanical Name: ***Terminalia chebula*** Retz.
2. Synonym: NA
3. Family: Combretaceae
4. Common Name

Assam:	Silikha
Bengali:	Haritaki
English:	Chebulic myrobalan
Gujarathi:	Hardo
Hindi:	Harra
Marathi:	Hirda
Oriya:	Haridra
Punjabi:	Har, Harar
Sanskrit:	Harra
Tamil:	Kadukai
Telugu:	Karakkai

5. Description: A deciduous tree up to 50 feet high. Leaves simple, opposite to alternate, exstipulate; stout, grooved above, pubescent, 2 sessile glands at the top; ovate, elliptic, obovate or elliptic-obovate, base round, obtuse, oblique or subtruncate, apex acute, acuminate, obtuse or apiculate, margin entire, glabrous above tawny villous beneath, coriaceous; pinnate, ascending, prominent, arched towards the margin, intercostae reticulate, prominent. Flowers bisexual, greenish-white, in terminal and axillary spikes with offensive smell; calyx villous, constricted above the ovary, lobes 5, creamy, triangular, petals 0; stamens 10 in 2 rows; filaments 4-6 mm; disc 5-lobed, villous; ovary inferior, densely villous, 1-celled; style 5 mm, subulate; stigma terminal. Fruit a drupe, obovoid, woody, obscurely 5 angled, glabrous, greenish-yellow; seed one.
6. Distribution: It is distributed to Sri Lanka, India, Nepal, and SE Asia; found in subtropical regions of India up to an altitude 1500mts.
7. Parts Used: Fruit, leaf and bark.



*Terminalia chebula* Retz.

## 8. Therapeutic/Medicinal uses

### 8.1. Uses described in pharmacopoeias and in traditional systems of medicine

It is one of the most used plants in traditional systems of medicine in Indian sub-continent and is also called “King of the medicine”. The dried ripe fruit is an important Indian herb, used extensively in the indigenous system of medicine (Ayurvedic) for its homeostatic, antitussive, laxative, diuretic and cardiotonic activities. The herb is used as tonic, in hepatic and spleen enlargements and in skin diseases in Ayurvedic system of medicine. Its paste with water is found to be anti-inflammatory, analgesic, and having purifying and healing capacity for wounds. These are used as astringent in hemorrhoids as well. Its powder is a good astringent, dentrifice in loose gums, bleeding, and ulceration in gums. The chebulic acid from fruit has shown antispasmodic action like that of Papaverina. It is good to increase the appetite, as digestive aid. Being a mild laxative, it is a mild herbal colon cleanser. Its decoction is used as gargle in chronic cough and sore throat. It is helpful in dysurea and retention of urine. It is useful in skin disorders with discharges like allergies and other erythematous disorders. It reduces the ill effects of the fat rich, creamy and oily food. Further it can supplement to cholesterol normalizing drugs. The extract is reported to inhibit the salivary bacteria and is a potential anti-caries agent. It is used in Ayurveda and Siddha for constipation, chronic diarrhoea, ulcer, gastroenteritis, asthma, cough, dyspnea, dyspepsia, hemorrhoids,

candidiasis, parasites, malabsorption syndrome, hepatomegaly, renal calculi, urinary discharge, tumours, skin disease, memory loss, epilepsy, diabetes, cardiovasular disease, anorexia and wounds (Upadhyay et al., 2014).

#### 8.2. Uses supported by clinical data

The fruit is mild laxative, stomachic, tonic, alterative, antispasmodic. It is useful in ophthalmia, hemorrhoids, dental caries, bleeding gums, ulcerated oral cavity. Its paste with water is found to be anti-inflammatory, analgesic, and having purifying and healing capacity for wounds. Its decoction is used as gargle in oral ulcers, sore throat. Its powder is a good astringent dentifrice in loose gums, bleeding and ulceration in gums. It is good to increase appetite, digestive aid, liver stimulant, stomachic, gastrointestinal prokinetic agent, and mild laxative. The powder of fruits has been used in chronic diarrhea. It is used in nervous weakness, nervous irritability. It promotes the receiving power of five senses. It is adjuvant in hemorrhages due to its astringent nature and good for chronic cough, chorizo, sore throat as well as asthma. Also, it is useful in renal calculi, dysuria, retention of urine and skin disorders with discharges like allergies, urticaria and other erythematous disorders (Bag et al., 2013).

#### 8.3. Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

Some of the folklore people used in the treatment of asthma, sore throat, vomiting, hiccough, diarrhea, dysentery, bleeding piles, ulcers, gout, heart and bladder diseases. The fruit is considered as the "king of medicines" by Tibetans and second-to-none by ayurvedic apothecaries, and also held in high regard by other folk medicinal practitioners (Bag et al., 2013).

#### 8.4. Special uses in North East India

Fruits are used in treatment of stomachache (Sajem et al., 2008).

#### 8.5. Dosage forms used in tradition: Used in single or mixture form.

### 9. Phytochemical profile

It contains (approximately) 32% tannins. The chief components of tannin are chebulic acid, chebulinic acid, chebulagic acid, gallic acid, corilagin and ellagic acid. Tannins are of pyrogallol (hydrolysable) type. There are about 14 hydrolysable tannins (gallic acid, chebulic acid, punicalagin, chebulanin, corilagin, neochebulinic acid, ellagic acid, chebulegic acid, chebulinic acid, 1,2,3,4,6-penta-O-galloyl-D-glucose, casuarinin, 3,4,6-tri-O-galloyl-D-glucose and terchebulin) which have isolated from fruits of *T. chebula*. Phytochemicals like anthraquinones, ethaedioic acid, sennoside, 4,2,4

chebulyl-d-glucopyranose, terpinenes and terpinenols have also been reported to be present. Triterpenoids and their glycosides have been isolated from stem bark. Recent studies show that it contains more phenolics than any other plant (Gupta, 2012).

## 10. Pharmacological Studies

It has a strong effect against wound healing, has antibacterial activity, and exhibits strong cardio protective. It also has antioxidant components, which indicates it can increase the life of tissues. Further few studies show the anti-tumor activity and another study shows that it has considerable effect in inhibiting the HIV virus which ultimately results in AIDS. There is a substantial evidence found that it can be used as Gastro-intestinal motility agent, Anti-aging substance. It also possesses properties like antilithiatic activity, Radio protecting ability and antifungal activity (Rathinamoorthy & Thilagavathi, 2014; Meher *et al.*, 2018).

## 11. Toxicity and safety

Aqueous, ethanol, and ethyl acetate extracts of fruits demonstrated that there is no cellular toxicity on sheep erythrocytes as well as acute oral toxic effects on rats at recommended and higher doses. Besides, hydroalcoholic extract of fruits demonstrated cytochrome P-450 inhibition potential in rats. It by itself had no genotoxic effect both in VITOTOX test and Ames assay. Rather, Thefruit could reduce the lead and aluminium induced genotoxicity. The hydrolysable tannins obtained from fruits also showed antimutagenic activity against direct acting mutagens like sodium azide and 4-nitro-O-phenylene diamine. These findings indicated that it is a safe substance to be used as drug ordinarily (Baget *et al.*, 2013).

## 12. Clinical studies

- Methanolic extract of ripe fruit containing phenolic compounds, chebulic acid and gallic acid are reported to bind to NMDA and GABA receptors and believed to promote intellect and memory (Dua *et al.*, 2009).
- In addition to laxative action, 'Triphala', a well-recognized and highly efficacious polyherbal Ayurvedic medicine is found to be effective for several clinical uses such as appetite stimulation, reduction of hyperacidity, antioxidant, anti-inflammatory, immunomodulating, antibacterial, antimutagenic, adaptogenic, hypoglycemic, antineoplastic, chemoprotective, and radioprotective effects, and prevention of dental caries. Polyphenols in Triphala modulate the human gut microbiome and thereby promote the growth of beneficial *Bifidobacteria* and *Lactobacillus* while inhibiting the growth of undesirable gut microbes. The

bioactivity of Triphala is elicited by gut microbiota to generate a variety of anti-inflammatory compounds (Peterson et al., 2017).

- Clinical trials on salivary *Streptococcus mutans* levels in children showed that *Terminalia chebula*, have substantivity in plaque reduction (Mishra et al., 2019).
- A novel composition prepared from extracts of *T.chebula* fruit, *Curcuma longa* rhizome, and *Boswellia serrata* gum resin was found to exhibit significant pain relief especially in osteoarthritis of knee in human beings (Karlapudi et al., 2018).
- Aqueous extract of fruit is reported to improve joint mobility, comfort, and functional capacity in healthy overweight individual (Lopez et al., 2017).
- A herbal combination including clover plants, Roman anis or Anisone, green anis or fennel, green raisins, *Alhagi maurorum*, violets, *Terminalia chebula*, senna and golqand is found to improved chronic constipation in postmenopausal women (Eliasvandi et al., 2019).
- The fruit extract in 50% ethanolic extract, chebulagic acid, chebulinic acid were found to have direct anti-viral activity against HSV-2 (Kesharwani et al., 2017).
- Three doses of fruit extract of 50, 100 and 200 mg/kg were administered orally and pioglitazone 2.7 mg/kg was used as a positive control. The result shows that the fruit extract exerts a significant and dose-dependent glucose lowering effect in the rat model of metabolic syndrome (Singh et al., 2010).
- The aqueous extract was found to be effective at a concentration of 25 µg/mL in the fluorogenic assay against HIV-1 protease (Xu et al., 1996).

### 13. Contraindications

Pregnancy, dehydration, emaciation. It is contraindicated in weak digestion, fatigue due to excessive sexual activity, with alcohol drink and in hunger, thirst and heat stroke (Chattopadhyay & Bhattacharyya 2007).

### 14. Precautions

Although, haritaki has a plethora of benefits, over consumption or consuming without consultation with an ayurvedic doctor or healer might cause diarrhoea, stomatitis, dehydration, acute fever, malnutrition, stiffness of jaw, fatigue and various pitta disorders. Since it reduces blood sugar, patients already taking sugar reducing

medicines should consult a doctor before taking haritaki. Pregnant women and lactating mothers are also forbidden to use any kind of haritaki formulation without prior doctor's consultation.

### 15. Adverse reaction

Most of the toxicological studies report that toxic effects due to the use of herbal medicine are associated with hepatotoxicity. Other toxic effects of the kidney, nervous system, blood and cardiovascular system, as well as mutagenicity and carcinogenicity have also been published in medical journals. Therefore, numerous advance biological experimental techniques have been used as standard safety test prior to the efficacy study. From the literature it has been noted that *Terminalia chebula* exhibited significant hepatoprotective (Tasduq *et al.*, 2006), cardioprotective, antimutagenic/anticarcinogenic (Kaur *et al.*, 1998), cytoprotective (Hamada *et al.*, 1997), radio protective (Gandhi & Nair 2005) and antioxidant (Cheng *et al.*, 2003) effects indicating that it is a safe substance to be used as a drug ordinarily.

### 16. Marketed formulation, if any

Formulation of *Terminalia chebula* available in the market include: Abhayarishta, TriphalaChurna, Agastyarasayana, Brahma rasayana, DashamoolaHaritaki etc.

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1. Botanical Name: *Tinospora sinensis* (Lour.) Merr.

2. Synonyms : *Tinospora cordifolia* (Willd.) Miers

3. Family: Menispermaceae

4. Common Name

English: Heart leaved moonseed, Giloy, Indian Tinospora

Hindi: Giloe, Gulbel, Gurcha, chinnaruha, giloy, gurch

Sanskrit: Amrita, Guduchi, agnishikha, chadmika, devanirmita

Manipuri: Ningthoukhong lee

Assamese: Aamoi lota

Tamil: Chintil, Chithi kodi.

5. Description: A large climbing perennial deciduous shrub. Leaves membranous, basal nerves 7. Flowers in axillary terminal racemes or panicles. Sepals 6, 2-seriate, the 3 inner larger and membranous. Petals 6, smaller than the sepals. Male flowers: stamens 6; filaments free, apex thickened, anthers obliquely adnate. Female flowers: staminodes 6, clavate; carpels 3, stigmas broad. Fruit a drupes 1-3; style scar terminal, endocarp rugose. Seed usually curved round the intruded endocarp, albumen ruminate.

6. Distribution: Distributed to Tropical Africa, S.E. Asia, Indo-Malaysia and Australia. In India almost all the states an altitude of up to 1500 mts.

7. Parts Used: Stem, Leaves.



*Tinospora sinensis*

## 8. Medicinal /Therapeutic Uses

The aqueous extract of stem has shown to produce immunological activity due to the presence of arabinogalactan. The plant is known for its antispasmodic, antipyretic, antineoplastic, hypolipidemic, hypoglycemic, immune potentiating, and hepatoprotective properties. It is also used in general debility, digestive disturbances, loss of appetite and fever in children, dysentery, gonorrhoea, urinary diseases, viral hepatitis, and anaemia (Mishra *et al.*, 2013).

### 8.1. Uses described in pharmacopoeias and in traditional systems of medicine

It is widely used in Indian Ayurvedic medicine as a tonic, vitalizer and as a remedy for diabetes and metabolic disorders. The plant stem has been considered as an indigenous source of medicines to have antidiabetic, immunomodulatory, antihepatotoxic and antipyretic actions. The leaves also possess an antidiabetic property in alloxan diabetic rabbits .The roots exhibit antiulcer and antistress actions (Prince *et al.*, 1998).

The stem has been used for anti fertility and birth control by the local people of Meitei (Devi, 2015).Traditional healers of North East India uses indigenous herbal formulations by using fresh stem juice which is taken orally twice a day for 7 days(Das *et al.*, 2018).

It has been used for inflammatory diseases in traditional and folk medicine, and experimentally proved using animal models (Rao *et al.*, 2005). It has reported that is antidiabetic and leaves and bark were used as decoction in Mizoram (Laha *et al.*, 2016).

### 8.2. Uses supported by clinical data (Antiviral)

Binding affinity analysis of the compounds resulted Tinosporides, a diterpenoid furanolactone to exhibit highest affinity for the binding site as scored by plants scoring function at  $-31.47$  (kJ/mol) and by Moldock function. Standard drugs were also docked the binding site which showed that the compounds exhibited better docking and affinity profiles. Thus, compounds Octacosonal, Cordifolioside A and Tinosporides were sorted as possible HA (hemagglutinin) inhibitors (Saikia *et al.*, 2019).

In the study, plant AgNPs were synthesized from aqueous extracts of *A. paniculata*, *P. niruri*, and stem of *T. cordifolia* and their antiviral activities were evaluated against CHIKV in vitro using Vero cells (Sharma *et al.*, 2019).

*T. cordifolia*, AgNPs also showed anti-chikungunya activity and increased the viability of virus-infected Vero cells to about 75 and 56% when treated with AgNPs at MNTD and  $\frac{1}{2}$ MNTD, respectively. *T. cordifolia* is known to possess immunomodulatory and immune stimulant properties due to the presence of different bioactive compounds including alkaloids, diterpenoid lactones, glycosides, and steroids (Kalikar *et al.*, 2008). The crude extract has been reported to have anti-HIV potential and inhibited HIV reverse transcriptase activity (Estari *et al.*, 2012).

First report of the presence of (-) epicatechin in *T. cordifolia*, it may be responsible along with other compounds in the prevention of various types of flu as the natural and semi-synthetic derivatives of (-) epicatechin are known to possess antiviral activity against influenza virus, including A/H1N1, A/H3N2 and B virus (Song *et al.*, 2005; Pushp *et al.*, 2013).

### 8.3. Traditional /Folklore Uses described in folk medicine, not supported by

experimental or clinical data:

#### 8.4. Special uses in North East India

Leaf extract is used in diarrhoea and dysentery dried powder stem is used in anemia and urinary troubles (Barbhuuya *et al.*, 2009).The juice of leaf and bark is mixed with honey and orally taken in Assam (medicinal). possess a definite pro-healing action in normal wound healing (Barua *et al.*, 2010).

Whole pant is boiled in water and taken to cure urinary disorders; whole plant is crushed and used in the treatment of arthritis; leaf decoction is used in the treatment of diabetes Tripura (Sen *et al.*, 2011).

Extract obtained from boiling of *Cucurma longa* and *T. cordifolia* is mixed with lemon juice and common salt is given against asthma patient by both Meitei and Meitei pangal communities (Khan & Yadava, 2010).

According to Sangma of Balading village, the vine (one-foot-long) and stems of *Cissus quadrangularis* and *Cissus triangularis* (twenty grams each) were pulverized into a sticky paste using a mortar and pestle or stone slab, then placed in a clean cotton cloth and tied around the fractured area for 7 days. The fern of *Adiantum lunulatum* (seven ferns), without the root was washed thoroughly to remove all dirt and soil. A decoction of it was made by boiling in half a liter of water and then allowed to cool. A cup of this decoction was taken as an analgesic. Beneficial effects for healing bone fracture was also reported (Marak & Mathew, 2020). Dried barks decoction and leaf juice is used in Assam (Sarma, 2020)

#### 8.5. Dosage forms used in tradition

*T. cordifolia* It has significantly reduce the increased activities of serum marker enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and total bilirubin level (Nagarkar *et al.*, 2013).Few ml of concentrated juice extract with leaf paste of *Ocimum sanctum* is taken daily antidiabetic activity instreptozotocin-induced diabetic rats leaf. (Tag *et al.*, 2012).

**Assam Stem, herb** About 100 g stem is crushed in 200 ml water and the filtered extract is given once in every alternate day for 3 months. Antidiabetic activity in streptozotocin-induced diabetic rats (Tarak *et al.*, 2011).

**Mizoram** The stem juice (5 ml, twice daily) is taken orally as antipyretic. Decoction of the dry stem (5–10 ml, 1–2 times daily) is given orally as an aphrodisiac. The juice of the leaf and stem is taken orally (10 ml, 2–7 times daily) as a diuretic and in gonorrhoea. (Sharma *et al.*, 2001).

## 9. Phytochemical profile

A variety of active components derived from the plant like alkaloids, steroids, diterpenoid lactones, aliphatics, and glycosides have been isolated from the different parts of the plant body, including root, stem, and whole plant. From the stem alkaloid berberin, tinosporin and palmitin are isolated while from roots, tinosporin and palmatine are isolated. From the whole plant, the diterpenoidal lactone tinosporide and tinosporon are obtained. Beside these compounds gilojin, gilonin and tinosporic acid are also isolated from the whole plant (Joshi & Joshi, 2013).

Alkaloids	Tinosporin (L), tinosporic acid (L) (W), berberine (S), palmitine (S) (R), tembatarine (S) (R), mangoflorine (S) (R), choline (S) (R), tinosporin (S) (R), isocolumbin (R), tetrahydropalmatine (R).	(Saeed <i>et al.</i> , 2020)
Glycosides	18 Nondendane glycoside (S), furanoid diterpene glycoside (S), tinocordiside (S), tinocordifolioside (S), cordioside (S), cordifolioside A, B, C, D (S), syringin (S), syringinapiosylglycoside (S), palmatosides C and P (S), cordifolioside A, B, C, D, E (S).	
Diterpenoid lactones	Diterpenoid (S), tinosporoncolumbin (S), clerodane derivatives (W), tinosporon (W), tinosporisides (W), jateorine (W), columbin (W),	

	tinosporal, tinosporide.	
Steroids	Sitosterol (S) (O), octacosanol (S), heptacosanol (S), nonacosan-15-one (S), tetrahydrofuran (S), hydroxyecdysone (S) (O), makisterone A (S), giloinsterol (S), ecdysterone (S)	
Sesquiterpenoids	Einocordifolin (S)	
Miscellaneous compounds	Jatrorrhizine (R), tinosporidin (W), cordifol (W), cordifelone (W), gilooin (W), giloinin (W), arabinogalactan (S)	

## 10. Pharmacological Studies

This pharmacological activities of the plant is due to its chemical constituents like diterpenoid lactones, glycosides, steroids, sesquiterpenoid, phenolics, aliphatic compounds, essential oils, a mixture of fatty acids, and polysaccharides and is present in a different part of the plant body, including root, stem, and whole part (Sharma *et al.*, 2019).

Immunomodulatory, Antioxidant, Anti-hyperglycaemic, Anti-diabetic, Antimalarial, Anti-inflammatory, Antitumor Anti-allergic, Antineoplastic activity, Antipyretic, Antiamoebic, Antihelmentic, Anti hyperlipidimic, Immunobiological activity, Antigout, Antiasthmatic, Antiasthmatic, Antigonorrhoeal, Antigonorrhoeal, Antiperiodic, Antiperiodic, Mental disorder, Androgenic, Radioprotective, Antifertility effects, Anticoagulant, Antiemetic and Antiicteric, Antigonorrhoeal, Antiatherogenic, Diuretic, Anticancer, Learning and memory enhance, Anti-depression, Anti-stress, Anti-ischemic, Anti hyperlipidimic, Hypolipidaemic, Antileprotic, Antispasmodic, Antimicrobial, Antiulcer, Analgesic, Help to dissolve urinary calculi, Malaria, Obstructive jaundice, Infections, Hepatoprotective, Prevent hepatotoxicity, Phagocytes, Hepatic and splenic injury, Diabetes mellitus (Choudhary *et al.*, 2013).

### 10.1.Experimental pharmacology

Stem proteins showed a strong trypsin inhibitory activity (greater than standard soybean trypsin inhibitor), while it also displayed  $\alpha$ -chymotrypsin inhibition. Both the protein extracts and protein hydrolysates showed considerable DPPH and ABTS radical scavenging activities, and moderate ferrous ion chelating activity. The strong gastrointestinal enzyme inhibition coupled with a high antioxidant activity suggests a probable prolonged antioxidant effect of the stem proteins after ingestion. The extremely high ABTS and superoxide scavenging activities of papain digest fractions indicated that the lower molecular weight peptides were efficient free radical scavengers than the higher proteins and peptides, owing to the hydrophobic and aromatic amino acids composition. Since is already an important composition of many traditional Indian medicine formulations, both its purified stem proteins and the derived peptides by enzyme hydrolysis could be incorporated into food products or nutraceuticals or developed to be a safe and efficient drug for treating oxidative stress and related disorders (Pachaiappan *et al.*, 2018).

The major biological activities of *T. cordifolia* include the following:

#### Anti-Diabetic Activity

Alkaloids from guduchi stated to possess the effect like insulin hormone and shows insulin mediated actions. Gestational Diabetes can increase the GSH content and other reactive species that can act as a threat to the mother as well as fetus. However, a study stated that when it has been given in daily diet to a diabetic-pregnant rat (streptozocin induced diabetes), it shows a protective effect by reducing the oxidative load thereby preventing the relative incidence of diseases and any sort of birth defect. In diabetic rat model, root extracts of guduchi attenuate the brain mediated lipid level and down regulates the blood glucose and urinary glucose level emphasizing its anti-diabetic and lipid lowering activity. The root extract of guduchi shows antihyperglycemic effect in alloxan induced diabetic model by decreasing its excess glucose level in urine as well as in blood to a range of normal. Medicinal herbal preparations like Ilogen-Excel, Hyponidd and Dihar consist of number of herbal plants including guduchi. When these preparations have been tested in diabetic rat models, it was seen that the anti-diabetic activity is solely due to *T.*

*cordifolia*. The effects by Ilogen Excel reported to turn down the level of excess glucose in blood and enhance the insulin efficiency by increasing its amount in the systemic circulation. Hyponidd is reported to maintain the oxidative load by decreasing reactive species and reduced the glucose mediated haemoglobin count. ‘Dihar’ when tested for one and half month in streptozotocin induced diabetic model decreased the urea as well as creatinine amount in blood with subsequent increase in enzyme activities. The stem extract is reported to have anti-diabetic potential by enhancing the insulin efficiency through its secretion from beta pancreatic cell and promoting various anti-diabetic pathway such as inhibiting glucose formation by enhancing glycogenesis etc. thereby decreasing the endogenous glucose. Extract of guduchi in a clinical study is reported to inhibit the glucosidase enzyme which thereby decreases the post meal increased glucose level. Oral administration of leaf extracts has also found anti-diabetic potential when tested in diabetic rat model (streptozotocin induced diabetes) through different peripheral pathways such as glycogen storage, transportation of glucose and other mechanisms (Tiwari *et al.*, 2018).

### Anti-Toxic Properties

The extract has been known to ameliorate the effects of thiobarbituric acid by increasing the glutathione peroxidase (GSH), ascorbic acid, superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), Glutathione Stransferase (GST) and glutathione reductase (GR) in the kidney. The alkaloids derived from the plants including choline (a member of terpenoid group of alkaloid family), tinosporin, isocolumbin, palmatine, tetrahydropalmatine, and magnoflorine ameliorate nephrotoxicity induced by aflatoxin. Swiss albino male mice liver is protected from lead nitrate toxicity by enhancing the deprived level of aspartate aminotransferase (AST), alanine aminotransferase (ALT), ALP (alkaline phosphatase) and acid phosphatase (ACP). The extract of stem and leaves prevent from lead toxicity on hematological parameters (Sharma *et al.*, 2019)

### Anti-Cancer Properties

Palmatine, an alkaloid derived from this plant, can reduce tumor size by restoring levels of glutathione (GSH), superoxide dismutase (SOD) and catalase as well as

reduce DNA damage. G1-4A can stimulate bone marrow derived dendritic cells which in turn activate cytotoxic T cells capable of killing cancer cell. Its ethanolic extract can reduce the population of drug resistant cancer cells (cells rich in ABC transporters) termed as cancer stem cells thus, helping chemotherapy to overcome such obstacles in cancer therapy. Chemically induced hepatocellular carcinoma, and MCF-7 human breast cancer can be prevented by epoxy clerodane diterpene (ECD) component (Dhanasekaran *et al.*, 2009).

#### Neuroprotective Property

This property as evaluated in 6-hydroxy dopamine-induced Parkinson's disease in rat model gave protection by increasing the dopamine levels and curbing iron accumulation (Kosaraju *et al.*, 2014). Its aqueous ethanolic extract has antipsychotic effect in amphetamine challenged mice leading a reduction in hyperactivity and locomotor activity induced by this drug. This mechanism of action is likely by the binding of extract with dopaminergic D2 (DAD2) receptor (Jain *et al.*, 2010). It has a good effect on children with the behavioural disorder and mental deficit leading to improved memory and teaching (Phukan *et al.*, 2015). Also, it has proved to be beneficial in patients with depression. (Dhama *et al.*, 2017).

#### Anti-HIV Activity

It has been evaluated to find its importance in treating HIV positive patients by decreasing the patient's resistance to the retroviral regimen. The anti-HIV activity uncovers its application in managing the disease by increasing the CD4 T-cells count and decreasing eosinophil- (a type of WBC) count in HIV positive patients. The extract showed significantly enhanced phagocytic and intracellular bactericidal activity. It will also stimulate peritoneal macrophage. Furthermore, it increases phagocytosis and intracellular killing property. It significantly stimulates B-lymphocytes, polymorph nuclear leucocytes and macrophages (Kalikar *et al.*, 2008).

#### Anti-Microbial Activity

A study reported that silver nanoparticles synthesized from the stem possess good antibacterial activity against the bacteria *Pseudomonas aeruginosa* found in the patient suffering from burn injury. Various bacterial strains such as *Salmonella typhi*,

*Klebsiella pneumoniae*, *E.coli*, *Aeruginosa* and other bacteria have been tested against extracts and showed potential anti-bacterial activity by either inhibiting their growth or mitigating the very existence of these bacteria. An active chemical compound that has been found from the stem as reported, found to be effective against bacteria like *E.faecalis* and *B.subtilis* and fungus like *T. simii* and *T.rubrum*. 87 A hydro alcoholic extract was effective in the mammary inflammation induced in bovine model by enhancing the activity of granulocyte. As mastitis is due to the infection of *S. aureus*, prevention of this inflammation showed the antimicrobial activity of this plant. (Tiwari *et al.*, 2018).

## 10.2. Clinical pharmacology

In a clinical study, 100% relief was reported from sneezing in 83% of the patients on treatment. Similarly, there was relief from nasal discharge was reported in 69%; from nasal obstructions 61% and from nasal pruritus, in 71%. In placebo group, there was relief from sneezing only in 21% patients; from nasal discharge, in 16.2%; from nasal obstruction, in 17%; and from nasal pruritus, in 12%. Thus, it significantly decreased all symptoms of allergic rhinitis and was well tolerated. The anti-allergic and bronchodilator properties of an aqueous extract of the stem evaluated on histamine-induced bronchospasm in guinea pigs, capillary permeability in mice and mast cell disruption in rats showed that it significantly decreased bronchospasm induced by 5% histamine aerosol, decreased capillary permeability and reduced the number of disrupted mast cells.

A clinical study has shown that *Guduchi* plays an important role in normalization of altered liver functions (ALT, AST) (Rao and Bairy 2007). The antihepatotoxic activity has been demonstrated in CCl<sub>4</sub> induced liver damage, normalising liver function as assessed by morphological, biochemical (SGPT, SGOT, serum alkaline phosphatase, serum bilirubin) and functional (pentobarbitone sleep time) tests. It revealed hepatoprotective action in goats. A significant increment in the functional capacities of rat peritoneal macrophages was observed following treatment. Addition of extract for the first 6 weeks to chloroquine showed regression of spleen by 37% to 50% after 6 weeks and 45% to 69% after 6 months from the start of treatment. Likewise, decrease in IgM and increase in Hb, as well as wellbeing (Karnofsky performance scale), were observed. It prevents antitubercular drugs and bile salts

induced hepatic damage, x and obstructive jaundice. The extract has also exhibited *in vitro* inactivating property against hepatitis B and E surface antigens in 48 to 72 hours (Upadhyay *et al.*, 2010).

TC significantly decreased all symptoms of allergic rhinitis. Nasal smear cytology and leukocyte count correlated with clinical findings (Badar *et al.*, 2005). It was reported that the root extract affects the immune system of HIV positive patient. The stem extract reduces the ability of eosinophil count, stimulation of B lymphocytes, macrophages, level of hemoglobin, and polymorphonuclear leucocytes ( Sharma *et al.*, 2019).

## 11. Toxicity and safety

No significant information on side effects is available so far. The drug is traditionally safe (Sinha *et al.*, 2004). The Ayurveda literature reports that it can cause constipation, if taken regularly in high doses; it has no side effect and toxicity. Yet the safety and the potential indications in human beings have to be established using modern methods (Singh *et al.*, 2003).

## 12. Clinical studies

It's reported medicinal properties are anti-diabetic, anti inflammatory, anti-arthritis, antioxidant, antistress, immune modulatory and anti-neoplastic activities. A study by Rawal *et al.*. (2004) showed that it exhibit strong free radical scavenging properties against ROS and reactive nitrogen species as studied by electron paramagnetic resonance spectroscopy. The herb also effectively elevates the level of reduced glutathione, expression of the gamma glutamyl-cysteine ligase and Cu-Zn superoxide dismutase genes. In addition, it significantly diminished the expression of iNOS (Inducible nitric oxide synthase) gene after 48 hours which play a major role in neuronal injury during hypoxia/ischemia. Another experiment by A Shaish Antony *et al.* 2014 showed that it has potential to reduce symptom of 6-hydroxy dopamine induced Parkinsonism by protecting dopaminergic neurons and reducing the iron accumulation. Ethanol extract exhibited significant increase in the dopamine levels. It also enhances Learning and Memory. Significant response has been found in children with moderate degree of behavior disorders and mental deficit, along with improvement in IQ levels. In a 21-day randomized, double-blind placebo-controlled

study, the pure aqueous extract of the root was found to enhance verbal learning and logical memory. It has also been shown to enhance cognition in normal rats and reverse cyclosporine-induced memory deficit. Both the alcoholic and aqueous extracts produced a decrease in learning scores in Hebb William maze and memory retention, indicating enhancement of learning and memory. The histopathological examination of hippocampus in cyclosporine-treated rats showed neurodegenerative changes, which were protected (Phukan *et al.*, 2015).

### 13. Contraindications

*T. cordifolia* at 20 mg identified no contraindications to the clinical use of this agent in pregnant women (Balachandran & Govindarajan 2005; Nemova *et al.*, 2007). Powder: 1–3 g, liquid extract: 56–112 ml , Safe side effects is Nausea, Excessive dose might inhibit Vitamin B assimilation (Balachandran & Govindarajan, 2005).

Oral administration of 70% methanolic extract of stem to male rats at a dose level of 100 mg/d for 60 days did not cause body weight loss but decreased the weight of testes, epididymis, seminal vesicle and ventral prostate in a significant manner (Gupta & Sharma, 2003).

### 14. Precautions

In a clinical study, it has been shown to be at a dose of 500 mg/d for a period of 21 days in healthy individuals. it can be concluded that it is safe at a dose of 500mg per day for a period 21 days in healthy volunteers for the parameters studied (Rao& Bairy, 2007).

### 15. Adverse reactions

It has also been shown not to exert any remarkable adverse effects on the cardiovascular system (Dhar *et al.*, 1968) renal system (Nayampalli *et al.*, 1988), central nervous system (Bairy *et al.*, 2004)and gastrointestinal system (Spelman, 2001).

## 16. Marketed formulation, if any

A polyherbal formulation AHPL/AYTAB/0613 containing Bhringaraja - *Eclipta alba* extract, Guduchi - *T. cordifolia* extract, Daruharidra - *Berberis aristata* extract, Kakamachi - *Solanum nigrum* extract, Punarnava –*Boerhaavia diffusa* extract, Bhumyamalaki - *Phyllanthus amarus* extract, Kutaki –*Picrorhiza kurroa* extract, and Kalmegha –*Andrographis paniculata* extract was assessed for its hepatoprotective activity. It was observed that AHPL/AYTAB/0613 significantly reduced levels of serum glutamic-oxaloacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, total bilirubin and also significantly increased total protein level. Therefore, it was concluded that AHPL/AYTAB/0613 possesses hepatoprotective activity in CCl4, ethanol, and paracetamol-induced hepatotoxicity in rats (Nipanikar *et al.*, 2017).

Two formulations named as Hemoliv and HP-1 showed protective effects against CCl4-induced hepatic damage in rats. A formulation, Caps HT2, containing a methanolic extract with other herbs was evaluated for its anti atherogenic, antioxidant, anticoagulant, platelet anti aggregatory, lipoprotein lipase releasing, anti-inflammatory and hypolipidemic activities. Two herbal formulations, Diasulin and Dihar, containing an ethanolic extract of roots showed anti hyperlipidemic, anti peroxidative and antioxidant activities. The therapeutic importance in Ayurveda and the pharmacological activities of different doses (*in vitro* and *in vivo*) have been validated (Singh & Chaudhuri, 2017).

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1. Botanical Name: ***Trachyspermum ammi* (L.) Sprague**
2. Synonyms : ***Ammi copticum* L.**
3. Family: **Apiaceae**
  
4. Common Name
 

English:	Carom, Wild parsley & Bishop's weed
Hindi:	Ajwain, Carom omum, Jevain
Manipuri:	Ajwain
Sanskrit:	Ajamodika, Bhutika, Deepyaka, Ugargandha, Yavanaka,
  
5. Description: An erect annual up to 75 cm high. Leaves petiolate, blade triangular-ovate in outline, 2–3-pinnatisect; ultimate segments linear-filiform. Flowers in umbels; bracts linear-subulate; rays 6–20; bracteoles 5–10, linear; umbellules 20-flowered; pedicels unequal. Calyx teeth conspicuous, minute, ovate or obsolete. Fruit densely covered in whitish minute papillae.
  
6. Distribution: Distributed to Europe, eastern Asia in the Himalayas.
  
7. Parts used: Whole plant

*Trachyspermum ammi*

#### 8. Medicinal/Therapeutic Uses

Ajwain has been commonly used in traditional medicine systems for a variety of medicinal and pharmacological aspects (Lateef, 2006). In Traditional Persian Medicine (TPM), Ajwain was well known from thousands of years. Persian

practitioners usually used seeds of Ajwain as the most useful part of the herb (Avicenna, 1998). According to its temperament, Ajwain is hot and dry in the third degree and possesses some bitterness and acridity. Oral application of seed was reported to be useful for paralysis, tremor, and palsy as well as other neural disorders in the field of neurology (Hejazian *et al.*, 2008). Persian practitioners also applied the eye and ear drop formulated from seeds of Ajwain to control the infected conditions and correct the auditory weakness (Hejazian, 2006). In the field of respiratory, Ajwain was said to be effective on cough, pleurisy, and dysphonia (Dashtiet *et al.*, 2007). Fruits were widely administered for liver spleen as well as gastrointestinal disorders such as nausea, vomiting, reflux, abdominal cramps, and loss of appetite (Shirazi *et al.*, 1992). They were also said to be beneficial in stomach troubles and possess stimulant and carminative properties. Ajwain was reported as an anthelmintic medicine and antidote for various natural toxic agents (Tonekaboni, 2007). It was also believed to be beneficial for dissolving the calculi and stones if taken with wine. Persian practitioners also considered the seeds as an aphrodisiac, galactagogue and diuretic agent (Shirazi *et al.*, 1992). As a cosmetic agent, local administration of Ajwain as a paint results in yellowish complexion on the skin. It was also incorporated in medicine prepared for pityriasis and leukoderma and plastered with honey in cases of all types of ecchymosis (Avicenna, 1998; Shirazi *et al.*, 1992). Persian practitioners also used the seeds in the form of fumigation for the female genital disorders. In the field of toxicology, it was reported that bathing the affected part with the decoction of Ajwain seeds alleviates the pain caused by scorpion's bite (Dashtiet *et al.*, 2007). Also, it was used for the reduction of undesired effects related to the opioid withdrawal. Ajwain was also introduced as a potent analgesic and anti-inflammatory agent. Therefore, it was applied on the affected area solely or in combination with egg white or honey. Persian practitioners used Ajwain in chronic fevers and gripes (Shirazi *et al.*, 1992; Tonekaboni, 2007). Hydrosol and oil extracted from the seeds of Ajwain was also used for medical purposes. Of those, management of paralysis, palsy, tremor and neurological disorders such as neuropathic pain as well as chronic pains are cited in Persian medical and pharmaceutical manuscripts (Shirazi *et al.*, 1992; Heravi, 1765). The Ajwain hydrosol combining with Borage and Cinnamon was highly recommended as a great enlivening medicine (Shirazi *et al.*, 1992).

## 9. Phytochemical profile

The chemical composition of ajwain seed essential oil is influenced by various factors. Different parameters such as pressure, temperature, and modifier volume and extraction time have significant effect on the percentage yield and composition of ajwain oil. Extraction yield based on the supercritical fluid extraction varied in the range of 1.0-5.8 % (w/w) under different conditions. Supercritical fluid ( $\text{CO}_2$ ) extraction (SFE) of ajwain oil, under pressure of 30.4 mpa, temperature 35 °C and dynamic extraction time of 30 min, only 3 components including  $\gamma$ -terpinene (14.2%), p-cymene (23.1%) and thymol (62.0%) constituted more than 99 % of the oil. It was

considered to be the most selective method for the extraction of thymol. However, in hydro distilled oil, there were 8 components including thymol (49.0%),  $\gamma$ -terpinene (30.8 %), p-cymene (15.7%),  $\beta$ -pinene (2.1%), myrcene (0.8%) and limonene (0.7%) were identified. The extraction yield, based on hydro distillation was 2.8 % (w/w) (Minija & Thoppil, 2002; Minija, *et al.*, 2002). Nutrition analysis of ajwain seeds indicated higher energy value (31.55%), carbohydrates (47.54%), protein (20.23%), fat (4.83%), moisture (11.6%), fibre (4.3%) and ash content (11.5%) in ajwain seeds (Javedet *et al.*, 2012). Gas Chromatography-Mass Spectrometry (GC-MS) analysis of ajwain seed essential oil revealed the presence of 27 compounds, of which thymol (40%) was present in the largest amounts, with p-cymene (15.6%) and  $\gamma$ -terpinene (11.9%) whereas  $\beta$ -pinene (4%), limonene (4%), carvacrol (5 %), camphene and myrcene present in trace amounts. However, oil obtained from aerial parts and a fruit of ajwain was found to contain thymol (42.7-46.2%),  $\gamma$ -terpinene (38.5-38.9%) and p-cymene (14.1-13.9%) as the main components (Krishnamoorthy *et. al.*, 1999; Abdolali *et. al.*, 2007; Bhattacharya *et al.*, 1998).

The phenolic components of the ajwain essential oil contained thymol (87.75%) and carvacrol (11.17%) as major constituents and major non-phenolic components quantified were p-cymene (60.78%) and  $\gamma$ -terpinene (22.26%) (Nagalakshmi *et al.*, 2000; Pruthi, 1992).

Variations in aroma compounds have been observed in seeds collected from different geographical regions and plant parts (flowers, seeds, leaves) of ajwain. In Algeria, isothymol (50%) was found to be the dominant constituent. Other components present were p-cymene, thymol, five new monoterpenoid glucosides, a new monoterpenoid, limonene and  $\gamma$ -terpinene. Essential oil of ajwain seeds collected from South India was found to be rich in thymol (98%). However, oil extracted from ajwain leaves was found to be composed of monoterpenoids and sesquiterpenoids: Cadinene (43%), longifolene (11%), thymol (5%), and camphor (3%) (Farooq *et al.*, 1953).

Watersoluble portion of methanol extract of ajwain seeds contained 25 compounds, including two new aromatic glucosides and two new glucides (Ishikawa *et al.*, 2001 & 2003). On analysis of the fixed oil from the seeds of ajwain in Indian origin, reported petroselinic acid as the major component (Dwivedi *et al.*, 1998). Major components present in acetone extract of ajwain seeds were found to be thymol (39.1%) followed by oleic acid (10.4%), linoleic acid (9.6%),  $\gamma$ -terpinene (2.6 %), p-cymene (1.6%), palmitic acid (1.6%) and xylene (0.1%). Thymol easily crystallizes from the oil on cooling and commonly known as ajwain ka phool or Sat of ajwain (Farooq *et al.*, 1953). A yellow, crystalline flavone and a steroid-like substance were also isolated from ajwain seeds which contained 6-O- $\beta$ -glucopyranosyloxythymol, a glucoside and a yield of 25% oleoresin containing 12% volatile oil (thymol,  $\gamma$ -terpinene, p-cymene and  $\alpha$ -pinene and  $\beta$ -pinene) (Garg, 1998). Dichloromethane extract of cell suspension culture of *Carum copticum* revealed the presence of 41 compounds. Major constituents were found to be elemol (11.5%), cadinol (10.6%), cadinene

(7.8%), caryophyllene (6.2%), muurolol (4.9%), eudesmol (3.1%), elemene (3.9%), muurolene (2.6 %), limonene (2.4 %) and humulene (2.0%) while other compounds were present in trace amount (Lockwood *et al.*, 2002). The sowing dates had significant effect on the percentage and composition of essential oil. Essential oil percentage was significantly influenced by planting time so that highest yield obtained in October was 3.3%. By delayed sowing date, essential oil yield decreased gradually. Lowest amount of essential oil was obtained (2.14% or 10.42 kg/ha) in March which was significantly different in comparison with other dates (at 5% of probability level). Ajwain seeds from all treatments contained normal to high amount of thymol. The other main constituents in the essential oil were  $\gamma$ -terpinene, p-cymene and  $\beta$ -pinene that are ranging from 12.52-27.35, 4.28-11.79 and 1.93-39.17%, respectively. The concentration of thymol and p-cymene were greater in seed oil from the first seedling date, whereas concentration of  $\gamma$ -terpinene was greater in January and a greater content of  $\beta$ -pinene was found in February. The highest amount (49.62%) of minor components was observed in March. October was suitable time to convert precursor's pcymene and  $\gamma$ -terpinene to thymol. It seems that higher temperature in October and long-time flowering had suitable time for synthesis essential oils. Effects of seeding date on ajwain essential oil yield and composition showed that for ajwain seed production, sowing in March was not preferable. Significant changes were attributed to long duration of crop which provided long photoperiod to synthesize more quantity of essential oil or in other words might be due to availability of higher temperature from flowering. The environment during seed development was a major determinate of seed quality. For successful seed production at this site, ajwain must be sown in early sowing date as delaying sowing until March reduced yield and composition (Syed *et al.*, 2015). Non-polar fraction of ajwain oil contained p-cymene,  $\gamma$ -terpinene,  $\alpha$ -pinene,  $\beta$ -pinene,  $\alpha$ -terpinene, styrene,  $\delta$ -3carene,  $\beta$ -phyllanderene, terpinene-4-ol and carvacrol. Also, oleic, linoleic, palmitic, petroselinic acid, resin acids were isolated from fruits of ajwain (Qureshi *et al.*, 2010). New glycosyl constituents such as 6-hydroxycarvacrol 2-O- $\beta$ -DGlucopyranoside and 3, 5-Dihydroxytoluene 3-O- $\beta$ -DGalactopyranoside were recently reported from fruits of ajwain (Gang *et al.*, 1980).

Phytochemical studies revealed that ajwain seed oil contained fiber (11.9%), carbohydrates (38.6%), tannins, glycosides, moisture (8.9%), protein (15.4%), fat (18.1%), saponins, flavone and mineral matter (7.1%) containing calcium, phosphorous, iron and nicotinic acid (Zarshenas, 2013; Bairwa, 2012).

Different geographical regions effect the chemical composition of ajwain oil. The results of these findings revealed the presence of thymol,  $\gamma$ -terpinene,  $\gamma$ -terpinolene, p-cymene, o-cymene and  $\beta$ -pinene as the major constituents. However, major component of ajwain oil collected from Pakistan was found to be p-cymene-3-ol. Other minor constituents present in ajwain oil were ethylene methacrylate, carvacrol,  $\beta$ -myrcene and  $\alpha$ -pinene (Balbaa *et al.*, 1973; Lucchesi *et al.*, 2004; Mahboubi *et al.*, 2011; Shojaaddini *et al.*, 2014; Singh *et al.*, 2004; Soni *et al.*, 2016). The chemical composition of ajwain seed oil collected from Sabzevar (Iran) was found to be

different as compared to other studies. Forty-four compounds consisting 91.6 % of the total oil were identified. The ajwain seed oil was rich in non-terpenoids (56.0 %) and the main components of the oil were hexadecanoic acid (27.5 %), ethyl linoleate (8.5 %), 6-methyl- $\alpha$ -ionone (8.0 %), isobutyl phthalate (5.8 %),  $\alpha$ -cadinol (4.7 %), germacrene D (4.3 %) and  $\delta$ -cadinene (3.5 %) (Hashem et al. 2014) [33]. Ajwain seed essential oil consist of monoterpenes such as p-cymene,  $\gamma$ -terpinene,  $\beta$ -pinene,  $\beta$ -phellandrene, myrcene, apinene,  $\alpha$ -terpinene,  $\alpha$ -thujene,  $\beta$ -selinene and their phenol derivatives such as thymol, terpinene-4-ol, carvacrol, terpinolene, trans-sabinenhydrate, linalool and  $\alpha$ -terpineol, reported in earlier studies (Kazemi et al., 2011; Chialva et al., 2004).

Current Pharmacological Findings shows analgesic and antinociceptive Effects In order to evaluate the analgesic and antinociceptive activity of Ajwain, an *in vivo* investigation was carried out using a Tail-flick Analgesiometer Device (Dashtiet et al., 2007). The study revealed that the ethanolic extract significantly increase in Tail-Flick Latency (TFL) within 2 hours postdrug administration. An experimental trial study has also been carried out to compare the antinociceptive effect of the hydroalcoholic extract of Ajwain with morphine sulphate using formalin test. Findings revealed that Ajwain extract exhibited antinociceptive effect on both early and late phases (Hejazian et al., 2008). Similar study has been done on the Ajwain total essential oil which was significantly effective on the late phase of formalin test (Hejazian, 2006) and it may be due to the presence of thymol in essential oil. In addition, under a randomized controlled placebo control clinical trial, the herb essential oil was assayed for the analgesic effect in neuropathic feet burn. Results revealed that Ajwain essential oil significantly reduced the feet burn compared to placebo (Petramfar, 2013).

## 10. Pharmacological Studies

Seeds have higher energy value that is 314.55%. It is rich source of carbohydrates 47.54%. Protein, moisture, ash and fiber contents are present in the range of 4.30%-20.23%; fat contents were in the range of 4.83% (Asif HM, 2014). From nutraceutical point of view, spices ajwain is served as important constituents of human diet supplying the body with enough proteins, carbohydrates, and energy. The presence of biologically active compounds also adds to its nutritive value and thus proved to be potential sources of useful foods (Javed, 2012).

It is used to treat anorexia, arthrosis, ascites, asthma, atony, boil, bronchitis, cachexia, cancer of abdomen, cardiopathy, cholera, cold, colic, congestion, cough, cramp, debility, diarrhea, dipsomania, dyspepsia, edema, emphysema, enteritis, epilepsy, escherichia, fever, flu, fungus, hemorrhoid, hepatosis, hiccup, high blood pressure, hysteria, laryngitis mycosis, nausea, nematode, nephrosis, ophthalmia, pain, paralysis, pneumonia, rheumatism, salmonella, sinusitis, snakebite, sore throat, stone, syncope, toothache, and wounds. It is used as antiseptic antispasmodic, aphrodisiac bitter, cardio-depressant, carminative, diaphoretic, diuretic,

emmenagogue, expectorant, fungicide, gastro relaxant, gastro-stimulant, hypotensive, lactagogue, laxative, litholytic, parasympathomimetic, sialagogue, spasmogenic, stimulant, stomachic, tonic and vermifuge(Duke, 1992).

#### Antidiarrheal activity

Antidiarrheal activity of 95% total alcoholic extract (TAE) and total aqueous extract (TAQ) of seeds at a dose of 100 mg/kg body weight was evaluated using experimentally induced castor oil diarrhoea, gastrointestinal transit of charcoal meal and entero-pooling activity in male Wistar rats and compared to standard drugs. In the study, the TAE and TAQ extracts of seeds at a dose of 100 mg/kg exhibited a significant inhibition of castor oil induced diarrhoea in dose dependent manner in experimental rats. TAE and TAQ extracts significantly decreased the diarrhoeal droppings when compared to castor oil group. The results obtained for TAE and TAQ extracts were like that of the standard drug loperamide (3 mg/kg) intestinal fluids in the small and large intestines(Balaji, 2012). Anti-diarrhoeal and anti-dysenteric properties of medicinal plants were found to be due to the presence of tannins, flavonoids, saponins, alkaloids, sterols, reducing sugars and triterpenes(Mehmood, 2011; Inayathulla, 2010). The phytochemical studies on seeds have revealed the presence of flavonoids, tannins, saponins and sterols. Thus, the anti-diarrhoeal activity might be due to these chemical constituents. Flavonoids have anti-diarrhoeal activity, which have ability to inhibit intestinal motility and hydro-electrolytic secretions which are known to be changed in diarrhoea conditions (Venkatesan, 2005). Tannins and tannic acid denature the proteins in intestinal mucosa by forming the protein tannates, which make the intestinal mucosa more resistant to chemical alteration, and hence reduce secretion (Mohammed, 2009).In conclusion, the results obtained in the present study suggest that the seed extracts have beneficial effect in controlling the diarrhoea in experimental animals.

#### Antibacterial activity

Thymol obtained from the seeds of the plant used in fourth generation antibiotic formulation for control of drug resistant bacteria. More particularly, compound thymol isolated from the oil distilled from the seeds of the plant kill the bacteria, resistant to even prevalent third generation antibiotics, multi-drug resistant microbial pathogens and thus useful as a plant based fourth generation herbal antibiotic. The Gram-positive bacteria such as *Bacillus cereus*, *Bacillus subtilis*, *Staphylococcus aureus*, and *Listeria monocytogenes* show good inhibition action compared to Gram-negative bacteria (such as *Escherichia coli* and *Pseudomonas aeruginosa*). Gram-negative bacteria generally have been reported to be more resistant than Gram-positive. The different antimicrobial effect of essential oils is due to differences in the lipopolysaccharide constitution of cell walls. Several hypotheses have been put forward which involve hydrophobic and hydrogen bonding of phenolic compounds to membrane proteins, which causes the partition into the lipid bilayer membrane disruption, destruction of electron transport systems and cell wall perturbation. The

high activity of the phenolic component might be due to alkyl substitution into phenol nucleus, which is known to enhance the antimicrobial activity of phenols. Depending on the concentration used phenolic compounds, such as thymol and carvacrol are known to be either bactericidal or bacteriostatic agents (Ramaswamy, 2010).

#### Gastroprotective activity

Fruit have traditionally been used as medicinal plant for the treatment of indigestion and dyspepsia and many other gastric disorders. Therefore, ethanolic extract of fruit was used for investigation of antiulcer activity by using pylorus ligation, as antisecretory model and indomethacin induced ulcer model, ethanol induced ulceration model, cold restraint stress induced ulcer model as cytoprotective model. The extract at dose of 100 mg/kg and 200 mg/kg showed significant protection ( $P<0.001$ ) by reducing ulcerative lesions when compared with control group of animals. The findings indicated that the fruit extract have significant antiulcer activity. Mucus is secreted by the mucus neck cells, serves as first line of defence against ulcerogens and covers the gastric mucosa preventing its physical damage and back diffusion of hydrogen ions. In the present study, increased mucus secretion. The major constituent of mucus is mucopolysaccharides which are responsible for viscous nature and gel-forming properties of the mucus. The gel is reported to be resistant to several ulcerogens including acid, NSAIDs, i.e. indomethacin, etc. Therefore, increase in the production of mucus may be one of the important contributing factors for ulcer protective role of fruit (Hejazian, 2007).

#### Relaxant effect on intestinal motility in ileum of rats

It has been reported that it possesses bactericidal, anticholinergic, and antihistaminic activities. In addition, it also has  $\beta$ -adrenergic stimulatory effects. In a previous report, specific effects on mechanical activity of ileum, both qualitatively and quantitatively were determined. Anaesthetized rats were used for mechanical recording through isolated organ bath and oscillograph in the study. The affect obtained on intestinal motility was also tested for receptors identification and differentiation with cholinergic and adrenergic agents. The results demonstrate the effective concentrations of acetylcholine causing 50% of maximum response (EC<sub>50</sub>) obtained in the presence of 0.01 extracts in all five sets of experiments, were significantly higher than those of saline ( $P<0.000$ ) and also the maximum response to acetylcholine obtained in the presence of extracts were lower ( $P<0.000$ ). The results of the study therefore specified a competitive antagonism effect at acetylcholine receptors (Gilani, 2005).

#### Antihypertensive, antispasmodic, and broncho-dilating studies

The antihypertensive, antispasmodic, and broncho-dilating activity of aqueous and methanol extract of seeds was studied to rationalize some of its traditional uses. It was observed that the extract causes dose dependent fall in blood pressure, inhibits the bronchoconstriction and has hepatoprotective effects and thus provides sound mechanistic basis for some of their folkloric uses (Thangam, 2003).

### **Anti-inflammatory potential**

Anti-inflammatory activity of the total aqueous extract and total alcoholic extract of seeds was evaluated and found by the result that total alcoholic extract and total aqueous extract exhibited significant ( $P<0.001$ ) anti-inflammatory activity (Arrigoni, 1977; Ahsan, 1990). Its anti-inflammatory activity might be due to an increase in the number of fibroblasts and synthesis of collagen and mucopolysaccharides during granuloma tissue formation(Farooq, 1953). The anti-inflammatory activity exerted by ethanol extract and aqueous extracts suggest that they have effect on kinin, prostaglandin, bradykinin, and lysozyme synthesis. Presence of terpenes, glycosides and sterols in plant has been found to exert active anti-inflammatory effects. Phytochemical analysis has revealed the presence of terpenes and sterols. The anti-inflammatory activity of the extract may be due to the presence of certain polar constituents such as flavonoids and glycosides that might be involved in the inhibition of prostaglandin synthtase (Arrigoni,1977).

### **Anti-lithiasis and diuretic activity**

Anti-lithiasis and diuretic activity was evaluated and found by the result that the traditional use in the treatment of kidney stones was not supported by their experimental evidence and also it was not effective in increasing the 24-hour urine production(Srivastava, 1988).

### **Antiplatelet-aggregatory activity**

Antiplatelet activity of dried ethereal extract was evaluated and found by the result that the extract inhibited aggregation of platelets induced by arachidonic acid, collagen, and epinephrine (Sethi, 1989).

### **Abortifacient activity**

It was commonly used as abortive plants from a survey in and around the villages of Uttar Pradesh. The seed aqueous extract at a dose of 175 mg/kg in rats was 62.5% effective as an abortifacient. In cases where pregnancy was continued despite herbal drug administration, various skeletal and visceral defects were noticed. This shows the remarkable potential of the putative abortifacient herbal drugs to affect foetuses adversely(Asif, 2014).

### **Antitussive activity**

Antitussive activity of areoles of two different concentrations of aqueous and macerated extracts and carvacrol, codeine, and saline were tested by counting the number of coughs produced. Significant reduction of cough number obtained in the presence of both concentrations of aqueous and macerated extracts (Boskabady, 2005).

### **Digestive stimulant actions**

Study demonstrated that the addition to the diet reduced food transit time from 780 min (control) to 554 min, a 29% reduction ( $P<0.05$ ) and also enhanced the activity of digestive enzymes and/or caused a higher secretion of bile acids. They suggested that the reduction in food transit time might be due to an acceleration of the overall digestive process because of increased availability and potency of digestive secretions (Platel *et al.*, 2001).

#### Enzyme modulation activity

Acetyl cholinesterase, lactic dehydrogenase, succinic dehydrogenase, and cytochrome oxidase activity in the nervous tissue of snails significantly changed by in vivo administration of *Lymnaea acuminata* to thymol and verified active molluscicidal. It also had significant activity against protease and also increased the activity of pancreatic lipase and amylase, which may hold its digestive stimulant activity (Velazhahan *et al.*, 2010).

#### Detoxification of aflatoxins

The seed extracts exhibited the maximum degradation of aflatoxin G1 (Velazhahan, *et al.*, 2010).

#### Ameliorative effect

Ameliorative effect of ajwain extract was evaluated against hexachlorocyclohexane induced oxidative stress and toxicity in rats and it was concluded that hexachlorocyclohexane administration resulted in hepatic free radical stress, causing toxicity, which could be reduced by the *T. ammi* extract (Anilakumar *et al.*, 2009).

#### Anti-hyperlipidemic activity

The cardiovascular ailments have increased in most developed and underdeveloped countries of the world. These cardiac problems are directly associated with hyperlipidemia. During the last two decades, both retrospective and prospective studies have revealed link between levels of circulating lipids and mortality rates from coronary atherosclerotic heart disease. Numerous synthetic drugs have been reported having severe side effects.

Anti-hyperlipidemic activity of methanol extract was evaluated and found that methanol extract possesses lipid lowering action by decreased total cholesterol, LDL-cholesterol, triglycerides, total lipids. Seed powder more efficiently reduced total cholesterol by 71% and then, in the descending order, LDL-cholesterol by 63%, triglycerides by 53% and total lipids by 49% on post-treatment Day 135. Researcher also recommended that the valuable effects on fat metabolism may be due to the considerable amounts of fibers (Soorya Kumari *et al.*, 1992).

#### Antioxidant activity

The methanol extract possesses strong antioxidant activity against DPPH and could be used as natural antioxidants in food or pharmaceutical industry(Aftab *et al.*, 1995).

#### Blood pressure lowering action of active principle from *T. ammi*

The actions of the thymol and the active principle on the blood pressure have been studied. Thymol (1–10 mg/kg) produced dose dependant fall in blood pressure and heart rate in anaesthetized rats. Atropine (1 mg/kg) did not block these effects and thymol did not change the pressure response of norepinephrine, which rules out the possibility of cholinergic stimulation or adrenergic blockade. Thymol caused decrease in force and rate of atrial contractions. In case of rabbit aorta, thymol caused relaxation of nor-epinephrine and potassium induced contractions in a concentration-dependent manner. These effects remained unaltered in the presence of atropine. These relaxant effects remained unchanged after the removal of endothelium. Moreover, atropine, propranolol, indomethacine and glibenclamide did not alter the vasorelaxation by thymol. These results suggested that it contains a calcium channel blocker-like constituent (thymol) which may explain the hypotensive and bradycardiac effects observed in the in vivo studies(Khan, 2010).

A novel compound against dental caries(4aS,5R,8aS) 5, 8a-di-1-propyloctahydro naphthalen-1-(2H)-one, a novel compound reported for the first time from the seeds was examined for its activity against cariogenic properties of *Streptococcus mutans*. Purification of the active compound from the seeds was performed by silica gel chromatography, and spectroscopic methods (Fourier transform infrared spectroscopy, nuclear magnetic resonance and mass spectroscopy) were used for its structure determination and identification. Confocal microscopy was performed to visualize the effect of the compound on biofilm structure of *S. mutans*. Approximately 50% reduction was observed in adherence. It was found effective against adherent cells of *S. mutans*, decreased water-insoluble glucan synthesis by glucosyltransferases and hydrophobicity and inhibited the reduction in pH. Confocal microscopy revealed scattered cells at sub-minimum inhibitory concentration of the compound, resulting in distorted biofilm architecture in contrast to clustered cells seen in control. This study revealed a naphthalene derivative, isolated first time from seeds with antibiofilm activity against *S. mutans*. Therefore, represents an interesting source of a novel compound, (4aS, 5R, 8aS) 5, 8a-di-1-propyl-octahydronaphthalen-1-(2H)-one, with a great potential to be used as a therapeutic agent against dental caries(Madhu *et al.*, 2009).

#### Antiepileptic effect

Epileptic disorder is an important health-care issue, as about 30 000 people around the world suffered from epilepsy every year. The condition affects about one person in 20 sometime in their lives. There are about 20–70 new cases of epilepsy per 100 000 people per year. Research reported that approximately 1% of the world's

population is suffering from epilepsy, and this is the second most common neurological disorder after stroke (Shorvon, 1990).

Evidence has suggested that imbalance between inhibitory and excitatory neurotransmission in the brain is the most important contributor to seizure development in both clinical and experimental conditions (Pérez-Saad *et al.*, 2008). The study was conducted to assess the potential of a methanol extract as an antiepileptic agent (Rajput MA, et. al., 2013). Tests were conducted with single- and multiple-dosing schedules using a strychnine induced seizure model for epilepsy in experimental animals. A total of 21 animals were used which were divided into three groups: control (vehicle), standard (diazepam) and test. It showed antiepileptic effects, since there was a highly significant delay in the onset of convulsions as compared to the control, whereas the percentage of animals that survived or ignored seizure was also greater compared to the control. However, the duration of convulsions was significantly increased with both the extract and diazepam as compared to the control. It exerts anticonvulsant effect may be due to the presence of thymol, which might excites gamma-aminobutyric acid responses by stimulating human gamma-aminobutyric acid type A receptors and increasing the chloride ion channel opening, a mechanism followed by many sedative/hypnotics, CNS depressants and anticonvulsants. Hence, it may be concluded that it possesses the antiepileptic effect similar to diazepam. However, further studies are required to evaluate the exact mechanism of action (García *et al.*, 2006).

#### Lithotriptic effect

It has been a well-known practice to use seeds and the essential oil as a strongly antiseptic, antispasmodic, aromatic, digestive, diuretic, expectorant and tonic. In one of the studies, the seeds of this herb were used as a urinary tract stone lithotripsy. The aim of the research was to use of seeds as a lithotripsy against different types of urinary stones and determine the efficiency of the preparation against which type of stone. A liquid solution was prepared from dissolving the seeds powder in cow milk and then concentrated. The preparation was done by boiling at 100 °C to reduce the volume of solution to the half. The treatment was given orally for 9 d before breakfast. A total of 350 patients with urinary stone of different type participated in this research. All patients were subjected to ultrasonography and intravenous pyelography examinations to determine the position and diameter of stone. The ultrasonography and intravenous pyelography examination and also biochemical tests for diagnosis of stones ingredients were repeated after the administration of treatment and excretion of stone fragments in urine. The results were so promising especially against pure ca oxalate stone (Sabar, 2010).The antilithiatic potential was confirmed by its ability to maintain renal functioning, reduce renal injury and decrease crystal excretion in urine and retention in renal tissue (Kauret *et al.*, 2009).

### **Analgesic effect**

Pain is a universal complaint, which needs further investigations to search novel pain-relieving agents. It is mentioned in the traditional literature has therapeutic effect on headache and joint pains. So, the study was conducted to design an experimental clinical trial study to assess and compare the analgesic effect of ethanolic extract of fruit with morphine by using a tail-flick analgesiometer device. Results of the study indicate that the test drug produced significant increase in tail-flick latency (TFL) during 2 h post-drug administration ( $P<0.05$ ). The peak of the effect was observed at 45 min after drug injection, which was comparable to that of 1 mg/kg morphine. Positive results in this type of analgesiometric test indicate that the antinociceptive action may be of the opioid type. The study supports the claims of traditional medicine showing that the extract possesses a clear-cut analgesic effect. This effect may be due to its parasympathomimetic action on descending pain modulating pathways (Dashti *et al.*, 2007).

### **The therapeutic effect of seeds on peptic ulcers**

Non-steroidal anti-inflammatory medicines are extensively used today and of their side effects is gastric ulcer. A study was conducted to examine the effect of aquatic extract on healing gastric ulcers induced using ibuprofen in an animal. A total of 30 adult Wistar female rats were used in this empirical study. The animals were divided into five groups. Then omeprazole or plant extract was administered (125, 250 and 500 mg/kg doses) twice a day for 2 weeks. In the end, the number and area of the animals' gastric ulcers were examined. To assess the side effects of the medicine on liver, the amount of liver enzymes aspartate transferase and alanine transferase was measured in the animals' serum. Plant aqueous extract had a significant effect on healing gastric ulcers comparing to the control group ( $P<0.05$ ). The mean number and area of the gastric ulcers in the extract treating groups were significantly less compare to negative-control group. The amount of liver enzymes had also significantly ( $P<0.05$ ) increased in the groups receiving the extract (250 and 500 mg/kg doses). The result of the study showed the plant seed extract is effective in healing gastric ulcers and its effect is comparable with omeprazole. Thus, it can be commented that this extract perhaps had the similar effect as that of omeprazole in affecting the stomach acid secretion pump. However, to confirm this theory, future studies should be conducted to measure the amount of secretion of gastric acid after consumption of seed extract, and thus to allow definitive comment on these mechanisms (Komeili, 2012).

### **Medical indication supported by traditional experiences**

#### **Gastro-intestinal disorders**

A teaspoonful of ajwain seeds with a little amount of rock-salt, mixed with water taken internally give relieve from flatulence, dyspepsia, and spasmodic disorders.

Ajwain seeds, dry ginger, and black salt ground together, the 3 g of this powder are taken along with warm water for colic.

Ajwain seeds and dried ginger in an equal quantity are soaked into two-and-half times the quantity of lime juice. After draining the water, they are dried and powdered with a little amount of black salt and about 2 g such powder mixed with warm water and taken internally, 2–3 times a day for relieving flatulence.

The volatile oil of ajwain seeds is given internally in a dose of 1–3 drops for cholera, flatulent colic, diarrhea, atomic dyspepsia and indigestion. Chewing ajwain seeds prevents bad breath.

#### Respiratory disorders

Ajwain seed powder mixed with buttermilk when given internally serves as an excellent expectorant even in difficult cases, such as when the phlegm is dried up. For pharyngitis in influenza, ajwain seeds mixed with clove and a pinch of common salt are chewed. For common cold, a tablespoonful of seeds crushed and tied in a cloth as a bundle which is then inhaled by the patient. And such bundle can be used in nasal congestion; it is covered in the same blanket with the patient during sleeping hours. For the acute pharyngitis, sore and congested throat, and hoarseness of the voice due to colds or making noise, infusions of the seeds with common salt are beneficial. In case of bronchial asthma, ajwain seeds are tied in the cotton cloth, heated in a frying pan, and applied on the chest and neck when still warm.

#### Aphrodisiac

Seeds with the kernel of tamarind seeds act as a potent aphrodisiac; they are prepared by frying an equal quantity of both in pure ghee, dried and then powdered; then preserve it in airtight container. This is taken at bedtime to enhance virility.

#### Earache

For an earache, a half a teaspoon of seeds heated in 30 mL of milk and then strained on cooling used as ear drops. It decreases congestion and relieves pain.

#### Migraine

Seeds can be smoked or sniffed frequently to get relief from migraine and delirium.

#### Rheumatism

Oil extracted from the seeds resolves rheumatic and neuralgic pains when applied on affected parts (Anilakumar *et al.*, 2009).

#### 11. Toxicity and Safety

Ajwain is toxic in high doses and can result in fatal poisoning. Avoid use during pregnancy due to documented adverse effects(Petramfaret *et al.*, 2016).

## 12. Clinical Studies

High quality clinical trials are very limited. The medical literature documents numerous pharmacological activities including analgesia (neuropathic), antifungal, antimicrobial, hypolipidemic, antihypertensive, antilithiasis, abortifacient, antitussive, nematicidal, anthelmintic, and antifilarial(Petramfaret *et al.*, 2016).

## 13. Contraindications

Hypersensitivity to any of the components of bishop's weed. Avoid use during pregnancy and lactation due to documented adverse effects(Petramfar *et al.*, 2016).

## 14. Marketed Formulation

Ajwain is commercially available as a single entity or herbal blend in numerous dosage forms including capsules, liquids, and powders. Internet sources list the product primarily marketed as "ajwain" and as an overall panacea. One herbal blend prescribes 1 or 2 capsules (200 mg/capsule) with a full glass of water for GI discomfort. The prescription drug methoxsalen, as documented by various Internet resources, was developed from bishop's weed (*Ammi majus L.*) and is used to treat several skin conditions. Use of a 10% topical cream twice daily has been supported by a clinical trial in adults with neuropathic pain.

- Methoxsalen is marketed in USA under the brand names8-Mop [DSC]
- Oxsoralen Ultra
- Uvadex

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1. Botanical Name: *Urtica dioica* L.

2. Synonym: NA

3. Family: Urticaceae

4. Common Name

Bengali: Paharabichuti

English: Nettle, Sting nettle, Himalayan stinging nettle

Hindi: Bichu Butt

Kumaon: Shisuun

Sanskrit: Vrishchhiyaa-shaaka

Unani: Anjuraa

5. Description: A dioecious, perennial herb up to 5 feet high with a dense indumentum of stinging hairs and angled stem. Leaves lanceolate to ovate, cordate at the base, margin serrate, apex acute-acuminate; stipules free lateral, oblong-lanceolate, ciliate. Racemes of cymes axillary, often longer than the subtending petiole, densely appressed pubescent, with scattered stinging hairs. Flowers pale-greenish, or whitish, bracteate; bracts of male flowers smaller than those of female flowers. Sepals pubescent. Fruit an achenes, ovoid-ellipsoid, pale green or greenish-brown.

6. Distribution: Native to Europe to temperate Asia and western North Africa; in India it is found in sub-tropical Himalayas, from Kashmir to Sikkim between 1200 to 3500 m above sea level.

7. Part used: Whole plant



*Urtica dioica*

## 8. Medicinal /Therapeutic Uses

### 8.1 Uses described in pharmacopoeias and in traditional systems of medicine

Root- in symptomatic treatment of micturition disorders (dysuria, pollakiuria, nocturia, urine retention) in benign prostatic hyperplasia at stages I and II). Uses described in pharmacopoeias and traditional systems of medicine as a diuretic and for the treatment of rheumatism and sciatica. (Khare *et al.*, 2007). Treatment of asthma, coughs, dandruff, diabetes, diarrhoea, eczema, fever, gout, haemorrhoids, nose bleeds, scurvy, snakebites and tuberculosis. The plant has also been used to stop uterine bleeding after childbirth, increase lactation and promote hair growth, and as a vermifuge (Farnsworth *et al.*, 1998).

### 8.2 Uses supported by clinical data

Effect of hydro alcoholic extract of Nettle on oxidative stress in type 2 diabetes was evaluated. Fifty patients (27 men, 23 women) with type 2 diabetes patients were studied. They received 100 mg kg<sup>-1</sup> of nettle extract of body weight hydro alcoholic for 8 weeks. After 8 weeks, the findings showed that the hydro alcoholic extract of nettle has increasing effects on TAC and SOD in patients with type 2 diabetes without no changes in Malon dialdehyde (MDA) and Glutathione Peroxides (GPX) after eight weeks intervention (Namazi *et al.*, 2012). In a randomized double-blind clinical trial, 74 patients with the signs and symptoms of allergic rhinitis and a positive skin prick test were selected and randomly divided into 2 groups who were taken 150-mg, Urtidin® F.C Tablet or placebo for one month. A statistically significant reduction in mean nasal

smear eosinophil count was observed after treatment with Nettle ( $P < .01$ ). The current study showed certain positive effects of Nettle in the management of allergic rhinitis on controlling the symptoms based on the SNOT-22 (Bakhshaei et al., 2017).

### 8.3 Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

Root paste is applied on minor bone fracture and dislocation. Root and seed decoction is taken to treat diarrhoea and cough. There is a belief that it shouldn't be eaten by a person who has been bitten with dog. Stems are beaten, dried and boiled to make threads and woven into traditional nettle clothing. Spines believed to stimulate milk production, when cows do not lactate, they are believed to be possessed and beaten with nettles for normal lactating. Curry, prepared using shoot tips, is given to female during child delivery as their slipperiness is believed to help delivering child. Shamans beat humans during exorcism rituals with nettles in a belief to drive away evil spirits from body; this should not be touched or eaten by family members of deceased person on the day of death. If the decease is one's father or mother, this prohibition remains for one year. Nettle is planted on the child's grave in a belief that the evil spirit of child will not come out to trouble other family members (Pradhan & Badola, 2008)

### 8.4 Special uses in North East India

Traditionally the Lepcha tribe of Sikkim used the plant for curing different ailments including diarrhoea and cough and the soup prepared from it is given to the pregnant women which helps in easy delivery of child. Root paste used on minor bone fracture and dislocation. Soups and curries made from the young and tender leaves are common dishes and are routine meals in Sikkim. According to the traditional belief the plant should not be taken by the person who has bitten by rabid dogs as consumption of the plant aggravates the problem (Pradhan & Badola, 2008).

Sprain: The root and Bhuichampa (*Kaemferia rotunda*) are ground into paste and bandage the affected area with it and leave it for 10-15 days.

Fracture and dislocation of bones: The root paste and paste of *Viscum articulatum* applied externally on bone fracture/ dislocation of bones.

### 8.5 Dosage forms used in tradition

Dried aerial parts, fresh aerial parts, dried roots, Extract, Leaves paste (Said et. al., 2015).

## 9. Phytochemical profile

The main chemical constituents are flavonoids, tannins, volatile compounds and fatty acids, polysaccharides, isolectins, sterols, terpenes, protein, vitamins and minerals (Krystofova *et al.*, 2010; Gul *et al.*, 2012). Agglutinin is a small plant monomeric lectin present in this plant. The compounds responsible for the burning sensation properties of leaves trichomes are acetylcholine, histamine, 5 hydroxytryptamine (serotonin), leukotrienes and formic acid (Joshi *et al.*, 2014). The main components of essential oils are carvacrol (38.2%), carvone (9.0%), naphthalene (8.9%), (E) anethol (4.7%), hexahydrofarnesyl acetone (3.0%), (E) geranyl acetone (2.9%), (E)  $\beta$  ionone (2.8%) and phytol (2.7%) (Gul *et al.*, 2012).

The flavonoids are mainly kaempferol,isorhamnetin, quercetin, isoquercitrin, astragalin, rutin and their 3 rutinosides and 3 glycosides. Carotenes such as  $\beta$  carotene, hydroxy  $\beta$  carotene, luteoxanthin, lutein epoxide, and violaxanthin are also present. Phenolics such as Phenylpropanes, caffeic acid, chlorogenic acid and scopoletin have also been identified from this plant. The carotenoid such as  $\beta$  carotene, hydroxy  $\beta$  carotene, luteoxanthin, lutein epoxide and violaxanthin are reported (Fu *et al.*, 2006). The leaves are rich in vitamins B, C, K and minerals such as calcium, iron, magnesium, phosphorus, potassium and sodium. Other chief constituents present are essential amino acids, glucokinnins and a very high content of chlorophyll (Bnouham *et al.*, 2003; Fu *et al.*, 2006).

## 12. Pharmacological Studies

*U. dioica* agglutinin (UDA), the small monomeric lectin (8.7 kDa) from *U. dioica* inhibits replication of SARS-CoV infection by targeting early stages of the replication cycle, namely, adsorption or penetration. The efficacy of UDA was tested in a lethal SARS-CoV-infected BALB/c mouse model (Kumaki *et al.*, 2011). UDA, the (GlcNAc) n-specific lectin from *U. dioica* exhibited inhibitory effect to HIV-1-, HIV-2-, CMV-, RSV- and influenza A virus-induced cytopathicity at an EC<sub>50</sub> ranging from 0.3 to 9  $\mu$ g/ml (Balzarini *et al.*, 1992).

The methanolic extract (at 60 °C) of leaves showed inhibitory effect against Dengue virus -2 (DENV2) by blocking replication. The fractionated compound exhibited higher antiviral activity. The compounds in the active fractions were, chlorogenic acid, quercetin derivatives and flavonol glycosides (quercetin and kaempferol) (Flores-Ocelotl *et al.*, 2018). Reports have confirmed the diuretic and hypertensive properties (Tahri *et al.*, 2000) as well as anti-hyperglycemic properties (Bnouham *et al.*, 2003), and has good antioxidant potential (Pieroni *et al.*, 2002).

The anti-inflammatory effect of the plant may be due to its inhibitory effect on NF- $\kappa$ B activation. The lipophilic dichloromethane extracts of the roots, stems and leaves exhibited potent anti-inflammatory effects  $\geq 1$  and may be superior to traditional tinctures for treating inflammatory disorders (Johnson *et al.*, 2013). Leaf of sting nettle provides significant reduction in pain in patients with osteoarthritic pain at the base of the thumb or index finger as reported in randomized controlled double-blind crossover study in 27 patients (Randall *et al.* 2000).

The leaf extract has shown antidiabetic efficacy. The leaf extract administered in perfused islets of Langerhans both in normal and streptozotocin induced diabetic rats

showed an enhancement in insulin secretion thereby decreasing the blood sugar level (Farzami *et al.*, 2003). The compounds present in the methanolic extract of the aerial parts of the plant have exhibited immunomodulatory activity include quercetin-3-O-rutinoside, kaempferol-3-O-rutinoside and Isorhamnetin-3-O-glucoside. The aqueous extract of the plant roots has exhibited anticancer potential by inhibition of the globulin binding to its receptor and directly inhibition of proliferation of HeLa cells and block binding of epidermal growth factor to its receptor. The antimicrobial as well as Hypotensive Effect of the plant has been reported (Joshi *et al.*, 2014).

### 10.1. Clinical pharmacology

*In-vitro*animal studies: Several *in vitro* studies using human cell lines suggest that nettle extract has an effect on COX enzymes, downregulates the inflammation cascade, may reduce primary T-cell response, and inhibits NF- $\kappa$ B. A new stinging nettle leaf extract called Hox alpha has been shown to significantly suppress MMP, which explains clinical efficacy of this extract in the treatment of RA (Schulze-Tanzil *et al.*, 2002). Animal studies suggest that the extract has analgesic and antinociceptive properties as well as the ability to reduce inflammation in induced paw edema (Marrasini *et al.*, 2010).

### 11. Toxicity and safety

The fixed oil of the herb has completely non-lethal even at dose reaching 12.8 ml/kg (Tekin *et al.*, 2009). In toxicity studies, rabbits of about 2 kg received orally 50 ml of a 50% ethanol extract for 10 days. Occasional diarrhoea was observed; Bodyweight decreased by 40% and death occurred after several days of treatment. Autopsy revealed purulent blisters around the injection site. Prior to death, the respiration increased, and a central excitatory behavior has been observed in the rabbits (Starkenstein & Wasserstrom, 1933).

### 12 Clinical studies

In a pilot study, Rayburn *et al.*, (2009) used a stinging nettle extract cream and observed improved function and reduction of pain. In a randomized study of 37 patients with acute arthritis, the effect of stewed stinging nettle herb combined with a sub therapeutic dose of NSAIDs (Diclofenac) was compared to a standard dose of Diclofenac. One group was given 50 g nettle and 50 g Diclofenac and the other group took 200 mg of Diclofenac. The clinical end points (verbal rating scale from 0 to 4, physician assessment for the pressure, pain, and stiffness) were complemented by the evaluation of the CRP levels. In both groups, median scores improved by almost 70% compared to the initial values. The authors suggested that stinging nettle herb may enhance the NSAID anti rheumatic effectiveness (Chrubasik *et al.*, 1997).

### 13. Contraindications

The use of nettle orally is contraindicated in pregnant women because of the risk of abortion and in children under 12 because of a lack of clinical studies in this area (Aswal *et al.*, 1984; Ghedira *et al.*, 2009).

### 14. Precautions

The adherence to dosage recommendations is essential. The recommended adult dosage of the dried aerial parts is 1.2 to 18g per day. For fresh juice, the recommended dose is 15 to 45 ml per day. Dosages for the dried root preparations are 0.3 to 24g per day. Recommended dosages and frequency of administration for each type of preparations should be done (Blumenthal *et al.*, 2000).

#### 15. Adverse reactions

Despite having anti allergic properties, nettle may cause allergies in sensitive people. Some rare hypersensitivity reactions like hives, itching, edema, oliguria and gastralgia have been reported (Joshi *et al.*, 2014).

#### 16. Marketed formulation, if any

- Urtica dioica L. homoeopathic tincture: A homoeopathic tincture of *Urtica dioica L.* for inflamed or oedematous conditions, burns, furuncles, cysts, glandular swellings, dislocations. It helps in correction of uric acid, gouty pains and joint pains manufactured by Dr. Willmar Brand.
- Nettle Leaf Herbal Tea: manufactured by Vedic Herbal Concept.
- Stinging Nettle Root 2x100 Capsules: Stinging Nettle Lowers Blood Pressure, Relieves Seasonal Allergies, Improve Circulation, Reduce Inflammation manufactured by Maui Herbs.

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1. Botanical Name: **Vitex negundo L.**

2. Synonym: NA

3. Family: Verbenaceae

4. Common Name

Assam:	Aagla-chita, Pasutia
Bengali:	Nirgundi, Nisinda, Samalu
English:	Chinese Chaste tree
Gujarathi:	Nagaol, Nagoda
Hindi:	Nisinda, Sambhalu, Shambalu, Shivari
Kannada:	Lakkigida, Nakkilu, Nekki
Malayalam:	Vellanochi
Marathi:	Nigudi, Nirgundi, Nisind
Oriya:	Begundia, Beyguna, Nirgundi
Punjabi:	Banna, Marwan, Shwari
Sanskrit:	Nirgundi
Tamil:	Nallanochi, Nirkkundi, Nochi, Vennochii
Telugu:	Tellavaaviti, Vaavili.

5. Description: A shrubs or small tree up to 10 feet high. Leaves 3-5-foliolate; leaflets narrowly oblong or elliptic to lanceolate, base acute, apex acuminate. Panicles terminal. Calyx 5-toothed obconic, teeth triangular. Corolla deep purple to violet in colour, hypocrateriform; tube 3-5 mm long, puberulent without, upper lip 2-lobed, lower 3-lobed with the middle lobe larger, obovate, undulate-margined, other lobes shorter, subequal, obtuse. Stamens 4, filaments purple. Style purple; stigma 2-fid. Fruit a drupe, globose, purple or black.

6. Distribution: Indo-Malaysia and China, cultivated throughout the tropics. In India it grows all most all the states.

7. Part used: Whole plant



*Vitex nigundo* L. (Photo source AN Shukla, BSI)

## 8. Medicinal /Therapeutic Uses

### 8.1 Uses described in pharmacopoeias and in traditional systems of medicine

Various parts including the leaves, roots and seeds, have been locally used as traditional folk medicines since antiquity, particularly in China to treat a wide range of ailments, such as cold, headache, migraine and ophthalmodynia (Huang *et al.*, 2013; Yao *et al.*, 2016).

### 8.2 Uses supported by clinical data

Test drug: Ethanolic leaf extract was used for the present study in volume of 10 ml/kg wt/orally. The doses were selected by preliminary trial (Tandon & Gupta, 2004).

### 8.3 Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

It is used for treating stored garlic pests as a cough remedy in the Philippines. It is also used to control mosquitoes. In Malaysia, it is used in traditional herbal medicine for women's health, including treatments for regulating the menstrual cycle, fibrocystic breast disease and post- partum remedies. It has antiseptic, astringent, anti-inflammatory and antipyretic properties. Folklore systems of medicine continue to serve a large segment of population, especially those in rural and tribal areas, regardless of the advent of modern medicine. The entries regarding the multifarious applications in folk medicine have been grouped regionally to emphasize the ethnobotanical diversity and ubiquity of the plant (Kosalge & Fursule, 2009). Its paste on affected site is painkiller and anti-inflammatory (Khare, 2004).

### 8.4 Special uses in North East India: NA

### 8.5 Dosage forms used in tradition

Male rats (n=9/group) were treated with 1.25, 2.5 and 5 g/kg of MFL at pre flowering stage of the tree, 5 g/kg of MFL at flowering stage, 5 ml/kg water and 5 mg/kg indomethacin, respectively (Forestieri et al., 1996).

## 9. Phytochemical profile

The various chemical constituents present in leaves of *V. negundo* Linn are Friedelin, carotene, casticin, artemetin, terpinen-4-ol,  $\alpha$ -terpineol, sabenine, globulol, spathulenol,  $\beta$ -farnesene, farnesol, bis (1,1dimethyl)methylphenol,  $\alpha$ -pinene,  $\beta$ -pinene, linalool, terpinylacetate, caryophyllene epoxide, caryophyllenol, vitexicarpin, viridiflorol (Singh & Nagvi, 2004).

Plant part	Phytochemical constituents
Leaves	6'-p-hydroxybenzoyl mussaenosidic acid; 2'-p-hydroxybenzoyl mussaenosidic acid viridiflorol; $\beta$ -caryophyllene; sabinene; 4-terpineol; gamma-terpinene; caryophyllene oxide; 1-oceten-3-ol; globulol; 5,3'-dihydroxy-7,8,4'-trimethoxyflavanone; 5,3'-dihydroxy,6,7,4' trimethoxyflavanone; 5-hydroxy-3,6,7,3',4'-pentamethoxy flavones; 5,7dihydroxy-6,4' dimethoxy flavonone; 5hydroxy-7,4' dimethoxy flavones; 5,3'-dihydroxy-7,8,4'-trimethoxy flavanone; betulinic acid [3 $\beta$ -hydroxylup-20-(29)-en-28-oic acid]; ursolic acid [2 $\beta$ -hydroxyurs-12-en-28-oic acid];

	n-hentriacanol; $\beta$ -sitosterol; p-hydroxybenzoic acid; protocatechuic acid; oleanolic acid; flavonoids angusid; casticin; vitamin-C; nishindine; gluco-nonitol;
Seeds	3 $\beta$ -acetoxyolean-12-en-27-oic acid; 2 $\alpha$ , 3 $\alpha$ -dihydroxyoleana-5,12-dien-28-oic acid; 2 $\beta$ ,3 $\alpha$ diacetoxyoleana-5,12-dien-28-oic acid; 2 $\alpha$ , 3 $\beta$ -diacetoxy-18-hydroxyoleana-5,12-dien-28-oic acid; vitedoin-A; vitedoin-B; a phenylnaphthalene-type lignan alkaloid, vitedoamine-A; five other lignan derivatives, 6-hydroxy-4-(4-hydroxy-3-methoxy-phenyl)-3-hydroxymethyl-7-methoxy-3,4-dihydro-2-naphthaldehyde, $\beta$ -sitosterol; p-hydroxybenzoic acid; 5-oxyisophthalic acid; n-tritriacontane, n-hentriaccontane; n-pentatriacontane; n-nonacosane.
Roots (Srinivas et al 2001)	2 $\beta$ ,3 $\alpha$ -diacetoxyoleana-5,12-dien-28-oic acid; 2 $\alpha$ ,3 $\alpha$ -dihydroxyoleana-5,12-dien-28-oic acid; 2 $\alpha$ ,3 $\beta$ -diacetoxy-18-hydroxyoleana-5,12-dien-28-oic acid; vitexin; isovitexin, negundin-A; negundin-B; (+)-diasyringaresinol; (+)-lyoniresinol; vitrofolal-E; vitrofolal-F, acetyl oleanolic acid; sitosterol; 3-formyl-4,5-dimethyl-8-oxo-5H-6,7-dihydronaphtho (2,3-b)furan.
Essential oil of fresh leaves, flowers and dried fruits	$\delta$ -guaiene; guaia-3,7-dienecaryophyllene epoxide; ethyl-hexadecenoate; $\alpha$ -selinene; germacren-4-ol; caryophyllene epoxide; (E)-nerolidol; $\beta$ -selinene; $\alpha$ -cedrene; germacrene D; hexadecanoic acid; p-cymene and valencene. viridiflorol (19.55%), $\beta$ -caryophyllene (16.59%), sabinene (12.07%), 4-terpineol (9.65%), $\gamma$ -terpinene (2.21%), caryophyllene oxide (1.75%), 1-oceten-3-ol (1.59%), and globulol (1.05%). Viridiflоро

## 12. Pharmacological Studies

- Anti-inflammatory activity
- Ant nociceptive activity
- CNS depressant activity
- Antifungal activity
- Antioxidant Activity
- Enzyme-inhibitory activity
- Anticonvulsant activity

- Antibacterial studies
- Antiallergic Activity
- Snake venom neutralization activity (Alam & Gomes, 2003)
- Effect on reproductive potential
- Histomorphological and cytotoxic effects
- Hepatoprotective activity
- Hypoglycemic activity
- Laxative activity
- Immunomodulatory activity.

### 10.1. Clinical pharmacology

#### Anti-Inflammatory Activity

Many plants from *Vitex* genus have been used for the treatment of inflammatory diseases. And pharmacological studies have also shown that some terpenes isolated from the genus have significant anti-inflammatory effects. Agnuside (3) exerted significant anti-inflammatory activity using carrageenan-, histamine- and dextran-induced acute inflammation models in rats. The inhibitory effect seemed independent of activation of the pituitary-adrenal (Pandey *et al.*, 2012).

#### Anti-Tumor Activity

It is also worth mentioning that some terpenes of the *Vitex* genus possess significant anti-tumor activities against several cancer cell lines. Wu *et al.* 2009 isolated ten diterpenoids 34, 48, 53, 54, 79, 80, 137–140, including three new compounds 34, 48, 137, isolated. All compounds were tested for their inhibitory effects on HeLa cell proliferation with the MTT assay, and their IC<sub>50</sub> values ranged from  $4.9 \pm 0.5$  to  $28.7 \pm 1.3 \mu\text{M}$ .

#### Antibacterial and Antifungal Activities

*Vitexilactone C* showed weak antibacterial activity against *Bacillus subtilis*, *Escherichia coli* and *Micrococcus tetragenus* at the same minimum inhibitory concentration (MIC) value of 500 µg/mL (Chen *et al.*, 2012).

#### Antioxidant Activity

Terpenes in the *Vitex* genus have significant antioxidant activities. The iridoid glucoside from leaves which could reduce the levels of blood glucose and glycoproteins, and increase the level of plasma insulin in streptozotoc in diabetic rats (Sundaram *et al.*, 2012).

#### **Anti-HIV activity**

The anti-HIV activity of ethanolic leaf extract was studied against HIV-1 reverse transcriptase. Using a nonradioactive HIV-RT colorimetric ELISA kit and with recombinant HIV-1 enzyme it was evaluated *in vitro*. The study concluded that the ethanolic extract exhibits anti-HIV activity and the flavonoids as anti-viral agents.

#### **11. Toxicity and safety**

Preliminary acute toxicity study of ethanolic leaf extract in albino rats by oral route carried out Tandon & Gupta (2005) indicated it to be practically nontoxic, as its LD<sub>50</sub> dose recorded was 7.58g/kg/wt. The stomach showed no histomorphological changes were observed in the specimens of the heart, liver, and lung.

The treatment with 5 g/kg/day of MFL for 14 days failed to produce any overt clinical signs of toxicity or stress. The treatment also did not significantly alter the body weights (control versus treatment: 232.0±8 g versus 251.8±5.6 g), serum creatinine (control versus treatment: 1.7±0.3 mg/dl versus 1.1±0.2 mg/dl), urea (control versus treatment: 33.6±3.0 mg/dl versus 38.6±1.2 mg/dl), random glucose (control versus treatment: 136.2±8.0 mg/dl versus 141.5±6.6 mg/dl) and the activity of ALT (control versus treatment: 12.0±2.1 U/l versus 15.0±2.0 U/l). However, the treatment caused a significant (P<0.05) increase in serum activity of AST (control versus treatment: 24.3±5.1 U/l versus 74.7±5.5 U/l). The treatment also did not cause haemorrhagic lesions in the gastric mucosa after 14 days of treatment (Dharmasiri *et al.*, 2003).

#### **12 Clinical studies**

No clinical studies or clinical trial has been reported

#### **13. Contraindications**

Nirgundi should be used with caution with the concurrent use of psychotropic drugs, including analgesics, sedatives, antidepressants, anticonvulsants, and antipsychotics. It is quite similar botanically to the better studied *V. angus castus* and thus may have similar range of contraindications, including concurrent use of progesterogenic drugs and hormone replacement therapies.

#### **14. Precautions: None reported so far**

#### **15. Adverse reactions :NA**

## 16. Marketed formulation, if any

The formulation contains the known potent drugs in Ayurveda. These herbs have been established as potent anti-inflammatory as well as analgesic action in the literature. The drugs to be used in preparation of the formulation are 1. *V. negundo*, 2. *Pluchea lanceolata*, 3. *Curcuma longa*, 4. *Clerodandrum phlomoides*, 5. *Solanum xanthocarpum* (Kirtikar & Basu 2000.). The formulation will contain a suitable base which will be either sesame oil or mustard oil.

Methods: The plant parts were obtained from the botanical garden from the campus. The plants were collected and washed thoroughly and cut into small parts. The respective plant parts were allowed to shade dried and then boiled in about 5 times of volume of water/solvent until 2 times of water was left. The heating was continued for over two hours until 2 times of water was left. The left-over water/solvent extract was filtered and boiled with the suitable base (Sesame Oil) until all the water/solvent is evaporated. The oil obtained was filtered for any residual particles if seen and was stored in suitable container as amber color container. Three different oil were prepared, one having more amount of *V. negundo* (25% more than the actual concentration in other combination) and *Pluchea lanceolata* (25% more than the actual concentration in other combination) respectively.

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1. Botanical Name: ***Zingiber officinale*** Roscoe

2. Synonyms: ***Amomum zingiber*** L.

3. Family: Zingiberaceae

4. Common Name

Assamese:	Ada
Bengali:	Ada
English:	Ginger
Gujarati:	Adu
Hindi:	Adaraka,
Kannada:	Sunthi
Kashmiri:	Shaunth
Khasi:	Wynad, Shing Bhoi
Malayalam:	Inchi
Manipuri:	Singkha
Marathi:	Ale
Oriya:	Ada
Punjabi:	Adaraka
Sanskrit:	Aadraka, Aadrika,
Tamil:	Inci
Telugu:	Allam
Urdu:	Adrak

5. Description: A erect, slender, perennial rhizomatous herb up to 4 feet high. The growing tips are covered over by a few scales. The surface of rhizome is smooth and if broken a few fibrous elements of the vascular bundles project out from the cut ends. Leaves sessile, linear-lanceolate, glabrous, narrowed to the base, acute or acuminate. Flower yellowish-green, with a small dark purple or purplish black lip, in radical, oblong, cylindrical spikes, ensheathed in a few scarious, glabrous bracts. Fruit a capsules, oblong. Seed many endospermic, globose and arillate.

6. Distribution: Native to SE Asia; now widely distributed across the tropics of Asia, Africa, America and Australia found under cultivation at tropical to subtropical regions of the district. In India, it is cultivated mainly in Kerala, Andhra Pradesh, Uttar Pradesh, West Bengal and Maharashtra, and to a somewhat less extent in Bengal and the Punjab.

7. Plant Part: Whole Plant.



*Zingiber officinale* (Photo: Priyanka Ingle, BSI)

## 8. Medicinal /Therapeutic Uses

### 8.1. Uses described in pharmacopoeias and in traditional systems of medicine:

Ginger is used in many forms (decoction, juice and oil) for the treatment of cough, headache, and asthma. Many medical conditions like gout, sciatica, rheumatoid arthritis and inflammations are also being treated with the use of ginger products. (Hakeem, 2002; Kabeeruddin, 1955; Ghani, 2002).

### 8.2. Uses supported by clinical data

This plant has been used for the treatment of motion sickness, nausea during the pregnancy, cancer chemotherapy, vomiting, and abdominal discomfort, leukemia, psychotic disorders, surgery, and pregnancy, anti-inflammatory agent for musculoskeletal diseases (Navaei *et al.*, 2008; Braun & Cohen, 2007; Barrett, 2004).

### 8.3 Traditional/Folklore Uses described in folk medicine, not supported by experimental or clinical data

Traditionally the rhizome is being administered orally to stimulate carminative effect and relief indigestion. It is also consumed as a decoction for relieving stomach-ache after childbirth. It may be applied on the skin for rubefacient and counterirritant purpose (Charles *et al.*, 2000).

### 8.5 Special uses in North East India

The rhizome juice in the north eastern states is being used in promoting digestive power, cleansing of throat and tongue, dispelling of cardiac disorders, and curing vomiting, ascites, cough, dyspnoea, anorexia, fever, anaemia, flatulence, colic,

constipation, swelling, elephantiasis and dysuria. It is also used to treat diarrhoea and to get rid of inflammation caused by caterpillar. In Sikkim, traditional practitioners use the ginger rhizome for the treatment of gastritis, dyspepsia, flatulence and as a remedy for bee bites (Tushar *et al.*, 2010).

### 8.6 Dosage forms used in tradition

For most purposes, a typical dose of ginger is 1-4 g daily, taken in divided doses. To prevent motion sickness, it is best to begin treatment 1-2 days before the scheduled trip and continue dosing throughout the duration of travel. For nausea and vomiting during pregnancy, ginger tea made from fresh ginger root, boiled, and diluted to taste, appears to work best.

### 9. Phytochemical profile

Ginger contains several pungent constituents and active ingredients. Steam distillation of powdered ginger produces ginger oil, which contains a high proportion of sesquiterpene hydrocarbons, predominantly zingiberene. The major pungent compounds in ginger, from studies of the lipophilic rhizome extracts, have yielded potentially active gingerols, which can be converted to shogaols, zingerone, and paradol. The compound 6-gingerol appears to be responsible for its characteristic taste. Zingerone and shogaols are found in small amounts in fresh ginger and in larger amounts in dried or extracted products (Govindarajan, 1982).

### 10. Pharmacological Studies

Ginger is a medicinal plant that has been widely used in herbal medicines in all over the world. Ginger also stimulates blood circulation (Shoji *et al.*, 1982) and contains very potent anti-inflammatory compounds called gingerols (Kwang *et al.*, 1998).

The acetone and ethanolic extract of rhizome is reported to exert antiemetic effect against cisplatin-induced emesis in dogs. The acetone and 50% ethanolic extract of ginger in the doses of 100, 200 and 500 mg/kg (p.o.) and ginger juice, in the doses of 2 and 4 ml/kg exhibited potential impact against cisplatin effect on gastric emptying in rats. The juice and acetone extract have been found to be more effective than the 50% ethanolic extract (Sharma *et al.*, 1998).

The rhizome has been reported to exhibit anti-fungal, anti-inflammatory, anti-diabetic, anti-bacterial, anti-arthritis, anti-cancer, neuroprotective, cardiovascular protective, respiratory protective activities (Mao *et al.*, 2019).

Ginger extract showed antioxidant effects in human chondrocyte cells, with oxidative stress mediated by interleukin-1 $\beta$  (IL-1 $\beta$ ). It stimulated the expression of several antioxidant enzymes and reduced the generation of reactive oxygen species (ROS) and lipid peroxidation. In a human mesenchymal stem cell model, ginger oleoresin was investigated for its effects on injuries that were induced by ionizing radiation. The treatment of oleoresin could decrease the level of ROS by translocating Nrf2 (nuclear factor erythroid 2 related factor 2) to the cell nucleus and activating the gene

expression of nicotinamide adenine dinucleotide phosphate (NADPH) quinone dehydrogenase 1 (Mao *et al.*, 2019). In rats, following cisplatin administration, significant inhibition of gastric emptying observed (Kishibayashi *et al.*, 1993).

### 10.1. Clinical pharmacology

Navaei *et al.*, (2008) conducted a double-blind placebo control clinical trial in hyperlipidemic patients. The Patients were divided into two unequal groups, treatment group was given ginger capsule 3 g/day in divided doses while the placebo group received lactose capsule of the same dose. The results of the study showed that ginger has a significant lipid lowering effect compared to placebo.

A randomised, double-blind, placebo-controlled, multicentre, parallel-group 6-week study of 261 patients found that a highly purified and standardized ginger extract (EV.EXT 77) moderately reduced the symptoms of osteoarthritis (OA) of the knee. Similarly, 250 mg of the ginger extract (Zintona EC) four times daily for 6 months was shown to be significantly more effective than placebo in reducing pain and disability in 29 OA patients in a double-blind, placebo-controlled, crossover study (Braun & Cohen 2007).

Another study explored the effects of ginger on motion sickness experienced by Navy cadets. Seventy-nine men were given either ginger (1 g powdered root) or placebo (lactose) on their first trip on the high seas. Ginger significantly reduced the tendency to vomit and experience cold sweats. The symptoms of nausea and vertigo were also reduced (Barrett, 2004).

### 11. Toxicity and safety

Ginger is on the U.S. Food and Drug Administration's GRAS (generally recognized as safe) list. The British Herbal Compendium documents no adverse effects of ginger (Bradley, 1992).

### 12. Clinical studies

In another study, patients with motion sickness were pre-treated with ginger (1,000 mg and 2,000 mg). Individuals then underwent circularvection during which nausea, tachygastria, and vasopressin were assessed. Ginger improved each of the above parameters, significantly prolonging the latency period before nausea onset and shortening the recovery time after vection cessation (Blumenthal *et al.*, 2003).

An experimental investigation where ginger was used to ameliorate symptoms of nausea in pregnancy was reported. Most recently, a double-blind, placebo-controlled, randomized clinical trial was conducted on 26 women in the first trimester of pregnancy. Subjects ingested one tablespoon of ginger syrup (containing 1 g ginger) or placebo in 4-8 ounces of water four times daily. Duration and severity of nausea was evaluated over a two-week period. Daily vomiting ceased in eight of 12 women in the ginger group by the sixth day, while only two of 12 in the placebo group reported a cessation of vomiting. At the end of the study, 20 women (77%) consuming the ginger

syrup reported a significant decrease in nausea, while 20 percent in the placebo group reported improvement (Blumenthal, 2003).

Cancer chemotherapy can cause severe nausea, vomiting, and abdominal discomfort, which can limit therapy. Anticancer agents such as cisplatin, cyclophosphamide, and methotrexate slow gastric emptying. In a double-blind study of chemotherapy-induced nausea, 41 patients with leukemia received either ginger or a placebo after administration of compazine; an anti-psychotic used to treat psychotic disorders. The results showed a significantly greater symptomatic benefit from ginger compared to placebo (Visnovsky, 1992; Kishibayashi *et al.*, 1993).

### 13. Contraindications

The Complete German Commission E Monographs (CGCEM) recommends against the use of ginger root for nausea and vomiting of pregnancy; however, American editors, citing thousands of years of use and no pertinent scientific validity for this contraindication, refute this recommendation. The commission E also mentions gallstones as a relative contraindication for ginger, without citing a rational (Blumenthal, 1998).

### 14. Precautions

Rhizome is not recommended for children less than 6 years of age (3) Contact dermatitis on the fingers has been found in sensitive patients (Seetharam *et al.*, 1987).

### 15. Adverse reactions

European scientific cooperative on Phytotherapy (ESCOP) lists heartburn as a possible adverse reaction, while the Commission E states that ginger has no known adverse reactions. The USP-DI also lists minor heartburn as the only reported adverse reaction to ginger (Barrett, 2004).

### 16. Marketed formulation, if any

There are many formulations available in the market some of them are presented below.

- Ginger Root (Kanakdhara)
- Dry Ginger (Orgherb)
- Ginger Rhizome Extract (Pukhraj Herbals)
- Zingiber Officinale* (SV Agrofood)
- Pure Ginger Extract (Ambe NS Agro products Private Ltd)
- Ginger Capsule (Good Luck Ayurveda Private Ltd)
- Organic *Zingiber Officinale* (A1 Oil India)
- Zingiber Officinale* Extract (Allpure Organics)
- Ginger Powder (Pass Agro Herbal Food Product)
- Sunthi (Fortune Health Care)
- Ginger Extract (Kuber Impex Ltd)

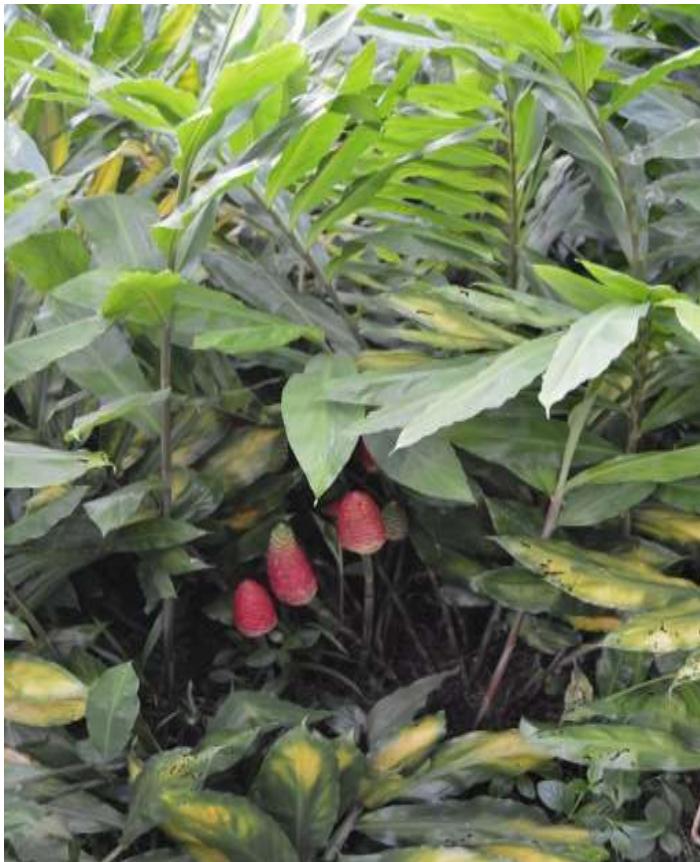
Ginger Tea Cut (Brand kindle)  
Herbs and Herbal extract (Goyal Ayurveda)  
Ginger CO<sub>2</sub> Extract (Nisarga Biotech Private Ltd)  
Ginger Dry Matter (Bharath Biozone)  
Ginger Tea Cut (Innoveda Herbs Private Ltd)  
Ginger Dry Extract (Bayir Group)

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1. Botanical Name: **Zingiber zerumbet** (L.) Roscoe ex Smith
2. Synonyms: *Amomum zerumbet* L.
3. Family: Zingiberaceae
4. Common Name
  - Bengali: Mahabaribach, narkachur,
  - English: Bitter ginger, pinecone, or shampoo ginger
  - Hindi: Mahabaribach, Narkachur;
  - Malayalam: Katinji, kattinjikuva;
  - Oriya: Gada, Pasukedar;
  - Punjabi: Kachur, Narkachur;
  - Sanskrit: Ahava, Avanti, Karpurharidra, Kolanjana, Kumbhika,
  - Telugu: Karallam, Karupasupu, Santapasupu, Karrallamu;
5. Description: An erect rhizomatous perennial herb up to 10 feet high. Leaves sessile or shortly petiolate; ligule entire, leaf blade lanceolate or oblong-lanceolate, glabrescent or abaxially somewhat pilose, base narrowed, apex acuminate. Inflorescences arising from rhizomes, conical or ovoid-oblong, apex obtuse; scale-like sheaths; bracts closely imbricate, green when young, red when old, slightly hairy, slimy adaxially, margin membranous. Calyx 1.2--2 cm, membranous, split on 1 side, apex 3-toothed. Corolla tube slender; lobes pale yellow, lanceolate, central one. Labellum pale yellow; central lobe suborbicular or sub-ovate, apex emarginate; lateral lobes obovate, free nearly to base. Stamen connective appendage beaklike. Ovary glabrous. Fruit a capsule ellipsoid. Seeds black.
6. Distribution: Native to Indo- Malay Peninsula and also found in Sri Lanka, Bangladesh, Nepal. In India found in moist places of subtropical regions.
7. Part Used: Whole plant



*Zingiber zerumbet*

## 8. Medicinal /Therapeutic Uses

### 8.1 Uses described in pharmacopoeias and in traditional systems of medicine

No reference regarding the drug sthulagranthi (*Z. zerumbet*) was found in vedic literature, samhitagranth as well as in different Nighantu (Prakash et al., 2011).

### 8.2 Uses supported by clinical data

The compound present in “zerumbone” is considered as a promising compound for the treatment of different types of cancer such as colon, breast, cervix, and liver cancer and that it inhibits their proliferation and shows selective action towards cancer cells compared to normal ones. It also has anti-inflammatory properties. It has Analgesic, Anti-inflammatory, and Anti-arthritis activities (Ahmadabadi et al., 2020).

### 8.3 Traditional /Folklore Uses described in folk medicine, not supported by experimental or clinical data

The *Maiba-Maibi* in Manipur used this plant for treatment of Cancer, joint pain, stomachache, morning sickness, vomiting (Deb et. al., 2015). In Arunachal Pradesh,

Assam and Manipur rhizome used to treat severe pain, tooth ache, asthma, worms, leprosy, stomachache and skin disorders (Tushar *et al.*, 2010). The fresh rhizomes used to treat flatulence in Thailand. In China, alcoholic macerate of rhizome used as tonic, purgative, stimulant, in Taiwan used to treat stomachache (as anti-inflammatory adjuvant), sprain and fever. In Hawaii, rhizomes used bruises, cuts, sore spots, headaches, toothache, ringworm/other skin disease, achy joints/sprains, stomach-ache (Yob *et al.*, 2011).

#### 8.4 Special uses in North East India

In Arunachal Pradesh, Assam, Manipur, Mixture of Rhizome powder along with ripe noni fruit (*Morinda citrifolia*) is applied on sprains. cooked and softened rhizome was pressed into the hollow and left for as long as was needed and Ground and strained rhizome is mixed with water and drunk. It is useful to treat severe pain, Tooth ache, cavity cough, asthma, worms, leprosy and other skin diseases and stomachache (Tushar *et al.*, 2010).

#### 8.5 Dosage forms used in tradition: Powder, decoction, juice

### 9. Phytochemical profile

The rhizome contains Terpene (Sesquiterpenes) including humulene, humulene monoxide, humulene dioxide, Zerumbone (2,6,10-cy-cloundecatrien-1-one, 2,6,9,9-tetramethyl-, (E,E,E)-), humulenol-I, humulenol-III, humulene epoxide-I, humulene epoxide-II, and humulenol-II. Most abundantly monoterpenes including camphene, Borneol,  $\alpha$ -pinene, linalool, sabinene, citral, zingiberene and lavandulyl,  $\alpha$ -terpineol, and  $\gamma$ -terpinene and polyphenol (Flavonoids) including kaempferol, kaempferol-3-O-methyl, kaempferol-3-O-(2,4-di-O-acetyl- $\alpha$ -L-rhamnopyranoside) and kaempferol-3-O-(3,4-di-O-acetyl- $\alpha$ -L-rhamnopyranoside), Kaempferol-3-O-(4-acetyl) rhamnoside, Kaempferol-3,4-,7-O-trimethylether (Yob *et al.*, 2011; Koga *et al.*, 2016).

### 10. Pharmacological Studies

#### Anti-inflammatory activity

Zerumbone which is used as anti-inflammatory folk medicine in Indonesia was a distinct potent inhibitor of 12-O-tetradecanoyl-13-acetate-induced Epstein Barr Virus (Murakami *et al.*, 1999; Vimala *et al.*, 1999). Elliot & Brimacombe (1987) reported that zerumbone also possessed an anti-inflammatory property especially in treating ulcerative colitis, which is an inflammatory bowel disease (Murakami *et al.*, 2003). Chaungab *et al.* (2008) reported the anti-inflammatory potential, especially in asthmatic patients and the capacity of water extract in protecting the lungs by inhibiting the release of inflammatory

mediators during short-term treatment and modulating cytokine gene expression during long term treatment. Murakami *et al.* (2003), Abdul *et al.* (2008) reported the chemopreventive, anti-inflammatory, free radical scavenging activities and activating properties towards phase II drug metabolizing enzymes. It is a medicinal ginger containing zerumbone which has been shown to have anti-inflammatory properties and inhibitory activities against Epstein Barr virus which can cause many cancers (Idris *et al.*, 2009). The association between inflammation and nociception has previously been reported (Roosterman *et al.*, 2006). Examined effect of zerumbone on the expression of pro-inflammatory genes in human colon adenocarcinoma cell lines, Caco-2, Colo320DM, and HT-29, using reverse transcription-polymerase chain reaction (RT-PCR) assays, and reported that zerumbone markedly induced the expression of interleukin (IL)-1a, IL-1b, IL-6, and tumor necrosis factor (TNF)-a in each cell line in

#### Anti-cancer and anti-apoptogenic activity

Recent research has demonstrated that zerumbone is a potential drug for the treatment of several cancers as well as leukemia (Kirana *et al.*, 2003; Murakami *et al.*, 2004; Sharifah *et al.*, 2007; Kaemferol derivatives components is a scaffold for developing agents that reverse P-gp-mediated Multi Drug Resistant (MDR) inhuman cancer chemotherapy (Han *et al.*, 2005). Hossain *et al.*, (2005) reported 2,6,9,9-tetramethylfrom *Z. zerumbet*. Further reported that the extract decreased the release of tumor necrosis factor-alpha and interleukin-4 (IL-4) in vitro and effectively suppressed LTC4 release from lung tissue *in vivo*. Zerumbone has been found able to exert anti-tumour activity (Kinghorn *et al.*, 1997; Koshimizu *et al.*, 2002). Zerumbone suppressed the activation of NF-KB andNF-KB regulated gene expression induced by carcinogens and reported that this inhibition may provide molecular basis for the prevention and treatment of cancer (Takada *et al.*, (2005). Mechanisms of inducing apoptosis in the hepato-carcinoma cells by zerumbone was carried out *in vitro* using a well differentiated transformed cell line HepG2 cells which have been widely used and considered to be a good model forliver cancer research (Rasmos *et al.*, 2005). It is identified that the inhibition of Epstein Barr Virus(EBV) early antigen (EA) activation which was induced by tumour-promoters *in vitro* correlated well with the zerumbone anti-tumor promoting effects *invivo* (Koshimizu *et al.*, 1988; Nishino *et al.*, 1988).It is reported that zerumbone component down regulated the expression of CXCR4 and HER2-overexpressing breast cancer cells in a dose and time dependent manner.The compound was shown to inhibit the proliferationof human colonic adenocarcinoma cell lines in a dose dependent manner, while the growth of normal humandermal and colon fibroblast was less affected (Nakamura *et al.*, 2004). Tanaka *et al.*, (2001) demonstrated the inhibition ability of zerumbone on both azoxymethane induced rat aberrant crypt foci and phorbol ester induced papilloma formation in mouse skin a further indication of its efficiency to prevent colon and skin cancer. The cytotoxic effect of zerumbone on leukemia cells was found

to be mediated through the induction of Fas receptors (Xian *et al.*, 2007). Murakami *et al.* (2004) did histological examination and revealed that pretreatment(s) with zerumbone suppressed leukocyte infiltration and reduced proliferating cell nuclear antigen-labeling indices, further suggested that zerumbone is a promising and rational agent for the prevention of skin cancers, whereas its oral activity to prevent skin cancers and issues of metabolism and absorption remain to be addressed. Huang *et al.*, (2005a&b) observed the cell cycle of HL-60 cells after treatment with zerumbone, which induced G<sub>2</sub>/M cell cycle arrest in HL-60 cells in a time and concentration-dependent manner, and decreased the cyclin B1/cdk 1 protein level and suggested that zerumbone is an active principal and are potentially a lead compound for the development of anticancer drugs. Zerumbone Downregulates Chemokine Receptor CXCR4 Expression leading to Inhibition of CXCL 12-Induced INVASION of Breast and Pancreatic Tumor Cells (Nigam & Levi, 1963b). Ohigashi & Murakami (2002) suggested that redox regulated mechanism may account for zerumbone's ability to suppress cancer cell proliferation, further suggested additional experiments like (1) Measurement of the intracellular [GSSG]/[GSH] of some normal and cancer cell lines which are treated, or not treated, with ZER. (2) Exploration of the relationships among the E values, phosphorylation states of RB protein and cell growth rates. (3) Confirmation of the production of anintracellular GSH-ZER adducts. Kirana *et al.*, (2003) reported that zerumbone inhibited the growth of human leukemia cell lines (HL-60 cell) and humancolon cancer (HT-29) *in vitro*. In 2005, Takada and his groups found that zerumbone suppressed the activation NF-kB and NF-kappa b regulated gene expression induced by carcinogenesis and reported that this inhibition may provide molecular basis for the prevention and treatment of cancer. Abdul *et al.*, (2008) demonstrated the MTT assay and reported the effective inhibition of zerumbone on cell proliferation of human cervical cancer cells (HeLa) in a dose dependent manner. Hoffman *et al.*, (2002) proposed redox model of cell proliferation which stresses the importance of intracellular redox potential E in the control of proliferation of normal and cancer cells. Further they pointed to the, b-unsaturated carbonyl group in Zerumbone as the likely source of the effect. They called the finding 'intriguing'. The stimulation of neoplastic cell death by Zerumbone was reported to be through the mitochondrial pathway of apoptosis (Abdel *et al.*, 2009). Zerumbone has also been reported having the capacity to induce apoptosis and morphological changes in different types of leukemic cells (Hamid *et al.*, 2007). Chung *et al.*, (2007) reported histone deacetylase inhibitors from the rhizomes. Histone deacetylase (HDAC) inhibitors that inhibit proliferation and induce differentiation and/or apoptosis of tumor cells in culture and in animal models have been identified. A number of structurally diverse histone deacetylase inhibitors have shown potent antitumor efficacy with little toxicity *in vivo* in animal models. The histone deacetylase (HDAC) activities of compounds 1 and 2 were determined *invitro* against HDAC enzyme assay and showed potential inhibitory activity

in histone deacetylase (HDAC) enzyme assay ( $GI_{50} = 1.25$  IM). It also exhibited growth inhibitory activity on five human tumor cell lines and more sensitive inhibitory activity on the MDA-MB-231 breast tumor cell line( $IC_{50} = 1.45$  IM).

#### Antinociceptive activity

The Methanol extract exhibited significant antinociceptive activity when assessed by the writhing, hot plate and formalin tests. Sulaiman *et al.*(2009) investigated the antinociceptive activity of zerumbone, a natural cyclic sesquiterpene isolated in acetic acid-induced abdominal writhing test and hot plate test in mice. The antinociceptive effect of zerumbone in the hot plate test was reversed by the non-selective opioid receptor antagonist naloxone, suggesting that the opioid system was involved in its analgesic mechanism of action. Zerumbone was obtained from repetitive recrystallization from the crude hydro distillate. They provided convincing evidence indicating that zerumbone isolated and possessed significant peripheral and central antinociceptive effects in laboratory animals at the doses investigated.

#### Antimicrobial activity

Kader *et al.*, (2010) isolated sesquiterpene, zederone from the crude ethanolic extract of the rhizomes. The antibacterial activity of this compound was determined against a number of multi-drug resistant and methicillin-resistant *Staphylococcus aureus* strains (SA1199B, ATCC25923, XU212, RN4220 and EMRSA15) and minimum inhibitory concentration (MIC) values were found to be in the range of 64–128 µg/ml. The oil showed significant inhibitory activity against the bacteria, *Staphylococcus aureus* (1.2 cm), *Lactococcus lactis* (0.8 cm), and the fungus *Aspergillus awamori* (1.5 cm), *Fusarium oxysporum* (1.0 cm), *Aspergillus acicularatus* (0.9 cm), *Candida albicans* (0.8 cm), *Trichoderma viridae* (0.8 cm), *Rhodotorula* sps. (0.8 cm) and *Aspergillus niger* (0.6 cm) Helen *et al.*, (2009). No inhibitory activity was observed against the bacteria, *Bacillus cereus* and *E. coli*. Voravuthikunchai *et al.* (2006) reported the effective activity of *Z. zerumbet* against *Staphylococcus aureus*, MIC (Minimum Inhibitory Concentration) values and MBC (Minimum Bactericidal Concentration) values reported were 0.79 mg/ml and [12.5 mg/ml, respectively. Zerumbone ring-opening derivative, 4 (10E/10Z = 3/2), inhibited auto phosphorylation of the essential histidine-kinase YycG existing in *Bacillus subtilis* constituting a two-component system (TCS). However, it did not inhibit drug resistant bacterium such as MRSA and VRE. Kiat & Richard (2006) screened selected zingiberaceae extracts for dengue-2 virus protease inhibitory activities and the results show that the methanol fractions of *Curcuma longa* and *Zingiber zerumbet*, and both the methanol and hexane fractions of CM were most potent against Den2 virus NS2B/NS3 protease activity and may provide potential leads towards the development of anti-viral agents. The percentage inhibition of Den2 virus

NS2B/NS3 protease cleavage of the substrate showed linear dose-dependent increment for all the samples tested.

#### Antiplatelet aggregation activity

Twelve compounds isolated from *Alpinia mutica*, *Kaempferia rotunda*, *Curcuma xanthorrhiza*, *Curcuma aromatica*, *Zingiber zerumbet* and three synthesized derivatives of xanthorrhizol were evaluated for their ability to inhibit arachidonic acid—(AA), collagen- and ADP-induced platelet aggregation in human whole blood (Jantan *et al.*, 2005), further they reported that methanol extracts of the fruit of *Alpinia mutica* and the rhizomes of *Kaempferia rotunda*, *Curcuma xanthorrhiza*, *C. domestica* and *Z. zerumbet* showed strong anti platelet aggregation activity at 100 mg/ml in human whole blood in vitro, with all extracts exhibiting 100% inhibition. Jantan *et al.*(2005) investigated forty-nine methanol extracts of 37 species of Malaysian medicinal plants were for the inhibitory effects on platelet-activating factor (PAF) binding to rabbit platelets, using <sup>3</sup>H-PAF as a ligand, where *Z. zerumbet* was one of the compounds, however it was not found to be PAF antagonistic.

#### Antipyretic and cytotoxic activity

The ethanol and aqueous extract of *Z. zerumbet* elucidate moderate to marked antipyretic activities which was dose dependent (Somchit & Shukriyah, 2005). Further added that the ethanol extract revealed dose dependent analgesic property which was significantly different than control. The aqueous extract was devoid of any analgesic effects 50 and 100 mg/kg. The analgesic activity of 10 mg/kg of ethanol extract was similar to 0.8 mg/kg morphine. Zerumbone has been found to exhibit cytotoxic activities on Hepatoma Tissue Culture (HTC), a neoplastic rat liver strain cultured in vitro and was found to be selective against normal mouse fibroblast (Murakami *et al.*, 2002). Murakami *et al.*, (2004) reported similar findings that the carbonyl group at the 8-position in zerumbone is the important structural element for its chemopreventive potential. Combination of both Cisplatin and toxol induce apoptosis in epithelial ovarian cancer (Havrilesky *et al.*, 1995; Ormerod *et al.*, 1996).

#### Antihyperglycemic activity

Reported screening of aqueous extract of *Phyllanthus niruri* (PL), *Z. zerumbet* (ZGr), *Eurycoma longifolia* (TA-a and TA-b) and *Andrographis paniculata* (AP) to determine their blood glucose lowering effect were conducted in normoglycemic and Streptozotocin induced hyperglycemic rats. Treatment using aqueous extract of TA-a, TA-b, PL and ZGr at dosages of 50 and 100 mg/kg BW did not show many significant reduction in blood glucose levels in hyperglycemic rats (data not shown) but at the dosage of 150 mg/kg bw, blood glucose level decreased at 37.88, 46.80, 13.94 and

22.19% when treated with TA-a, TA-b, PLr and ZGr, respectively, in hyperglycemic rats ( $P \geq 0.05$ ,  $P \leq 0.001$ ) showed that no antihyperglycemic activity was observed in both raw and freeze-dried aqueous extract of PL and ZG at all concentration used.

#### LPS (lipopolysaccharide)-induced NO production

Jang *et al.*, (2005) reported the isolation of a novel humulene derivative, 5-hydroxyzerumbone, from *Z. zerumbet* and its inhibitory activity on lipopolysaccharide(LPS)-induced nitric oxide (NO) production in RAW 264.7 mouse macrophage cells. Treatment with 5-hydroxyzerumbone also induced the expression of hemeoxygenase-1 (HO-1) in macrophage cells. In addition, 5-hydroxyzerumbone inhibited LPS-induced transcriptional activation of NF- $\kappa$ B, indicating that regulation of NF- $\kappa$ B activity might be involved in the inhibition of NO production by 5-hydroxyzerumbone. 5-Hydroxyzerumbone, however, did not affect the degradation of I $\kappa$ B- $\alpha$  and the activation of p38 and ERK in LPS-treated cells. They summarized the study and suggested that 5-hydroxyzerumbone inhibits LPS induced NO production in macrophage cells through down-regulating iNOS protein and mRNA expressions.

#### Antioxidant activity

Murakami *et al.*, (2002) reported that zerumbone was able to suppress free radicals (superoxide anion) generation from NADPH oxidase xanthine oxidase, expression of iNOS (inducible nitric oxide synthase) and COX (cyclo-oxygenase)-2 as well as release of TNF- $\alpha$ . Ibrahim *et al.*, (2009) reported the preventive effect of zerumbone in cisplatin-induced liver dysfunction and organ damage in rats via prevention of lipid peroxidation and preservation of anti-oxidant glutathione. Further reported that morphological features of liver from zerumbone injected animals are similarly near to the morphology with normal hepatocytes, Kupffer cells and sinusoids.

#### Chondroprotective activity

Al-Saffar *et al.* (2010) revealed curative effect of zerumbone in a dose dependent manner on the osteoarthritic knee joints, reported that oral administration of zerumbone in a dose of 2 ml/kg b. wt. of 0.4% w/v diluted with corn oil for a period of 4 weeks had some chondroprotective effects on the kneeosteoarthritis of the Sprague–Dawley rats. *Z. zerumbet* is used in herbal medicinal practice for the treatment of rheumatological conditions and muscular discomfort (Bordia *et al.*, 1997; Langner *et al.*, 1988).

#### Anti-AD (Alzheimer's disease)

Bustamam *et al.*, (2008), had done a study where the inhibitory effect of ZER towards acetyl cholinesterase was evaluated using thin layer chromatography (TLC)

bioautography and compared concurrently to tacrine, as positive control. The results obtained showed that ZER had an enzymolytic effect towards AChE (Acetyl Cholinesterase). It could be suggested that ZER might be a potential candidate for the development of anti-AD (Alzheimer's disease) treatment.

#### Chemopreventive activity

Taha *et al.*, (2010) reported potential chemopreventive activity of zerumbone from the rhizomes of the subtropical ginger (*Z. zerumbet*) against diethylnitrosamine-initiated and 2-acetylaminofluorene-promotedhepatocarcinogenesis.

#### Hepatoprotective activity

The hepatoprotective activity of ZER may be through the enhancement of drug-metabolizing enzyme activity(Nakamura *et al.*, 2004). It is postulated that in the hepatocytes, the antioxidant effect of ZER is through the neutralization of lipid peroxidation.

#### Immuno-modulatory activity

Keong *et al.* (2010) reported the immune modulatory effects of zerumbone towards the lymphocyte proliferation(mice thymocytes, mice splenocytes and human peripheral blood mononuclear cells, PBMC),cell cycle progression and cytokine (intraleukin 2 and12) induction.

#### Anti-edema

Zakaria *et al.*, (2010) reported methanol extract of *Z. zerumbet* (MEZZ) showed significant anti-edema activity when assessed using the carrageenan –induced paw edema test and the cotton-pellet induced granuloma test. *Z. zerumbet* has been shown to inhibit prostaglandin induced paw edema, a commonly used acute inflammatory reaction and the efficacy is equivalent to the non-steroidal anti-inflammatorydrug, mefenamic acid.

#### Anti pancreatitis activity

Szabolcs *et al.*, (2007) reported zerumbone to be supressor of Cholecystokinin octapeptide induce acute pancreatitis in rats and increases in survival of p388bearing CDF-1 mice. Zerumbone ameliorated the changes of several parameters of acute pancreatitis probably by interfering with I-jB degradation, but in the applied dose, it failed to influence the histology of the disease.

### Antiallergic activity

Ethanol and water extracts, together with volatile oils from the rhizomes of six selected Zingiberaceous plants, including *Curcuma mangga*, *Kaempferia galanga*, *K. parviflora*, *Zingiber cassumunar*, *Z. officinale* and *Z. zerumbet* were investigated or their antiallergic activities using a RBL-2H3 cell line (Supinya & Sanan, 2007).

### Anti-oomycete activity

In molecular docking studies, a linear polymeric molecule of (1,3)-B-D-glucan, a major constituent of the oomycete cell wall fitted favorably into the surface cleft of ZzPR5 (*Z. zerumbet* Pathogenesis Related Protein 5) and interacted with acidic amino acid known to be involved in glucan hydrolysis, suggesting a potential anti-oomycete activity for ZzPR5 protein. Elucidation of the molecular mechanism of ZzPR5 may provide important insight towards engineering soft rot resistance into the obligatorily sexual ginger (Aswati *et al.*, 2010).

### Antiepileptic seizures and angiogenic activity

Fengnian *et al.* (2008a, b) reported the various beneficial effects of b-eudesmol on human health and were considered to be a lead compound for treat seizures (Chiou *et al.*, 1997), angiogenic diseases (Kimura, 2005) and dementia (Obara, 2006).

### Micronucleus formation

The chromosomal aberrations (CA) assay and micronucleus (MN) test were employed to investigate the effect *in vitro* of zerumbone (ZER) on human chromosomes. The results of chromosomal aberrations assay showed that ZER was not clastogenic, when compared to untreated control, meanwhile MN test results showed a dose-dependent increase in MN formation (Al-zubairi *et al.*, 2007).

### Enzyme activation activity

Zerumbone also activated phase two drug metabolizing enzymes, such as GST (Glutathione S-transferase), epoxide hydrolase and hem oxygenase via the transcription factor Nrf2-dependent pathway (Nakamura *et al.*, 2004) and was able to inhibit HIV (Dai *et al.*, 1997). Harada *et al.* (2009) reported that when the a-humulene synthase (ZSS1) gene of shampoo ginger was expressed in the transformant, the resultant *E. coli* produced 958 Ig/ml culture of a-humulene with a lithium acetoacetate (LAA) supplement, which was 13.6-fold increase compared with a control *E. coli* strain expressing only ZSS1. Fengnian *et al.* (2010) reported *Z. zerumbet* CYP71BA2 catalysis the conversion of a-humulene to 8-hydroxy-a-humulane in zerumbone biosynthesis. Further reported co-expression of a genecluster encoding four enzymes of the mevalonate pathway with

CYP71BA1 and ZSS1 in *E. coli* leads to the production of 8-hydroxy-a-humulene in the presence of mevalonate, suggesting the possibility of microbial production of this zerumbone intermediate from a relatively simple carbon source by metabolic engineering. Zerumbone is known to be a potent suppressant of cyclo-oxygenase (COX) and inducible nitric oxide synthesis expression (Murakami *et al.*, 2003). Fengnian *et al.* (2008b) isolated a terpenecyclise gene(ZSS1) from shampoo ginger *Z. zerumbet* and identified ZSS1 as the a-humulene synthase gene that mediates the conversion from FPP to a-humulene (a-caryophyllene).

#### Anti-HIV

Dai *et al.*, 1997 reported that Zerumbone displayed HIV inhibitory and other cytotoxic activities. Zerumbone was found to exert anti-HIV effects (Ozaki *et al.*, 1991; Kirana *et al.*, 2003; Xian *et al.*, 2007).

#### Other activities

In southeast Asia, *Z. zerrumbet* is used for the treatment of fever, constipation, and to relieve pain (Peri, 1980). *Z. zerumbet* is commonly used to treat cases of diarrhea in Thai Traditional medicine (Farnsworth & Bunyaphraphatsara, 1992). Zerumbone found in some edible parts, including young stems and inflorescence are used in traditional cooking. Bensch & Akesson (2005) reported the amplified fragment length polymorphism (AFLP) as an ideal marker technique for genetic diversity studies of poorly characterized plant species. The *Z. zerumbet* and *Kaemferia galangal* were found to express Epstein-Barr virus early antigen (EBV-EA) activation inhibitory activity in Raji cells (Vimala *et al.*, 1999). Huang *et al.*, (2005a, b) identified that zerumbone inhibited the growth of p-388 D cells and induced DNA fragmentationin culture and significantly prolonged the life of p-388 D (1) bearing CDF (1) mice. The sesquiterpene zerumbone isolated and inhibited Gli1-and Gli2-transcription with IC<sub>50</sub> values of 7.1 and 0.91 μM, respectively, showing sevenfold selectivity for Gli2 over Gli1 (Neeraj *et al.*, 2009).

### 10.1. Clinical pharmacology

The details of the clinical pharmacology of *Z. zerumbet* rhizome is listed in the table below

S. No	Extract	Pharmacology Study	Reference
1	Methanol	Biological activities	Kitayama <i>et al.</i> (1999), Kitayama <i>et al.</i> (2001)
2	Methanol	Anti-inflammatory property	Murakami <i>et al.</i> (2003)
3	Methanol	Antiflatulant and anti-inflammatory agent	Wutthithamav <i>et al.</i> (1997)
4	Methanol	Anti-inflammatory activity	Chaungab <i>et al.</i> (2008), Dambisiya and Lee (1995)
5	Methanol	Chemopreventive, anti-inflammatory, free radical scavenging activities and activating properties	Abdul <i>et al.</i> (2008)
6	Methanol	Potential drug for the treatment of several cancers as well as leukemia	Kirana <i>et al.</i> (2003), Murakami <i>et al.</i> (2004), Sharifah <i>et al.</i> (2007), Xianet <i>al.</i> (2007)
7	Methanol	Anti-tumour activity	Kinghorn <i>et al.</i> (1997), Rasmos <i>et al.</i> (2005)
8	Hexane	Inhibit the proliferation of human colonic adenocarcinoma cell lines in a dose dependent manner, while the growth of normal humannormal and colon fibroblast was less affected	Nakamura <i>et al.</i> (2004)
	Methanol	Anti-tumour promoting effect	Koshimizu <i>et al.</i> (1988), Nishino <i>et al.</i> , (1988)
	Methanol	Prevent colon and skin cancer	Tanaka <i>et al.</i> (2001)
	Methanol	Redox regulated mechanism may account for zerumbone'sability to suppress cancer cell proliferation	Ohigashi & Murakami (2002)
	Methanol	Anti-tumour/anti-apoptotic activity	Abdel Wahab <i>et al.</i> (2009), Hamid <i>et al.</i> (2007) and Chung <i>et al.</i> (2007)
	Methanol	Antinociceptic activity	Sulaimanet <i>al.</i> (2009), Helen <i>et al.</i> (2009)
	Methanol	The effective activity of Zingiber zerumbet against <i>Staphylococcus aureus</i>	Voravuthikunchai <i>et al.</i> (2006)
	Methanol	Elicitate moderate to marked antipyretic activities which was dose dependent	Somchit & Shukriyah, (2005)

	Methanol	Against normal mouse fibroblast	Murakami <i>et al.</i> (2002)
	Methanol	Suppress free radicals (superoxide anion) generation fromNADPH oxidase xanthine oxidase	Murakami <i>et al.</i> (2002)
	Methanol	Curative effect of zerumbone in a dose dependent manner on the osteoarthritic knee joints and reported that oral administration.	Al-Saffar <i>et al.</i> (2010)
	Methanol	Development of anti-AD (Alzheimer's disease) treatment	Bustamam <i>et al.</i> (2008)
	Methanol	Chemo preventive activity	Taha <i>et al.</i> (2010)
	Methanol	Hepatoprotective activity	Nakamura <i>et al.</i> (2004)
	Methanol	Immune-modulatory activity	Keong <i>et al.</i> (2010)
	Methanol	Anti-edema activity when assessed using the carrageenaninducedpaw edema test and the cotton-pellet inducedgranuloma test	Zakaria <i>et al.</i> (2010)
	Methanol	Ant pancreatic activity	Szabolcs <i>et al.</i> (2007)
	Purchased	The various beneficial effects of b-eudesmol isolated	Fengnian <i>et al.</i> (2008)
	Purchased	Treating epileptic seizures	Chiouet <i>al.</i> (1997)
	Methanol	Angiogenic diseases	Kimura (2005)
	Pentane	Dementia	Obara (2006)
	Ethanol	HIV inhibitory and other cytotoxic activities	Dai <i>et al.</i> (1997)

11. Toxicity and safety: No major toxicities have been reported

12 Clinical studies: No clinical studies or clinical trial has been reported

13. Contraindications: So far, no contraindications have been identified or reported

14. Precautions: None reported so far

15. Adverse reactions: Research reveals little or no information regarding adverse reactions of *Z. zerumbet*.

16. Marketed formulation, if any:

No reported so far apart from traditional use.

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