A REVIEW REPORT ON PLANT BASED BIOACTIVE COMPOUNDS: POTENTIAL REMEDIES TO TREAT MALIGNANCIES

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2018-2022

RESEARCH COMPLETION CERTIFICATE

It is certified that Ms. Ramsha Shahid of B.Sc. Honors (Session 2018 – 2022), Department of Food Sciences and Human Nutrition has carried out research work entitled

“a review report on plant based bioactive compounds: potential remedies to treat malignancies” under my supervision. All changessuggested by examiners during defense are incorporated in this final copy.

It is assured that the research work is original and has not yet been published anywhere else.

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LIST OF ABBREVAITIONS

T3	Tocotrienols
NRPS	Non-ribosomal peptides synthetases
PKS	Polyketide synthases
1H NMR	Proton nuclear magnetic resonance
LCMS	Liquid chromatography mass spectrometry
PCA	Principal components analysis
MAE	Microwave Assisted Extraction
UAE	Ultra-Sound assisted extraction
SFE	Supercritical fluid extraction
ASE	Accelerated Solvent Extraction
SOD	Superoxide dismutase
NPD-4	Nitro-phenylenediamine
TIDM/T2DM	Type 1 and type 2 diabetes mellitus
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
CVD	Cardiovascular disease
ATP	Adenosine triphosphate
SERMs	Selective estrogen receptor modulator
ER	Estrogen receptor
TP	Triptolide
AP	Andrographolide
NFT	Neurofibrillary tangles
PPAR	Peroxisome proliferator activated receptors
EGCG	Epigallocatechin-3-gallate
SQM	Squamous metaplasia
RO1	Reactive oxygen intermediated
OH	Hydroxyl radical
0_2^-	Superoxide
NO	Nitric oxide
$ONOO^-$	Proximities
SFN	Sulforaphane
MMP-2	Matrix metalloproteinase-2
FAK	Focal Adhesion Kinase
ERK	Extracellular signal-regulated Kinase
EMT	Epithelial Mesenchymal Transition
HPLC	High performance liquid Chromatography
AD	Alzheimer disease
XO	Xanthine oxidase
COX	Cyclo oxygenase
NHANES	National Health and nutrition examination survey
P-GAP	P-glycoprotein

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ABSTRACT

Medicinal Plants have a history in using them as a treatment for different disease. With the rapid onset of cancer as abnormal malfunction, natural compounds came into interest due to their exceptional extra-nutritional properties and immunomodulatory effect on malignant tumors. However, due to unhealthy dietary habits, improper routine, unhygienic conditions and use of chemicals the cancer is leading towards unfavorable tumor prognosis. The current treatments involve chemotherapy, immune therapy, surgical removal of tissue and glands, and laser treatment. Anti-metabolites, anti-tubulin agents and hormones are also being used as drugs to treat malignancies. Unfortunately, being an intensive therapeutic therapy, they come with adverse side effects such as gastrointestinal lesions, bone marrow suppression, leukopenia, loss of hair, kidney disease, diabetes and hypertension. Herbal treatment is used as an ancient medical practice. With advancement of technologies, plant based bioactive compounds are now being extracted successfully. Plant based bioactive compounds have profound effect on malignant tumors overcoming the side effects of chemotherapies. These bioactive compounds are mainly antioxidants and anticancer minuting the adverse tumors and cancers which are leading cause of death. These bioactive compounds such as Flavonoids, Revestrol, Geraniin, Curcumin, Phytosterols, Carotenoids, Phytoestrogens, Anthocyanidins, Saponins, Cucurbitacin, Myricetin and Tocotrienols are present in nuts, fruits, vegetables, cereals, oils, and tea. They are known to have protective antioxidant and favorable properties against tumors, cancer and thrombosis. Soy, whole grains, flax seed oils are rich in phytoestrogens whereas citrus fruits and herbs are rich with monoterpenes. Garlic and onion have organosulfur properties with anticarcinogenic effect. Tomatoes contains lycopene which is excellent antioxidant protecting against prostate cancers inhibiting the tumor and cancer cell lines. Diet rich in vegetables. greens, fruits, nuts, legumes, whole grains help to combat the tumors and life-threatening diseases. Thus, this report reviews plant based bioactive compounds and its effect on malignant tumors and highlights the remedies which is feasible to use against the cancer and malignancies. The focus is on mechanisms of natural substances against cancer and potential solutions and treatments along with their sources and roles and how they are exceptional anti-cancer agents.

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CHAPTER 1

INTRODUCTION

As the world is progressing, the cases of cancerous tumors are spreading worldwide and globally malignant tumors are considered as epigenetic dysfunction. “Bioactive compounds” consist of important nutritional active agents that normally occurs in minute amounts in dietary plants. Bioactive constituents from plants are categorized into saponins, phenolic acids, alkaloids, flavonoids, polysaccharides, and others. The widespread occurrence of malignant tumors and development of resistance to chemotherapy and immunotherapeutic agents is increasing the interest of medical experts in the use of ethnomedicinal study and extract phytochemicals for the treatment and prevention of disease. Medicinal herbs have been used in Pakistan since a long time. As malignant tumor is considered as a leading death cause so plant based bioactive compounds such as, tocotrienols (T3), curcumin, geraniin and myricetin have phenomenal anticancer properties. (Penny, Kari, Andrea, Stacie, Amy, Kristen &Terry D, 2003).

To fight tumors, the immune system of cancer patient is activated and boost up to fight the cancer. There are many reports which are evidence for natural bioactive compounds as a cure for cancerous tumors. Some of the agents have oncogenic or mutagenic or teratogenic features which can mediate an immune response in Cancer patients (Shonia, Kanga & Ammo 2019). Cancer is still identified as leading prominent disease all over the world. In United States, Sub-Saharan Africa and many other countries the mortality rate for Cancer is estimated to increase to 50%. The risk for cancer is divided on basis of modifiability and biological nature which includes extrinsic (Non-intrinsic) and Intrinsic factors. Whereas, Intrinsic factors are defined as simple endogenous risks (inflammation, gender, genetic, hormones, susceptibility, growth factors). Non-Intrinsic Factors are known as exogenous risk which includes smoking, tumor causing viruses, radiation, lack of exercise, nutrition imbalance and bad lifestyles (Chota, George & Abrahamse, 2020).

Malignant tumors are being treated with different approaches such as gene therapy, immunotherapy, radio therapy, surgery and chemotherapy. These therapies are successfully being used but they have some long-term life-threatening side effects too. Therefore, this research focuses on plant based bioactive compounds and

remedies to treat cancers. (Alexander et al., 2020). The cancer features limitless replication exhibiting apoptosis, inducing angiogenesis, self-sufficient growth signals, invading of tissue, metastasis and insensitive to anti-growth signals. These featur2es have given cancer prolonged survival chance which leads to decay of health. Here comes Phyto chemicals, bioactive compounds to rescue by its immune modulating effects (Subramaniam et al., 2019).

Geraniins are mainly found in medicinal plant geraniums and is dehydroellagitannin with antibacterial, high anti-oxidant -hyperglycemic, anti-viral and anticancer properties. Corilagin, ellagic acid and gallic acid are hydrolyzed compounds of Geraniins and have profound effect on breast cancer cells. Whereas Tocotrienols is fat soluble anti-oxidant. Tocotrienols are also known as vitamin E. Major sources for tocotrienols are palm kernel oil and rice bran oil. Tocotrienols have anti-oxidant, neuro-protective, anti-thrombin, cardio protective and immune modulatory properties. Tocotrienols have anti-tumor properties and can inhibit malignant tumors of prostate, breast, skin liver, pancreatic and lungs (Zhihui Yu et al., 2015).

Curcumin is extracted from curcuma longa and is bioactive compound known as Diferuloylmethane. Curcumin is also present in turmeric responsible for yellow color and flavoring. They have low bioavailability due to rapid elimination from body and declined absorption but can be increased by several approaches such as liposomes, protein nanoparticles and phospholipid complex. A bioflavonoid myricetin found in berries, plants were first isolated from Myrica Nagi. Myricetin has therapeutic effects on in cardiovascular disease, diabetes mellitus and cancers. (Subramania et al., 2019). Saponins are isolated from Allium species and are promising anticancer agents inhibiting human cancer cell line (Zhihui Yu et al., 2015).

For this review report eleven bioactive compounds have been discussed (Geraniin, tocotrienols, curcumin, flavonoids, myricetin and Cucurbitacin, saponins, Anthocyanidins, Phytoestrogen, Phytosterols and Carotenoids).

Definition of Keywords:

Plant based bioactive compounds:

A chemical found in medicinal plants which have profound effects on body and diseases. They are being used worldwide to treat the cancerous cells deleting the side effect of chemotherapy. There are six categories namely polysaccharides, flavonoids, alkaloids, phenolic acids and saponins.

Malignant tumors:

These tumors are cancerous and cells rapidly divide themselves growing out of limit and becoming a threat for life. These cells then spread through the other parts of body and growing there in a large number. They can destroy other tissue by invading the cells and rapidly multiplying the cells.

RATIONALE

Medicinal plants have a history. They were widely used historically and now after a long journey it is possible to extract the potential compounds from plants to target various cells and diseases. Anticancer cells are being treated with invitro and in vivo methods. Plant based bioactive compounds are branched into several categories known as saponins. Phenols, flavonoids along with polysaccharides having anticancer, antioxidant, antiviral, antibacterial advantages over different treatments. The review reports about different sources of bioactive compounds and how they affect the malignant tumors. It also enlightens the solutions for using bioactive compounds in daily diet routine and treating cancerous tumors.

As there is far-flung outspread of cancer and tumors in world that it is potential to isolate various distinct phytochemicals to incorporate it into our diet and lives in order to treat cancerous cell lines. This review is designed and put together to confined the effects of cancer and isolate bioactive compound in ethnomedicinal plants significant to treating malignant tumors. This study is focused on bioactive compounds and concerned to its use for cancelling the effect and cells of malignant tumors.

CHAPTER 2

LITERATURE REVIEW

2.1 Historical Importance of Plant Based Bioactive Compounds

It is very idealistic to look into all the years man have evolve. About 5 to 7 million years ago when humans were wandering here and there and came into contact with new unusual organisms, species, plants, diseases and from then to now the future is humans and wandering has not stopped yet (Wilford, 2002). People have always keen observation towards the nature, its beautiful gigantic aspects and colors and ingredients that make them either so vulnerable to them or make them powerful. Plants are one of them with a broad spectrum and traditional use. Historically, plants are and were like a magic potion to people of all centuries. Plants are symbolic to human beings, medicine and food to homo sapiens and animals. Those plants that are used for the purpose of cure or medicine is termed as medicinal plants (Santic, Bevanda & Galic, 2017)

Plants were consumed as dietary compounds but what makes these plants so special that they were started to be used as medicines. A simple answer is the creative ingredients including phytochemicals, bioactive agents and much more. When man came to the world, they required food for survival and this demand led them to use plants. It manifested that it was great idea to use them as they encountered spectacular medicinal properties. This knowledge of healing and cure was not a simple thing. It came with immense experiments, experiences, time from generation to generations. The lessons learned by empirical experiments have a huge working behind it. When human faced diseases one after another these plants were used as a treatment in history and will be accompanied till future or end of this World! (Santic et al., 2017).

This inheritance of the knowledge of medicinal plant is being evolved in various cultures with various experiments. They are safely used as therapeutic modality over the verge of thousands of years. This healing efficacy transferred from centuries, however modernity to extraction, treatment and experiment is changing with the discovery of new techniques. But this modernity along with culture discrepancy has not interfered with the poise sanity of medicinal plants rather people have accepted its natural medical divinity. No modern medicine can claim on its transcendent cure for diseases along with malignant tumors. (Khan, 2014).

Looking into the golden era of history, there are various evidences inscribed on Sumerian clay plate in Nippur. Books of Greek physicians, Old Testament, Egyptian papyri, Charaka Samhita, dated 700 B.C described 300 medicinal plant and the works done by romans, Pliny, Socrates, Theophrastus, Galen are of great interest (Santic et al., 2017).

Traditional systems involve different techniques with contrasting prototypes, concepts, protocols which transformed to homeopathy, allopathy, Chinese treatment. Every culture has its own story of their ancestors for healing knowledge that led to development of individually modified book (Materia medica of civilizations and nation) penned by Dioscorides. The details compiled with interaction and exchange of knowledge and books and emerged as incredible human pharmacopoeia of natural origin. The foundation to medicinal plants revolutionized the health care system and laboratories (khan, 2014).

Ever since the discovery of medicinal plants, people look into them and then with the invention of iatrochemistry they were valued more as prophylaxis, anti-oxidants, anti-cancer drugs. They got popularity with time but the decreased efficacy of chemical synthetic drugs promoted them more. Plants with bioactive compounds is favorite for food experts, pharmacological analyst and scientist and is topical (Petrov ska B. B, 2012). The use of plants was found in the bible written in 1200 BC, Indian holy books (Vedas), Chinese books, Egyptian painting along with discovery of beneficial spices, herbs, roots, stems, leaves and seeds. Different recipes were given by Egyptian papyri that were used in old times (Santic et al., 2017).

Continuous investigations on medicinal plant identified the forms to be used such as the crude raw or isolation of compounds from plants indicates the ancient mode of medication. The Indian medicine ayurvedic of 2000 BC with references in Atharvaveda verifies the witness for the usage of medicinal heirloom. As Mesopotamians demonstrated the use of clay tablets followed by Egyptians, Indians, Asians, revealed in Materia medica and the Ching classic by pen Tsao concede with the fact that knowledge of medicinal plant is mammoth (khan, 2014).

Eber's papyrus is a compilation of Egyptian texted from 1550 BC, the oldest work on medicinal plant. It involves 800 remedies which uses numerous plant species describing the detailed physiology of circulatory system. This was acquired by George Maurice in 1873 (Tikkanen, 2019). The drugs were composed of onion, fig, aloe, castor oil, willow, garlic, senna, juniper etc. The Talmud and bible involved the treatment from aromatic plants such as incense and were widely accepted. Plant based compounds from Egyptian, Mycenean pharmacotherapy were more referrable. Many plants names were derived from the Greek words such as *Artemisia,* from Artemis referred as ``healthy``. Surprisingly different names common today is basically named after the discoverer (Petrovska BB, 2012).

Castor oil plant is named as Herodotus in 500 BC whereas Orpheus referred to the strong smell of hellebore and garlic. Similarly, sea onion, mustard and cabbage are termed as Pythagoras. these were used against different diseases. Hippocrates

worked on 300 medicinal plants. In his works, fever was treated by Centaurium umbellatum Glib and wormwood whereas the antioxidants of garlic were used against intestine parasites and worms. Deadly nightshade, henbane, mandrake and opium were famous narcotics whereas emetics included hellebore and European wild ginger. Oak and pomegranate were used as astringents while the onion, asparagus and garlic were benefited for hydration (Petrovska BB, 2012).

Theophrastus worked on botanical science writing "De Causis Planetarium"—Etiology of Plants and "De Historia Planetarium"—History which is quite famous. He worked on 500 medicinal plants such as hellebore, pomegranate, mint, iris rhizome, cinnamon cardamom garlic and monkshood. He also defined the line of toxicity of herbs and plants so that humans can be saved from the plant's toxin. The doses were elaborated for the first time of plant-based compounds. His merits and classifications of medicinal plant accomplished popularity and gained the title of `father of botany`. Celsus wrote `De re medica` explaining the usage of 250 medicinal plants known at that time and his discoveries led to the saving of lives. The plants more commonly stated were aloe, cinnamon, hellebore, cardamom, star gentian, flax seeds, pepper, henbane and poppy (Petrovska BB, 2012).

The most extrusive writer Dioscorides changed the history by his prominence work of "De Materia Medica." Dioscorides is the pharmacognosy`s Father who travelled with roman army which made him discover the exotic medicinal plant. His works are translated to several languages. The book described 944 drugs out of which 657 were plant based describing the origin, mode of extraction, locality, and their therapeutic effect on human and mode of action. The book contains the plants with dominant effect and alkaloids such as poppy, henbane, jimson, Ranunculus and belladonna. Dioscorides described the Chamomile and used it as antiphlogistic to cure and heal the bee stings, wounds, burns, ulcers and sterilizing and cleansing eyes, nose and mouth mostly in children. The most pronounced domestic plants explained are willow, mash-mallow, parsley, sea-onion, coriander, sage and false hellebore (Petrovska BB, 2012).

Not only wound treatment, chamomile had abortive action accelerating menstruation, discharge of urine, renal stones and reproductive actions. This statement was first not believed by other botanist of times but then were embraced lately by romans and Arabs. The Matric aria was named after mother and uterus. Dioscorides used Mentha for the treatment of aches such as of stomach and head.

while sea onions and parsley were used as diuretics for the body. Oakbark worked for gynae disorders. Scillae bulbus was applied to cardiac arrests and as expectorant. An apprentice of Dioscorides Pliny the Elder travelled at Germany and Spain writing "Historia Naturalis'' describing 1000 medicinal plants incorporating the knowledge of his mentor. (Petrovska BB, 2012).

Moving towards the journey of Greek Era, Greek civilization is epitome of philosophy, art and science with markable works in the book of history. Aristotle is eminent philosopher who described 500 pharmaceutical drugs used to cure the pathological conditions and influencing branch of phytopharmaceuticals. Hippocrates of 337 to 460 BC is a renowned Greek philosopher famous as father of allopathy. Describing the physiology of human systems Hippocrates explained number of diseases with their specific treatment which included the normalizing of imbalance of body-systems and hormones. He included 400 medicinal samples while his student Theophrastus mentioning 500 crude drugs. Galen prepared drugs originated from vegetable using several different extraction techniques termed as Galenical's (Khan, 2014). An ancient Greek holistic medical system old enough as 2500 years which is named as Unani having a profound effect. It considered traditional medicines and gained attention in India, Arab countries adding to national health care system (Yuan et al., 2016).

Arabs have great named in the pharmacology and introduced bundle of bioactive compounds emerging as leaders of pharmacotherapy. Many medicinal plants were persisted in pharmacopoeias of today's world. the most named plants are aloe vera, cinnamon, senna, rheum and pepper while Senna folium was used as mild laxative replacing the mild drugs with strong action drugs. Before Senna, euphorbium the purgative was known and used. Middle age European acknowledged the work of John Mesue preferably De Re Medica. Who is not aware of the greatest Cannon medicine of Avicenna who gave a new look to the medicine and surgery (Petrovska BB,2012). Ibn Sina (Avicenna) is father of Greco-Arabic school of medicine. Ash-Shifa is a methodical encyclopedia with sea of knowledge about the healing, treatments and toxicity of plants. the therapeutic effect of drugs is also explained in his book which still inspires the scientist of 21st century. Abu Musa Jabir Bin Haiyan wrote the books on plant poisons and antidotes of those poison (Khan, 2014). "Liber Magnae Collectionis Simplicum Alimentorum Et Medicamentorum" by Ibn

Beitar was famous for its description of over 1000 medicinal plants (Petrovska BB, 2012).

Arab physicians translated Greek roman books and introduced the portion control and healthy means of living with physical activity as Arabs are pioneers of basics of pharmacy. They set the foundation for drug store, diagnostic criteria for diseases and drug extraction and formulation. Jaber Bin Haiyan was a Muslim chemist who extracted alcohols, sulfuric acids, nitric acids. Quran already termed various medicines and led to new beginnings in the science of medicine. The Islamic books and Sunnah specified the hygienic lifestyle years ago but now they are being proved by the scientist of today. Ali ibn Rabb an Al Tabari was a Muslim scientist famous for his works of Firdous Al Hikmet with 11 parts out of 7 were dedicated to pharmacology drugs and medicines and poisons (Khan, 2014). Arabs also traded plants and spices from Indians, the Ayurveda famous as mother of therapies is a traditional Indian medicine. This is the oldest set of treatment described as ancient scriptures, a Rigveda and Atharvaveda. This is a natural healing system comprising of physiologic and holistic medicines as it describes the man made of 7 basic tissues which work side by side and any misinterpretation leads to disease (Khan, 2014).

China used its traditional Chinese treatment for centuries until western medicine was introduced finally and was in use in 19th century with advancements of field. Traditional Chinese medicine has important role in medical practice and experience as it is enriched with long experimental techniques with evident effectiveness and efficacy saving millions of lives. China has advancement in development of techniques of dosage, preparation techniques and processing of materials and time of extraction of parts of plants (Yuan et al., 2016).

This oldest system has surprised the scientist with is glory of unique theories and therapeutic approaches towards treatments. The evidence-based approach is now recognized as truer which makes the traditional Chinese medicine to be influential to field of medicine. Fu His received Global recognition as he addressed the exogenous factors engaged in pathology field. Shen Nung and Hong Ti are also famous emperors significantly worked in medicine. Pen Tsao penned his work in Chinese Pharmacopoeias describing remedies for medical problems but the crown goes to Shen Nung for his exceptional work (Khan, 2014).

Cao Yun but Wang Tao contributes to the Chinese medical knowledge by publishing The Waitai Miyao portraying 600 prescriptions and known as “The Medical Secrets of an Official”. His philosophy surrounded the pathophysiology of tongue and diseases related to it along with symptoms. More reputable names are Li shizen and Ben Ca Gang My whose books are used as guide in schooling and the knowledge is passed from generation to

generations in academic curriculum (Khan, 2014). However, there is increasing convergence between traditional Chinese medicine and modern medicine with the advancements in technologies as it is possible to determine the mode of action of herbs along with chemical analysis and evidence of active compounds and theoretical background (Yuan et al., 2016).

As the world progressed towards 19 and 20th century in its full glory, the medicinal plants became endangered. The threat for elimination of medicinal plant was at risk and the therapy started to move from medicinal to chemical based synthetic drugs. This movement was due to the mode of action on enzymes and the changes during medicinal plant drying as the mode of action is based on mode of drying of medicinal plant. The pure form of glycosides, therapeutic drugs and alkaloids were deracinating the drugs from which they had be extracted. The scientist and pharmacologist and botanist investigated and invested their time, experience and knowledge in conventional and traditional medicinal practices and proposed techniques of manufacturing, cultivation and the stabilization of freshly isolated compounds and plants as it was observed that pure form of alkaloids were faster in action but the drug form were long-lasting and fully activated (Petrovska BB, 2012).

Phytotherapy is most commonly used to identify and extract the active components and test their efficacy corroborated by experimental analysis (Petrovska BB, 2012). The cure is behind those active compounds in seeds, skin, flowers, roots or whole plant which can be used as direct or indirect soothing and therapeutic medicinal approach. In the parts of these plants, certain gents are produced and stored referred as bioactive compounds or active agents having a physiological effect on human and animals. These active agents may have synergistic properties which cure different diseases. The compounds can affect others and become stronger cancelling the negative effect pf toxins. These compounds can not only eliminate the drastic toxic agents but can treat cancer as well. The agents are characterized according to their potential to treat. The harmful effect of synthetic and allopathic medicines has encouraged herbal drug scientist too seek more knowledge about plant-based compound. (Jamshidi, Lorigooini, Khoei, 2018).

With the increase of tumors, cancers, infectious and viral diseases the natural products are again under considered by the experts due to multi-drug resistant by bodies. This resistance is risk for efficiency of antibiotics as it makes the pathogens strong to fight them. The urgency of requirement of antimicrobial plant-based compounds has seek the attention of researches and pharmacopeia towards the diversify plant-based drugs, active compounds and phytochemicals. The malignant tumors are becoming resistant to strong medication and chemotherapeutics which recommends the screening for potential medicines with long term effect. This effect underlies in active particles of plant extracts which makes it vital to be extracted and isolated as soon as possible such as Geraniin, polyphenols, Flavonoids,

carotenoids, saponins, Curcumin, Tocotrienols etc. acting on different organ's tissues, cancerous cells (Mustafa et al., 2017).

2.2 Extraction of Bioactive Agents and Its Nutritional Value

Bioactive compounds have gained the interest of scientists when epidemiologic studies showed how efficient it is against cancers and heart diseases along with diabetes. These compounds are present in limited quantity in medicinal plant yet it never fails to amaze the scientist with its sparking extra-nutritional properties. Till now many bioactive compounds have been discovered and is used to in treatment as well such as Flavonoids which are subcategory of phenolic acids and are mainly present in nuts, fruits, vegetables, cereals, olive oil and tea. Phenolic acids have protective antioxidant and favorable properties against tumors, cancer and thrombosis. Soy, whole grains, flax seed oils are rich in phytoestrogens which also have antioxidant properties and immunomodulatory effect on malignant tumors. It can become complex ad they are antagonist and estrogen agonist. An antioxidant hydro-oxysterol is dominant in olives and belongs to phenolics group (Etherton et al., 2002).

Resveratrol is potent antioxidant as it inhibits cancer due to its antithrombotic and anti-inflammatory effects. They are widely found in nuts and red wine. Citrus fruits and herbs are rich with monoterpenes whereas Garlic and onion has organosulfur properties with anticarcinogenic effect. One of vegetables have isothiocyanates which help to cancel the tumors. Tomatoes contains lycopene which is excellent antioxidant protecting against prostate cancers inhibiting the tumor and cancer cell lines. Diet rich in vegetables. greens, fruits, nuts, legumes, whole grains help to combat the tumors and life-threatening diseases (Etherton et al., 2002).

Secondary metabolites are basically Bioactive compounds which consist of flavonoids, peptides, terpenoids and polyketides and the list goes on. These compounds are produces by plants or bacteria as a defense from other organisms and are used by humans in different drugs for its exceptional properties. These active compounds are antibacterial, antifungal, antiviral, antioxidant, antitumor, immunosuppressive and are potential in curing against countless human diseases. These bioactive agents and phytochemicals have complex molecular structure which makes them unique and their biochemical pathways help to fight the tumors as well. The secondary metabolites which exhibit important roles as a biological activity in drugs in phytotherapy involves non-ribosomal peptides and polyketides which are synthesized by non-ribosomal peptides synthetases (NRPS) and polyketide synthases (PKS) enzymes. Many other enzymes are present in the structure of bioactive compounds which have key role against diseases (Graca, Calisto, Lage, 2016).

The secondary metabolites exist in plants for the plant growth and development. They have a biosynthetic and metabolic route for the development of plant and constituting of

carbohydrates, amino acids, lipids and proteins for different biochemical process in plants. these metabolites can be randomly synthesized mainly as a defense against other toxins to plants. phylogenetically these could play an important role for human or toxins for human cells. Flavonoids act as fighter to free radicals during the process of photosynthesis whereas terpenoids are seed dispersers inhibiting the competing plants. Alkaloids are also very crucial as they protect the plant against phytoalexins while other compounds help in cellular signaling and as functional foods. The medicinal plants are important and till the 20th century they were used as powder of whole plant or the parts and extracts of plants. With the development of modern science, the pure compounds are now extracted and isolated direct from desired plant and used against diseases (Bernhoft, 2010).

Ethnopharmacology is branch of science in which plants and micro-organisms are used to extract bioactive compounds and chemicals. This field is defined as the identification, Observation, description, and experimentation of the ingredients and compounds potential for treatment of diseases and effect on indigenous drugs by use of traditional or modern medicinal plans (Bernhoft, 2010). The complete analysis of small molecules, cells and compounds in an organism is known as metabolome, metabolomics, metabolic fingerprinting or metabolic profiling. For the extraction of metabolites from plants the variation is studies under the decisive and complex level of postgenomic metabolomics analysis. Transcriptomic and proteomic analysis are used to measure and analyze the changes in gene expression and formation of metabolites fluxes along with analyses of post-translational control of enzymes involved. Whereas metabolite fingerprinting is a complete screening of tissue with discrimination and comparison to other (Mustafa, Atta, Sharif & Jamil, 2017).

The metabolome is extracted when the medicinal plant is verified and identified in phytotherapy. The bioactive compounds are observed and located in fractions by the process of `` Bioassay guided isolation``. This isolation technique has successfully extracted bioactive agents. The process uses solvent with increasing polarity, the identifies compounds are then tested by bioassays by use of relevant enzymes and micro-organisms. When bioactivity of the chemical agents is classified and button downed to specific fractions, these fractions are then separated by chromatographic technique based on properties of hydrophobicity, size and charges. The journey from desolation of pure natural compound in original plantae is complex. The compound isolated than move to next step of structural elucidation which is performed by spectroscopic methods. These methods include MS, IR or NMR methods and x-ray crystallography. Then the bioactive compound undergoes toxicity test and at last clinical trial for efficacy, side-effects and the 24-hour dose testing (Bernhoft, 2010).

The through qualitative along with quantitative investigation of intercellular metabolites

reveals the biochemical status of the plant used. This analysis helps to monitor the genes involved, transmission, mode of action and functions. Liquid chromatography-mass spectrometer LC-MS and proton nuclear magnetic resonance (1H NMR) detects metabolites for the metabolic fingerprinting. Different chromatography including liquid & gas chromatography combined to mass spectrometer which becomes as most efficient method for comprehensive analysis and investigation of ultracomplex metabolite samples. The segregation of molecules in biofluids using liquid chromatography can decreases the ion suppression by reducing the number of competing metabolites placed in mass spectrometer ion source at a time. The selective approach for the quantification and structural information is acquired by this chromatography technique. The traditional isolation techniques of biological, fluorometric and immunological approaches are being recouped by the combination of chromatography with mass spectrometer with benefits of increased sensitivity along with selectivity (Mustafa, Atta, Sharif & Jamil, 2017).

Proton nuclear magnetic resonance is an accurate, quantitative and comprehensive metabolomic technique to isolate bioactive compounds from the plants. The NMR is used in two basic approaches. The first technique involves only spectral patterns such as chemical shifts and intensities. The statistical tool used is named as PCA (Principal components analysis) known as chemometric approach. The other approach the known compounds in extract are identified using a spectral library for quantification. The second approach is named as targeted metabolomics approach (Dayrit & Dios, 2017). As plant based active compounds are important commercially in pharmaceutical food and drug industries which enhances need for significant and potent extraction method. The active compounds are reextracted from conventional and modern methods determining the source nature, the chemical structure and science of compounds (Azmir et al., 2013).

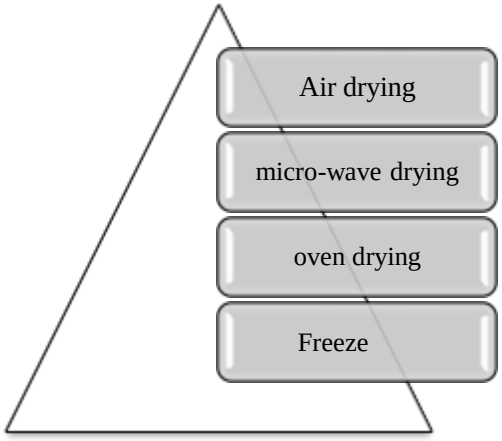
The classical conventional methods include the techniques of maceration infusion, hydro-distillation, steam, decoction, percolation and digestion along with Soxhlet extraction. Whereas the unconventional method is termed as green technologies including ultrasound, pulsed electric field-assisted extraction, microwave, supercritical fluid extraction, microwave and pressurized liquid extraction. In this non-conventional the organic solvent consumption is decreased along with energy which makes them profitable and safe for environment. The yields of bioactive compound are affiliated to methods, temperature, solvent and pressure of extraction which makes non-conventional methods beneficial as conventional methods have a long processing time and involves high temperatures with high consumption of pure organic solvents and lower extraction efficiency (Omeroglu et al., 2019).

2.2.1 Pre-Extraction Method of Bioactive Compounds

To identify bioactive compounds the medicinal plant first undergoes pre-extraction method.

The plant samples are observed for biomolecules which include roots, bark, stems, fruits, seeds or flowers of the plant. These samples can be isolated from fresh or dried plants and then are grinded or dried ad required for the preservation of bioactive compounds in the final step of extraction. Dried samples are the preferred as fresh samples are fragile and deteriorate faster. The sample can be grinded to lower the size while increasing its surface area. Grinded sample have coarse smaller particles of extract whereas the powdered one is homogenized with butter surface contact with the solvents. The smaller the particles the efficient the extraction therefore pre-preparation is an important step. Millis, electric blenders, mortars, rollers can be used to reduce the size as particle size influences the extraction using enzyme (Azwanida, 2015).

For drying the sample for techniques are observed as following (Figure 1.1)



Air Drying is a technique which takes week to months and up to year depending on sample size and type of sample. The extracts are dried at ambient temperature preserving the heat-sensitive compounds. the disadvantages involve the risk of contamination and prolong time. Microwave drying involves the use of electromagnetic radiation. while electric radiations cause proper equal heating by dipolar rotation with oscillation which causes collision of molecules that results in quick heating. The disadvantage includes degradation of phytochemicals. Oven-drying uses thermal energy to remove the moisture and lowering water activity. This is easiest and rapid preparation method which preserves the bioactive compounds. the other preparation step is freeze drying working on principle of sublimation. The temperature is -80°C to -20°C before lyophilization. Sublimation can be defined as the change of solid residue to is change to gas directly. The sample observes 12 hours of freezing and then is immediately lyophilized to prevent the sample from melting. This method is efficient but expensive and complex (Azwanida, 2015).

2.2.2 Extraction of Bioactive Compounds

The next final step is of extraction which separate the plant metabolites, phytochemicals and bioactive compounds leaving the insoluble cellular residue. The processing techniques

involved in extraction of various categories with pros and cons such as (Azwanida, 2015)

Microwave assisted extraction (MAE)

Ultrasound-assisted extraction (UAE) or sonication extraction

Supercritical fluid extraction (SFE)

Accelerated solvent extraction (ASE)

Maceration, infusion, percolation and decoction

Soxhlet extraction or hot continuous extraction

Microwave assisted extraction uses the energy of microwave which segregate the analytes in the used solvent. The radiation combines with dipoles heating the surface and transferring it through conduction. The hydrogen bonding is disrupted by dipolar rotation, the ions migrate and enhances the solvent penetration. The non-polar solvents heating is low when energy is transferred by dielectric absorption. MAE has less extraction time and solvent volume with improved recoveries f metabolites but can cause degradation of heat sensitive compounds. Ultra sound assisted extraction consist of waves from 20 kHz to 2000 kHz. These ultrasound waves increase the surface contact of metabolites to solvent and permeability of the cell walls by mechanic effect of acoustic cavitation. The plant cell wall ruptures and releases the compounds. the UAE is simples low-cost process with less extraction time but can cause formation of free radicals (Azwanida, 2015).

The other method which involves the dense-gas is termed as Supercritical fluid technique. The factors pressure and temperature are important determinants. The initial cost of equipment makes it complex. Another important method is ACE method which involves the use of minimum amount of liquid solvent. The sample is first packaged into inert material (Sand) in stainless steel extraction cell to avoid aggregation. ASE technique depend on solvent types and require less time of extraction. In Maceration technique the sample is first soaked in solvent and then is rested for 3 days at room temperature with frequent agitation. This step softens the cell wall and breaks it to release the phytochemicals. Followed by filtration heat is given by conduction along with convention. In infusion, plant sample is added in boiled with option of cold water. Whereas Decoction is best for materials which are stable to heat. Percolator is used in percolation and done at moderate rate until the extraction process is completes before the evaporation. This is done for extraction of concentrated compounds. The Soxhlet technique involves the use of porous bag made of cellulose. In this sample is added to thimble than in chamber. The solvents are subjected to heat which hen vaporizes and condenses in condenser and then drip back in container. This can be dangerous as the sample can come in contact to flammable solvent with toxic emission and is costly contributing to pollution. The factors under considered are the dry powder, agitation speed, solvent-sample ratio, temperature which makes it complex to use (Azwanida, 2015).

2.2.3 Isolation of Bioactive Compounds

Isolation of bioactive compounds from plants is a developing technique undergone several improvements over the years. The advanced technique allows the availability of bioassays and offering more precision of techniques. The technique involves the simpler, specific and speedy methods which search for bioactive compounds screened for properties such as anti-bacteria, toxicity, anti-oxidant and cytotoxicity. In vitro methods are more desirable and inexpensive. Isolation could be different for different parts of plants as different tissues produce similar or unique compounds with diverse physiology and chemical properties. The selection and collection followed by retrieval of ethno-botanical information to differentiate bioactive molecules are the essential steps of isolation. To purify and isolate extracts are made experimenting with different solvents that are responsible for the bioactivity of compounds. Column chromatographic techniques, high pressure liquid chromatography, UV-visible, mass spectrograph and nuclear magnetic resonance with Infrared comprises of potent techniques for isolation and purification. Moreover, chromatography consisting of Silica gel is also known for extracting bioactive compounds (Ammar et al., 2017).

2.3 Nutritional Importance

Bioactive compounds known as nutritional compounds are being researched to evaluate the impact on health. Epidemiologic researches conclude its protective and beneficial effect on several diseases. Several bioactive compounds have been discovered and grouped accordingly to their structures and properties (Etherton et al., 2002). Vegetables, legumes along with fruits are reservoirs of bioactive constituents. Bioactive compounds have a great effect on health as it fights with different diseases of humankind and possess antioxidant, immunomodulatory, anti-bacterial, anticancer, antihypertensive and anti-osteoporotic along with antidiabetic properties. They are also effective in cardiovascular diseases (Rashmi et al., 2020). These nutritional properties are discussed as below;

2.3.1 Anti-Oxidant Importance of Bioactive Compound

Bioactive compounds are known for its rich antioxidant properties. Antioxidants are defined as compounds that can scavenge the oxygen free radicals as they have unpaired electron in the outer orbits. These free radicals result in their instability and high reactiveness. Cumulative oxidative damage in human body is really dangerous leading to onset of different diseases and cancer. The body has defense system against the free radical such as oxidative stress. Dietary source of antioxidants is important as it helps to manage to decrease the oxidative stress due to free radical induced damage. Antioxidant dietary compounds are associated to prevention of benign or malignant tumors and carcinoma (Skrovankova et al., 2015).

With exposure to pathological and different physicochemical states, our body generates reactive nitrogen species along with free radical reactive oxygen species. But balances are maintained by our body for proper physiological functions by endogenous systems. If free radicals exceed disturbing the ability to regulate immunity, body undergoes oxidative stress. It destroys cells altering the chemical composition of lipids, fatty acids, proteins, enzymes and DNA leading to number of diseases. An external source of antioxidant helps to fight the oxidative stress. Some synthetic antioxidants such as butylated hydro-oxynisole or butylated hydroxytoluene could be brutally dangerous to human health so natural bioactive compounds are life saver (Lobo et al., 2010).

Free radical damage occurs highly in lipids causing lipid peroxidation that results to adverse effects. However, damage in protein alters enzyme activity. carcinogenesis occurs when damage is done to DNA. Similarly, mutagenesis is also caused by damage to DNA. Plants are enriched with bioactive compounds which has endowed us with antioxidant properties such as glutathione peroxidases, vitamin E (tocopherols and tocotrienols), vitamin C, catalase, superoxide dismutase (SOD), and phenols and flavanols (Devasagayam, 2004). Berries, tomatoes, carrots, Mushrooms, plant-based oil such as sunflower oil etc. Berries such as strawberries, black berries, raspberries are rich in bioactive compounds. the key compounds are phenols, anthocyanins and carotenoids which add color to them. The phenolics such as hydro benzoic and hydroxycinnamic are present in diversity along with flavonoids and tannins such as proanthocyanins and hydrolysable tannins (Skrovankova et al., 2015).

2.3.2 Anti-Mutagenic Importance of Bioactive Compound

DNA mutation can occur when oxygen free radicals induce hydroxyl radical and super oxides. Damage in the DNA lining causes autoimmune diseases, cancer, diabetes, chronic inflammation, sclerosis and heart diseases. Damage includes the denaturation of protein or DNA Mutation which can cause cancer. Bioactive compounds are also anti-mutagenic including ascorbic acids, vitamin E, polyphenols and flavonoids. Carotenoids also provides favorable protection to consumers (Kadum et al., 2019). The action of these compounds helps to maintain the balance in the body. These compound act as protective agents against carcinogenesis at its initiation, or progression stages or they may destroy complete the mutagens which block the DNA functions or damage them. Hence cell mutations are avoided in such a way. Flavonoids have antigenic property and are stable to heat, light and oxygen, and are moderately acidic (Horn & Vargas, 2003).

Environment is present with various genotoxic chemicals which have not only caused cancer but alterations in genetic makeup. These genotoxic chemicals cause disability by production of free oxygen and nitrogen radicals and dimers causing tumors. Whereas, Cancer is known by unstoppable number of cells causing formation of tumors.

Mutagenicity and carcinogenicity are correlated as mutagens leads towards the progression of cancer to last stage. To counteract its effect antioxidants are given which inhibit the oxidation of compounds breaking radical chains and chelating the catalyst metals. Mutagens are counteracted by antimutagens. Antimutagens are the bioactive compounds in plants which minimized the mutagenic effects of mutagens or carcinogens. The antimutagenic properties of plant products are due to presence of flavonoids, phenols along with secondary metabolites present in plants (Sharma & Adarsh, 2016).

Some of the plants which are determined as anti-mutagenic are Citrullus colocynths, Asparagus racemose, Ipomoea batatas, Glycyrrhiza glabra, Curcuma zedoaries, Panax ginseng, Withania somniferous. Citrullus Colocynths belongs to Cucurbitaceae and is known as bitter apple. Mainly its seeds are used to extract the anti-mutagenic bioactive compounds. Asparagus Racemose are plants which promotes wellbeing by increasing the cellular activity and are potent antiepileptic, antimutagenic, anticancer and helps in treatment of male genitalia and spermatogenic irregularities. A. Racemose have shown anti-cancerous effects on sodium azide induced mutation and tumors by 4-nitro-ophenylenediamine (NPD). Ipomoea Batatas are sweet potatoes belonging to Convolvulaceae containing tannins. Phenols, saponins, coumarin and triterpenes. Roots are used for extraction of these. Cymbopogon citratus are lemon grass with its leaves containing tinnevellin glycoside, along with D-3-O-methyl inositol and anti-cancer kaempferol. Senna is planting whose leaves are filled with potential compounds such as flavonoids, apigenin, quercetin consisting of anti-mutagenic activity (Akram et al.,2020).

2.3.3 Anti-Diabetic Importance of Bioactive Compound

Bioactive compounds from medicinal plants are effective anti-diabetic for the type 1 and type 2 diabetes. Plants which are termed to be anti-diabetic include aloe vera, Curcuma Longa, perilla frutescens, Caesalpinioideae, Allium sativum, Syzugium Cumini, coccinia grandis, Vachellia nilotica and Artemisia dracunculus are major medicinal plants in controlling diabetes. Bioactive compounds used in the for cure are resveratrol, hesperidin, epigallocatechin-3-gallate, naringin, anthocyanin, lycopene, ascorbic acid, vitamin D and tocopherols (Awuchi, 2021).

Plant derived bioactive metabolites includes steroids, lignans, phenols flavonoids which are antiallergic, anticancer, antidiabetic and anti-inflammatory. Diabetes mellitus is chronic diseases which occurs due mutations in pancreas β -cells. Hyperglycemia is due to decrease insulin production by means of pancreatic (type 1 diabetes mellitus) or insufficiency of insulin and insulin resistance in type 2 diabetes mellitus. Contemporary medications for diabetes cognizance on maintaining and reducing serum glucose ranges. However, maximum current capsules have many consequences inflicting a few critical medical issues throughout a duration of treating. (Tran N et al., 2020).

The growing attention of the protection of medicinal flora, dietary therapy, and treatments are used widely for illness including Diabetes (DM). Medicinal Bioactive agents helps in metabolic activities in human beings, generally ensuing in advanced fitness and preferred well-being. They may be in large part observed in fruits and veggies, medicinal plants, complete grains, and so on., consuming daily. The activity of these compounds is generally pronounced in cell research, frequently including cellular pathway, free radicals, with reducing infection. Thus, safer treatment is a healthy outcome of bioactive plant constituents (Awuchi, 2021).

Vitamin A, Vitamin D, tomatoes, garlic, Gray Nicker, Brazilian orchid tree, cinnamon, ginseng, cow plant, mango, sweetie, fenugreek, bitter ginger, S. spinosum, Asparagus, buckwheat, figs, apples, Citrus fruits, liver oil of fish, carrots, broccoli, sweet potato, Grapefruit, pumelo, tomatoes, grapefruit juices are rich sources of anti-diabetic bioactive compounds. Vitamin E consist of antioxidant structures in tissue with fat soluble vitamins (4 tocotrienols and four tocopherols). It is thought as effective healing opportunity for diabetes (Awuchi, 2021).

2.3.4 Anti- Aging Importance of Bioactive Compound

Aging is a natural biological process in which a person undergoes various bodily changes over the time. Reactive oxygen species and free radicals have great deal of effect on aging and are correlated to each other. Ageing, a gradual process of physical deterioration that in every dwelling organism which occurs with time. As seen in reality, growing old is linked with substantially increased illnesses such as diabetes, tumors, Alzheimer's disorder, cardiovascular ailment (CVD) leading to deaths. Ageing biologically is differentiated through the deterioration and damage of functional capacity by decrease of intracellular activity contact, homeostasis, and regeneration of cells. About one hundred fifty thousand humans internationally die with cause of old age and around -thirds die due to sicknesses related to ageing. Numerous toxins are associated with age-related decrease of capabilities including reactive nitrogen and oxygen species. (Dhalaria et al., 2020).

Free radicals such as reactive oxygen species are produced through various process including genetics, environmental toxins and physiological activity. Consequently, an hyperproduction of free radicals destroys biological system resulting in oxidative pressure, which is the leading issue within the improvement of numerous degenerative and age-related continual problems. (Dhalaria et al., 2020).

Antioxidants are the natural components of fruits along with greens shielding the cellular lining from oxidative radicals. They work by first neutralizing the radicals then by scavenging. Nutrients in fruits have amazing significance and are center of attraction globally for scientist because of their nutrition, scrumptious palatableness, nutrients, and fiber thus lowering occurrence of diseases. Polyphenols, tannins, isoflavones, lignans,

Pterostilbene, resveratrol, and quercetin have positive effect on antiaging as it reduces oxidative stress and have beneficial effect on human health. Anti-aging compounds are present in apples, berries, grapes, oranges, cherries. They help to control cellular damage by senescence and oxidation and chronic illness such as CVD and cancer. Bioactive compounds scavenge the reactive species, induces endogenous antioxidant responses through Nrf2-dependent gene, decreasing the oxidative radicals by diminishing production NADPH oxidases and electron leaking in mitochondria (Dhalaria et al., 2020).

2.3.5 Anti-Hypertensive Importance of Bioactive Compound

Hypertension is disease in which blood pressure rises indicating > 140 mmHg as systolic with greater than 90 mmHg as diastolic, results based on 24 h. Hypertension is a leading cause of death (Malinowski et al., 2020). "Bioactive compounds" are enriched with components which generally arise in portions in plants. They're being thoroughly studied to assess outcomes for fitness. The clinical research stated proven defensive outcomes of healthy diets on cancers. (Etherton et al., 2002).

Phenolic compounds, which includes their flavonoids, are found in all flora thus researched significantly in nuts, grains, legumes, oils, veggies, wines and green tea. Phenols are antioxidants specifically studied for its reaction against tumor and thrombi formation. Despite the fact that a few epidemiologic research have pronounced defensive associations among these categories of phenols with diabetes, CVD and malignant tumor. While other research has now rejected these links. Diverse Phyto-estrogens are found in soy plant, seed oil, and veggies. They are antioxidants as few research validated beneficial impact on different factors causing cancer. (Etherton et al., 2002).

Hydroxytyrosol are found olives as phenols, is a robust compound. Resveratrol, located in crimson wine, and nuts has anti-thrombotic properties, preventing carcinogenesis. Lycopene in tomatoes are essential carotenoids used as defense against cancers, and slows down the tumor cell growth. Organosulfur compounds, isothiocyanates and monoterpenes in orange, lemons, cherries, and herbs have anti-carcinogenic effects (Etherton et al., 2002). Bioactive peptides are more likely to be effective against hypertension and CVD. Angiotensin 1- converting enzyme regulates the blood by catalyzing the hydrolysis of angiotensin 1 to angiotensin II. Angiotensin II is strong vasoconstrictor and octapeptide. Hypotensive effect is induced by ACE-inhibition. Another way is that Angiotensin 1-converting enzyme inactivates bradykinin, a vasodilator which regulates biological process such as release of vascular endothelial nitric oxide (NO). Increased protein intake has tackle CVD and have reduced blood pressure. Bioactive peptides have crucial role as they are inactive within the parent protein. the type depends on sequence of the source protein and the enzymes specific to generate peptides. The hydrolysis of these peptides has produced various opioid, anti-hypertensive, immunomodulatory, and antioxidative peptides. Thus,

proteins from plants have great impact on CVD and hypertension (Pihlanto & Mäkinen, 2013).

2.4 Treatment of Diseases with Medicinal Medicines

Intake of dietary compounds that are nutritionally active such as flavonoids, terpenoids. Anthocyanidins, phenolic compounds are associated to counteract the illness and chronic diseases along with cancers. They are enriched in greens and fruits. These active agents have shielding outcomes working by a systematic mechanism. Malnutrition have led towards severe diseases (Silva, 2019). Following are the diseases and related bioactive compounds that have helped to cope the illnesses.;

2.4.1 Diabetes

The compounds that are biologically active in different species are enrich with antioxidant, immunoprotected and anti-inflammatory effects have defended against chronic illness such as diabetes Mellitus, malignant tumors, osteoporosis, hypertension etc. Flavonoids, lycopene, genistein, Anthocyanins and anthocyanidins are effective anti-diabetic components. Flavonoids and Iso-flavonoids are polyphenolic compounds. enriched in various fruits (Melon, Berries, Apple, Bananas etc.) & vegetables and makes great portion in diet. Flavonoids have anti-inflammatory effect and according to studies flavonoids have lower the severity of diabetes along CVD. It has also lowered the LDL-cholesterol, endothelial cellular function and insulin sensitivity. Lupine, soybeans, fava beans are sources for Genistein which have been essential in treatment of diabetes and exhibiting healthy impact on β-cell. According to reports, genistein was given to postmenopausal women. The results shown that it helped in decreasing the fasting glucose levels and increasing the insulin sensitivity (Aanchal Walia, 2019).

Lycopene is present in tomatoes and pink grape fruit. Lycopene works by lowering the free radicals decreasing the glucose level and improving the serum lipid profile. Anthocyanins and anthocyanidins are coloring agents in vegetables and fruits which stimulates the insulin secretion having defensive impact on β-cells located in pancreas. Berries enrich with anthocyanins specially cyanidin-3-glucoside decreases serum glucose levels improving weakened glucose sensitivity. A study done by Weddick resulted that blueberry, apples, pears have considerably lessened the impact of diabetes. Pomegranate have anti-oxidative property which reduces lipid peroxidase and oxidative states of monocytes. Thus, Anthocyanins are considered as functional foods and great bioactive compounds to treat patients with diabetes (Aanchal Walia, 2019).

Allium cepa known as Onion belongs to Liliaceae is known to be enriched for phytonutrients that can survive under harsh conditions. Onions consist of phytonutrients such as flavonoids, phenolics, amino acids, vitamins, this sulfates and essential oils

exhibiting anti-inflammatory, anti-diabetic and ant-oxidant properties. Quercetin, allicin and alliin are major biochemical constituents. Allium Cepa consist of S-methyl cysteine sulfoxide and Organo-Sulphur's such as S-allyl cysteine sulfoxide which have been proven to fight diabetes by lowering blood glucose levels with hypoglycemic potential. They work by stimulating insulin production, absorption and use of insulin in body. Similarly, Allium sativum, scientific name for garlic is proven to control the insulin excretion from β-cells of pancreas enhancing the glycogen synthesis. Its ethanol extracts restore the delayed insulin response and decreases blood glucose levels. Aloe vera water consist of antioxidant, antimicrobial, antidiabetic, anti-cancer properties along with essential bioactive compounds such as nitrogenous alkaloids, flavanols, terpenes, phenols and macronutrients which remarkably decreases glucose and work against DM (Tran, N., Pham, B., & Le, L., 2020).

2.4.2 Osteoporosis

Osteoporosis is more common in women and is a skeletal disease in which bone suffers from fractures and weakness due to several reasons other than injuries. Normal bone strength consists of optimal bone mineral content and quality. The complete bone process starts from childhood and is complete during early twenties and the reaching peak bone mass during youth. After bone has reached its peak, a continuous remodeling occurs in the rest stages of life. The process of remodeling starts with osteoclast removing resorption pit, switching place with osteoblast which fill the bone with new bone cells. Women tends to suffers from osteoporosis more as the bone remodeling slows at menopause and a rapid bone loss is observed after post-menopause. Plant protein such as soybean isoflavones, n-3 PUFA, vitamin D and calcium are important for healthy bone structure (Sa'eed Bawa, 2010).

According to the Research by (Professor Brenda Smith, 2015), dried plums belonging to group of Prunus domestica L. is excellent source for treating osteoporosis. Dried plums are enriched with phenolic constituents that are not only immunomodulatory but anti-oxidant. Dried plums work by restoring the bone mass by its anabolic effects on bones preventing bone loss. Along with dried plums, tart cherries are also having high amount of phenolics giving promising results against bone loss. Dried plums have also demonstrated the prevention of bone depletion due to ageing and osteoporosis due to menopause. Phenolics in plums have proved to be therapeutic against bone metabolism, and in regulation of osteoblast and osteo clast differentiation, inhibiting osteoclast genesis and promoting osteoblast. Moreover, the research is going on to test its potent immunomodulating properties to suppress T cell and monocyte activation in cases of ovarian hormone deficiency (impacting osteoblast formation causing postmenopausal bone loss) which will prove a great deal towards osteoporosis and bone loss (Smith, 2015).

The most modern therapy against osteoporosis is Hormone replacement therapy in which estrogen loss is ameliorated as estrogen decreases with onset of menopause. Similarly, phytoestrogens have been in interest since then. Isoflavones are Selective estrogen receptor modulators which improves bone loss and heals hip fractures. Raloxifene are non-steroid compound with bind to estrogen receptors and helps in prevention of osteoporosis. Soy protein consist of flavanols and aromatic phenols. Flavonoids are formed by phenylpropanoid-acetate pathway formation occurs due to enzyme chalcone synthase. This is followed by as reaction of condensation using malonyl CoA consisting of anti-osteoporotic property. They can be consumed from legumes which consist of iso-flavonoids category of flavonoids made with one phenolic ring. Genistein and daidzein are also phytoestrogens consumed through legumes and are hydrolyzed in gut to aglycons. Genistein is a miracle towards bone tissue as it has potency of estradiol-1 acting as SERMs interacting with ER acting as estrogen antagonist inducing a response in mammary glands, reproductive glands, endometrial, vascular, endothelial and bone cell lines. So, flavonoids are important in osteoporosis. (Sa'eed Bawa, 2010).

2.4.3 Rheumatoid Arthritis

Rheumatoid Arthritis is a bone disease an erosive autoimmune condition determined by bone destruction as a typic feature of disease. Mostly the bone destruction occurs after the 8 weeks of onset of disease. The principal factor which is a problem is imbalance in bone metabolism as excessive osteoclast mediated bone resorption is under considered along with suppressed osteoblast accumulation in bones. The modern treatment includes the use of non-steroidal drugs, anti-rheumatic drugs, hormones possessing treatment along with side effects if used long term. (Yingjie et al., 2020).

Rheumatoid arthritis treatment involves a lifestyle change, exercise, supplementation and therapies. Chinese have used traditional medicines for a long term in clinical practice and have a quite history of thousands of years. Herbs including Rhizome Drynariae, Fructus Psoralea, Herb Epimedin, Cortex Eucommia along with icariin and naringin are more reported to be effective (Wu L et al., 2017). Soy isoflavones are gonad corticoids metabolizers, inhibiting biological features. They are protective towards bone mass and are favorable to heart diseases and anti-tumorigenesis (Sa'eed Bawa, 2010).

Bioactive compounds known to be effective are extracted from traditional Chinese medicines and are uses for the therapeutic effect on bones. These compounds include flavonoids, saponins, alkaloids and etc. (Shen et al., 2019). Experimental studies have proved that these constituents slow down the destructive factors of bone and increase the regulation of immunoregulators (Cai X. et al., 2018). Terpenoids are also effective anti-inflammatory, immunoregulatory isoprene unit. its bioactive compounds effective in bone

development are triptolide (TP), celastrol, artesunate, parthenopid, andrographolide (AP) which have remarkable effect against bone destruction. Triptolide is anti-rheumatic bioactive compounds with effects such as inducing apoptosis, immunosuppression, and anti-inflammatory reaction. It works by regulating T-cells, dendritic cells and macrophages and immune related mediators which treats synovitis in rheumatoid arthritis. Another mechanism is to delay or completely destroy the bone destruction mediators (Yingjie et al., 2020).

Phenols also have strong impact on bones with its anti-oxidation, anti-infection, anti-atherosclerosis and ani-osteoporotic effect. Along with phenols, resveratrol, curcumin, ferulic acids and terpenoids have protecting effect on osteoblast and osteoclast. According to research by (Baur and Sinclair, 2006), Resveratrol has positive effect on life span of human functioning on heartbeat, Anti-inflammation and centrum restraint along with role as anti-cancer and in treatment of rheumatoid arthritis. It enhances apoptosis of synoviocytes, fibroblast and inhibiting angiogenesis along with regulation signaling pathways such as Janus kinase-signal transducer and activator of transcription (JAK/STAT), p38 MAPK (mitogen-activated protein kinase), NF-κB (Nuclear factor kappa B) etc. They also act as phytoestrogen promoting bone growth. Saponins improves body immunity by promoting ASA VI and Ginsenoside Rg1 (G-Rg1). Saponins pharmacological features include neuro-protection along with improving osteoblast in bone mass, anti-tumorigenesis and decreasing pain. Alkaloids are also been proven as to release histamine and act as sedatives exhibiting pro-inflammatory reaction, pain reduces, and anti-osteoporotic. (Yingjie et al., 2020).

2.4.4 cardiovascular disease

With rise in environmental changes and decrease in intake of healthy fruits and green vegetables, oxidative stress in body has also raised high bars in health chart along with inflammation which has led to cardiovascular disease and atherosclerosis and osteoporosis. Those compounds with anti-hypertensive and anti-inflammatory constituents are more considerable to treat cardiovascular disease (Walia, 2019). CVD and atherosclerosis are chronic inflammatory disease in which Atherosclerotic lesions are present in blood vessels or arteries causing angina, acute myocardial infarction, or cerebrovascular accident. The disease occurs due to formation of plaque which leads to platelet rich thrombi blocking arterial lumen causing ischemia. There may be several factors leading towards plaque formation in which one high lipid accumulation and thinning of fibrous cap. This can be counteracted by used of bioactive compounds (John W. Erdman, 2007).

Flavonoid from plants have reversed the effect of mortal cardiovascular disease and biologically active agents such as quercetin, myricetin, kaempferol, cyanidins, luteolin, and

phenols, ficetin have lowered cholesterol levels and low-density lipoproteins effective in lowering incidence of myocardial infarction. According to women`s Health study subject that women who include berries and green veggies in their dietary habits have lower severity of myocardial infarction along lower rate of stroke. Oxidized LDL cholesterol act as free radical in body and are atherogenic factors leading towards CVD. When these oxidized free radicals increase in number they serve as chemotactic factors initiating plaque formation. Hence antioxidants are exposed to free radicals which stops the progression of disease laying important role in decreasing of accumulation platelet, maintaining cholesterol, decreasing blood pressure and synthesis of prostaglandin hormones (Ilkay Gok, 2021).

Polyphenols and anthocyanins from berries have proved to be effective against CVD. Berries are packed with bioactive compounds, micronutrients with fiber. Since they are best for improving heart health they have been used in treatment for a long while. Berries such as blueberries, cranberries, strawberries, have purified anthocyanins extracts which act as antioxidant improving LDL oxidation and glucose metabolism along with blood purification. The bioactive compounds in berries work by decreasing inflammatory factors and enzymes that digest Carbohydrates along with promoting endothelial cells and decreases oxidative stress and reactive oxygen species. Isoflavones are researched for its properties such as insulin sensitivity, endothelial function and anti-inflammatory effect on body. Flavones, Flavanones, Anthocyanidins, Flavan-3-ols and pro-anthocyanidins all have proved to improve risk of atherosclerosis (Aanchal Walia, 2019).

Bioactive peptides are particles of protein actively used in the treatment of hypertension and CVD. These peptides are opioid, antihypertensive, antioxidative, immunomodulatory or antimicrobial decreasing oxidative stress and reactive oxygen species. These peptides can be extracted from potatoes tubers, flax seeds, milk protein, legumes, rape seeds and cereal grains along with pea and rice proteins that yields the immunomodulatory and anti-inflammatory peptide, oryzatensin best for CVD (Pihlanto & Mäkinen, 2013).

2.4.5 Alzheimer's Disease

Alzheimer is characterized by dementia and is neurodegenerative disease in which an individual suffers from chronic gradual degeneration in brain and cortical areas. According to WHO, in 2015, 29.8 million people suffered from Alzheimer disease leading towards death. Alzheimer disease could be caused by a number of possible factors but mains are age, genetic inheritance, poor diet, obesity, smoking, hypertension, depression, diabetes or head trauma. FDA have allowed certain drugs to manage Alzheimer and it includes use of acetylcholinesterase inhibitors some antagonists but they have side effects and are not the ultimate treatment to prevent progression of disease (You et al., 2020).

Alzheimer occurs due to deposition of plaques especially misfolded Aβ peptide in senile

plaques which causes brain atrophy and inflammation in intracellular neurofibrillary tangles (NFTs). When Aβ peptide production increases it cause neurotoxicity and accumulation causes aggregation into plaque in different forms such as fibrils, monomers, oligomers (most toxic form and insoluble). According to reports, diabetes and Alzheimer share characteristics and are associated along with nephropathy, retinopathy, neuropathy, and atherosclerosis and CVD. Alzheimer is a cognitive disease which impairs one's memory, ability to communicate and perform daily chores and routine work. Oxidative stress, inflammation, glucose intolerance, cognitive impairment, insulin resistance are characteristics involved In Alzheimer disease which requires effective anti-oxidants, anti-inflammatory bioactive factors (Ramesh et al.,2019).

As per research by (You et al., 2020), Qiong Yu Gao which a traditional Chinese herb effective anti-ageing medicine along with Rahmanian Radix used for purification of blood and treating fever, hypertension and work as antioxidant treating autonomic nervous disorder. Moreover, Black currant is rich source for isorhamnetin, anthocyanidins, phenolics and flavonoids. Black currant is also enriched with quercetin, myricetin, and vitamin C giving black currant high anti-inflammatory and antioxidant characteristic. Black currant possesses phenolics which work against cancer, neuropathy, chronic inflammation and Alzheimer disease. Black currant is enriched with flavanols which work against oxidative stress in brain and nerve cells. Moreover myricetin, quercetin and isorhamnetin also have anti—inflammatory neuroprotective activity (Karjalainen R., Anttonen, M., Saviranta, N et al., 2009).

A polyphenol resveratrol can be used to enhance neuroprotection by protecting P12 cells that work against Aβ-induced cell apoptosis. They regulate SIRT1 and promote non-amyloidogenic processing by production of α-secretase enzyme. They also reduce macrophage cell line (RAW 264) activation protecting microglia from Aβ-induced inflammation which causes Alzheimer. Genistein conducts anti-apoptosis by reducing inflammatory properties. Genistein is anti-inflammatory protecting microglia by preventing oxidant mediators and activation of peroxisome proliferator-activated receptors (PPARs). Genistein is a phytoestrogen which also improves learning and memory by reducing oxidative stress through binding estrogen receptors and mediating estrogen mediated process. Epigallocatechin-3-gallate (EGCG), Hesperidin, Curcumin and rutin are bioactive compounds that work as anti-oxidant against Alzheimer (Rongzi Li et al., 2019).

2.5 Rise of Malignant Tumors

Hippocrates, a great Greek philosopher and physician of time and father of medicine describe the word cancer for the first time calling it Karakinos. Carcinos were used to

describe crab in Greek, thus Hippocrates named cancer as Carcinos as they looked like lumps in form of crab. The history of cancer starts earlier than Hippocrates, he did not discovered cancer but termed the disease as ``cancer`` for first time in history. First case of cancer was discovered in 1500 BC in Egypt on papyrus. 8 cancerous tumors were reported highest of breast cancer. Back in history, cancer was treated by a process of cauterization which tissue with tumor is destroyed using the fire drill which was extremely hot instrument. This was the palliative treatment; however, no proper treatment was done (Lisa Fayed, 2020)

Different theories were given to describe the pathophysiology. Hippocrates believed that body consist of phlegm, blood, yellow and black bile. Hippocrates stated that when a body is in excess of black bile it transforms to cancer. This thought was led by people till next 1400 years where as Egyptian named them curse by GOD. After the bile theory came, lymph theory in 17th century, in which it was stated that cancer was caused by abnormalities in the lymphatic system of body. The lymph nodes transform to tumor and cause cancer. Then, in 19th century all the theories were cancelled when Rudolf Virchow discovered that cancerous cells are cells derived from their cells. Different theories stated that cancer spreads through parasite, trauma or like liquid flowing in body. A German Surgeon, Karl Thiersch concluded that cancel spread through malignant cells that spread out in body and organs. Now modern techniques can recognize cancer and treatment such as chemotherapy, radiation therapy is successfully done (Lisa Fayed, 2020)

Cancer is occurred when abrupt multiplication of cells forms a mass and thus due to these hundred different types of cancer exist which behave differently in behavior, pathophysiology and treatment. Cancer is identified on basis of tumors (Cooper GM, 2000). Tumor is defined as abnormality in tissue which occurs when cells grow abruptly in vast numbers and divide continuously without dying (National Cancer Institute). Tumors may vary from size and place of origin. They can be a tiny nodule or large mast of cells. They can appear anywhere on the body and is divided into two types of tumors; (Brazier et al., 2019)

Benign tumor

Premalignant tumor

Malignant tumor

Tumors is defined to be abnormality in body. A benign tumor however is non-cancerous and a common skin intrusion which is not moveable and remains at a place where they first outgrowth. They do not invade normal tissue (Cooper GM, 2000). Benign tumors are not cancerous and they grow very slowly. The treatment involves removing the benign tumors and after removal they usually do not return. Premalignant Tumors are those tumors which have potential to invade other tissues and destroy normal tissue cells. They are not

cancerous but can come malignant (Brazier et la., 2019). However malignant tumor id dangerous to health as they have ability to invade surrounding tissue and organs and can spread through blood or lymph. Malignant tumors are cancer causing as they can metastasize and invade normal cells. Malignant tumor is resistant requires chemo and radiations. However, they often come back after removal. Benign tumors are removed usually by surgery but malignant tumors are difficult to remove and if treatment is not done on first stage it can rapidly progress to the last stage of cancer which have no treatment and can completely destroy the organ or tissue where it has invaded. It can spread throughout the body (Cooper GM, 2000).

2.5.1 Benign Tumor

Benign Tumors are the outgrowth or ingrowth that remain in their location where they grow. They do not invade other sites and do not spread to other tissues or other part of the body. They grow gradually with visible lines. They are painless and do not cause any trouble until increase in size and harden or push the tissues and cells. The compression can cause pain and rashes and inflammation. If a tumor is formed in lungs, it can compress windpipe causing difficulty to breath. Benign tumors are surgically removed and are not likely to reoccur once removed from the body. Common benign tumors are fibroids in uterus. These kinds of tumors can turn towards malignant so it's important to monitor them closely (Patel A, 2020).

Benign tumors are divided on the basis of their location (Brazier, 2019);

Adenomas

Fibroids

Hemangiomas

Lipomas

2.5.1.1 Adenomas

Adenomas are nodules of epithelial tissue they grow in the pulmonary parenchyma compressing other tissues in neoplastic epithelial tissues. Adenomas are solitary with multiple patterns ranging from solid or mixture of papillary (F.F. Hahn, J.A. Hutt, 2010). Adenomas grows beside glandular organs. They can grow in other parts such as adrenal adenoma, colon polyps, parathyroid adenoma, pituitary adenoma, and pleomorphic adenoma. Pleomorphic adenoma occurs in salivary glands and has dual origin from epithelial to myoepithelial. They have noticeably changeable structure with presence of stroma matrix (Bokhari MR, Greene J., 2021) Symptoms of adenoma include abdominal pain, fatigue, headache, anemia, nausea, and rectal bleeding (National Cancer Institute. Adenoma, 2021)

2.5.1.2 Fibroids

Fibroids are also benign tumors that grown on the fibrous of any organ and on connective

tissue. Fibroids are also termed as fibromas. Fibroids are more common in women. Uterine fibroids cause vaginal bleeding, pain, discomfort and urinary incontinence. Fibroids can soft tumors or hard depending on the number of fibrous and cells. Fibromas can appear as red bumps on face known as Angio fibroma or on lower legs as dermatofibroma. Fibroid can become cancerous if not treated especially fibroid in uterus. Fibrous turns to fibrosarcoma's and become malignant. Fibroids can be classified into subserosa fibroids, intramural fibroids and submucosal fibroids depending on its location (Brazier, 2020)

2.5.1.3 Hemangiomas

Hemangiomas are benign tumors that occurs when blood vessels develop excessively. They are able to seem as red pink "strawberry marks" at the pores and skin or they can broaden within the body. They are often developed at birth of child and disappear all through formative years. Hemangiomas do no longer usually want treatment, but laser surgical procedure and other options are to be had if they do now not depart (Brazier, 2019).

2.5.1.4 Lipomas

A lipoma is a spherical or oval-formed lump of tissue that grows just underneath the pores and skin. It's manufactured from fats, actions easily when you contact it and doesn't typically cause any pain. Lipomas can grow anywhere at the tissues and organs, but they're mostly common at the spinal area and shoulder, trunk (torso), hands, shoulders and neck. Lipomas are benign tender tissue tumors. They develop slowly and aren't cancerous. mostly lipomas don't need remedy. Lipomas are very not unusual. about 1 of each 1,000 human beings has a lipoma. Lipomas grows most usually between ages forty and 60, but they could broaden at any age. they can also grow at time of at birth. Lipomas aren't normally painful, but they can be uncomfortable if they press towards a nerve or develop close to a joint. Many human beings who've a lipoma doesn't observe any signs. Lipomas are normally: (Charifa A et al., 2020)

Encapsulated: They don't unfold to the tissues surrounding them.

Painless: some lipomas can cause severe pain and soreness relying on their location, size and presence of blood vessels.

spherical or oval-fashioned: The fatty lumps of rubbery tissue are commonly symmetrical.

moveable: they can be malignant, can settle on the skin and can form bumps.

Smaller than 2 inches in diameter: In a few instances, lipomas may be larger than 6 inches huge.

2.5.2 Pre-Malignant Tumor

Premalignant condition is defined as, which we also may also refer to as precancerous situations, related to abnormal cells that are not cancerous have the possibility to turn into cancerous cells if an affected person doesn't obtain proper treatment and therapy. some of these cells can also have slight changes that can disappear without remedy, but they are

able to take a long time to turn into malignant tumor (Breast Care Center). Premalignant tumor is divided into

Actinic keratosis

Cervical dysplasia

Metaplasia of the lung

Leukoplakia

2.5.2.1 Actinic Keratosis

Another name for actinic keratosis is solar keratosis, this tumor is made of patches of crusty, scaly, and thick skin cells. It is much more likely to have an effect on faired-skinned human with less melanin, and sun exposure will increase the chance. every now and then, actinic keratosis will remodel into squamous cellular carcinoma, so medical doctors typically suggest treating it (Brazier et al., 2019). Actinic Keratoses develops due to proliferation of skin cells due to damage of DNA by Ultraviolet rays' exposure. They may appear due to ageing, high sun exposure, sun burns, predisposing disease or poor immunity (D de Berker et al., 2007).

2.5.2.2 Cervical Dysplasia

The cervix forms a canal, is small tapered end of the uterus. It is positioned between rectum and bladder, opening into vagina. Abnormal growth of cells and tumor formation on cervix is termed as cervical dysplasia. Recognized, as premalignant tumor, occurring due to Human Papillomavirus which transmitted sexually. The cancerous cells can move deeper towards the cervix and other tissues. It mostly occurs in women ageing above 40 and consisting of squamous cell carcinomas and adenocarcinomas (John Hopkins Medicine 2021).

2.5.2.3 Metaplasia of the lung

Metaplasia of lung is also termed as Squamous metaplasia (SQM) which is a precancerous change of bronchial epithelial cells. it is observed in the lung tissue in response to toxic injury by smoke, SQM is neoplastic multistage tumor which can leads towards lung cancer (Rigden et al.., 2016).

2.5.2.4 Leukoplakia

Leukoplakia is pre-malignant condition in which white rough patches are form in mouth which can be painless, irregular in shape, slightly raised and cannot be scrapped. Leukoplakia occurs mainly due to excessive smoking (Brazier et al., 2019).

2.5.3 Malignant Tumors

These are cancerous tumors that have cells which grow uncontrollably and in large number and escalate to tissues or organs. They invade other tissues by lymphatic system and blood flow. Metastasis is spread of Malignant cancer. It can be formed in any site of body tissue

such as lung tissues, neuropathy, bones and liver cells (Patel A 2020). Malignant Tumors can be divided into Carcinoma, Sarcoma, Germ cell tumor and Blastoma.

2.5.3.1 Carcinoma

Carcinoma are tumors that form on epithelial cells of skin, tissue and organs. Carcinomas are malignant and can be formed in colon, breast, pancreas and prostate (Brazier et al., 2019). Carcinoma are abnormal cells that can be divided into Adeno carcinoma with Basal-cell, ductal and renal along with squamous cell. Invasive Ductal Carcinoma is also its type. (Marta & Felson, 2020).

2.5.3.2 Sarcoma

Sarcomas are malignant tumors that forms in bone or muscle tissues. They usually form in soft tissues thus named as soft tissue sarcoma. They can form in muscle mass, fatty stores, vessels, skin linings and nerves and tissues but mostly initiates in Brachium (arms) or lower limbs. Sarcoma develops at neck, abdomen, breast or **retroperitoneum**. They are divided into fifty different types of sarcomas (Singer S et al., 2011).

2.5.3.3 Germ Cell Tumor & Blastoma

Germ cell tumors develops in male and female reproductive system. They may also appear in brain, chest but mostly in male and female genitalia. Blastomas are embryonic tumors develop before birth. these tumors can grow move towards eye or can damage nervous system prostate (Brazier et al., 2019).

2.5.4 Pathophysiology of Cancer

Cancer is characterized by tumor clonality which is defined as the development of cellular mass from single cell that begin to outgrow abruptly in mast and malignant tumors. the single cell of tumor starts with inactivation of X chromosome by conversation to heterochromatin. this inactivation of X chromosomes develops while embryo development. Normal tissue in an individual consists of mixture of cells with indifference of X chromosome activity. this inactivation results in expression of both alleles if we look in heterozygous female. When tumor is studied it states that they are developed from origin of single cell in which X inactivation is fixed. The clonal origin of tumor acquires all the characteristics of cancerous cells. the multistep stages develop into tumor into cancerous cells which progress with series of alterations into tissue. cancer appears late in life. It forms earlier but due to its multistage proliferation it appears with symptoms later on life and ageing. ageing increases the chances of cancer and develops into dramatic multiple abnormalities. This accumulation of cells occurs over period of time (Cooper GM, 2000).

The tumor formation is multifactorial leading towards mutation, proliferation and metastasis. This outgrowth of cell leads to alteration in genetic makeup and causes clonal formation. This clone rapidly forms a mast cell and can travel towards organs and tissues destroying the area where it grows. They can also become resistant malignant due to

invasion and damage of cell lines (Cooper GM 2000).

Oncogenes are cancerous genes which are expressed in high levels and alters the normal genes during the mutation causing cancer. Another gene which prevents cancer is tumor suppressor genes which stops the progression of cell division. they prevent those cells that have damaged DNA. When an individual has cancer, these genes are disabled due to genetic changes. Genomic amplification occurs when cell receives several copies more than 20 of a small chromosomal locus comprising of various oncogenes and genetic material. Along with Genomic Amplification, Point mutations can occur which leads towards cancer. In point mutations, single nucleotides are formed. the mutations develop on the promoter region that changes the protein code and disrupt the gene formation. these leads to formation of single gene from the integration of genomic from virus. retrovirus based gene causes formation of oncogene (Dr. Ananya Mandal, 2019)

Cancer progress into four stages

Stage 0

Stage 1

Stage 2

Stage 3

Stage 4

In earlier stage 0, the cancer I curable and the tumor is in its place. This tumor is usually removed by surgery. Whereas at stage 1 cancer, the tumor has not invaded deeper to tissues and haven't spread throughout the lymph nodes. It detects the early stage of cancer and can be cure. The next stage is the stages in which cancer invades to lymph nodes but not throughout the body. Fourth stage is the last stage of cancer which is often nor curable and it invades through the body damaging main organs and tissues (Cancer.Net Editorial Board, 2021). In the earliest stage of the tumor, increases outgrowth of epithelial cells occur in form of colonies. This proliferation gives rise to benign adenomas or polyps and neoplasm. this adenoma grows and increase in size by multiple rounds of clonal selection and proliferation. These benign adenomas transform to premalignant and then due to continues clonal formation they become malignant. Tumor cells invade nearby tissue and due increase number of cells they spread through the wall of organs and tissues penetrating to other nearby organs. the tumor enters lymphatic system and circulatory system reaching fourth stage cancer and vessel allow them to metastasize throughout body damaging the organs (Cooper GM, 2000).

UV rays and many cancer-causing agents uses detrimental Deoxyribonucleotide promoting mutations. Cancer agents are contaminants invading cells targeting genes and immuno-factors leading to most cancer initiation. A number of products readily available in the market are the contributions to human cancers because they consist of solar ultraviolet

radiation, carcinogenic chemical compounds in tobacco smoke, and aflatoxins. The carcinogens and toxins in tobacco smoke are the reasons of human most cancers. It is cause of almost eighty percent of lung tumors along with oral hollow space and different organs. (Cooper GM, 2000).

Carcinogens also work by cell proliferation, inducing mutations and promoting tumors. they increase cell apoptosis require for the growth of tumor. for example, protein kinase C are activated by phorbol esters. this initiates the process of tumorigenesis (Cooper GM, 2000). The continual inflammatory states related to contamination and infection leading to damage in human genome and formation of tumor. Body fights of any invasion by production of some oxygen species combine to nitrogen and oxides such as super oxides and reactive nitrogen oxides. The signaling pathways are activated by proinflammatory enzymes. High number of radicals damages the DNA (Rakoff-Nahoum S., 2006).

High inflammatory defensive reaction leads to factors in progression of tumor causing movement of cancer cells and invasion into other tissues. They also induce angiogenesis which progress the invasion through vascular system thus growing the tumor. Some proteases along with their inhibiting factors are important for mechanism restructuring the matrix of cells. Permeating leukocytes may also be progressed towards tumor (Rakoff-Nahoum S. 2006). Hormones such as reproductive hormones (estrogens) can promote cancer by invasion of cells in the endometrial lining of uterus causing cancer (Cooper GM, 2000).

2.6 Immunomodulatory Impact of Bioactive Compounds on Cancerous Tumors

Bioactive compounds are the compounds which have ability to interact with the constituents of tissue, cells, enzymes and growth factors having a possible effect on them. The origin of bioactive compounds could be different sources such as plant flora, animals, marine or microorganisms including fungi. However bioactive compounds could be synthetically made and can be used to derive drugs or nom-steroid inflammatory drugs and medicines (Guaadaoui et al., 2014). Bioactive compounds are also termed as phytochemicals, anti-oxidants, anti-cancer, anti-mutagenic depending upon the impact on physiological and cellular level on humans. There are several bioactive compounds which include flavonoids, anthocyanins, carotenoids, phenols, saponins, sterols, tannins and glycosylates. Bioactive compounds are use long ago in history to treat different metabolic disease and due to their protective properties, they are used to develop different functional foods (Aanchal Walia et al., 2019).

2.6.1 Mechanism of Action

Cancer has been the most hectic and major health problem which is leading cause of deaths.

Cancer is able to spread rapidly via metastasis. It is global disease. Many treatments are developed. Chemoprevention is concept in which bioactive compounds, drugs, vitamins, supplements are used to reduce development or progression of tumor. According to different researches, consumption of whole plant is recommended for chemoprevention. The research named as "Sulforaphane Modulates AQP8-Linked Redox Signaling in Leukemia Cells" of authors "C. Prata et al. (published in Vol. 2018)" identifies the cells causing cancer. Some cells such as sulforaphane and leukemia cell exhibits anti-cancer activity (Teodoro, 2019).

2.6.2 Food with Immunomodulatory Compounds

Different compounds have different effects on the cancer. Diosgenin is bioactive compound which have shown various chemoreceptive properties against cancer on various organs. This property has marked great importance of this molecule as anti-mutagenic agent. Diosgenin is a plant whose anti-tumor activity depends on the type of cell and the concentration. Diosgenin has been widely used against lung cancer (A549 cells) breast cancer (MCF-7), (Colon carcinoma (HCT-116 and HT-29 cells), prostate cancer (PC-3 and DU-145 cells), squamous carcinoma (A431, Hep2, and RPMI 2650 cells), hepatocellular carcinoma (HepG2 and HCC cells), erythroleukemia (HEL cells) and gastric cancer (BGC-823 cells) (Mustafa A et al., 2018).

Regarding mechanism of action, many studies reports that diosgenin is associated with exchange of numerous cellular signaling events that are essential for cellular increase/proliferation, differentiation, epithelial-mesenchymal transition migration, and apoptosis, as well as oncogenesis and angiogenesis. in the numerous phases of tumorigenesis, Diosgenin is assumed to set off apoptotic cellular death in diverse ranges of tumorigenesis and thus averting their malignant transformation. The antitumor results of diosgenin have been confirmed, to occur thru p53 activation, immune-modulation, cell cycle arrest, modulation of caspase-3 activation, and activation of the transcription STAT3 signaling pathway (Mustafa A et al., 2018).

Concerning this angle, research have discovered that diosgenin inhibits the growth of osteosarcoma cells via the induction of apoptosis and cell cycle arrest in G1 section and also inhibits the vast metastasis of breast most cancers cells (MCF-7 cells) by way of inducing the proapoptotic p53 protein and an enhance in caspase-3 ranges. except it, the propagation of pc-3 human prostate tumor cells is repressed by diosgenin in a relying on the dose. Diosgenin also shows antimetastatic impact via lowering the cell migration and incursion by using diminishing matrix metalloproteinase expression. Diosgenin is studied to have antioxidant property, due to which it constitutes an interesting approach for lung tumor therapies and treatments. The diosgenin-brought about apoptosis of human erythroleukemia cell line turned into related to growth in range of receptors of

Cyclooxygenase2. Diosgenin have also shown antimetastatic effects by inhibition human breast cancer MDA-MB-231 cells and by partially decreasing Vav2 protein activity (Mustafa A et al., 2018).

Plant Bioactive compounds work by inhibiting cellular activities are activities harmful to health. When carcinogens enter the genome, it interferes with genetic materials causing mutations. The free radicals induced interacts with protein and enzymes and growth factors of cells. This leads to formation of cancerous cells and continuous proliferation transforms cancerous cells to tumor formation. Plants bioactive compounds have been used from centuries to treat different diseases in Egypt and Asian countries. The immunomodulatory impact of bioactive compounds depends on the quality, type and concentration of phytochemicals in it. When bioactive compounds are treated to administer cancel cells the cancel cells go into two fates. In one fate the cancer cells become normal after its contact with phytochemicals. The second fate is the death of cells by the action of phytochemicals. Bioactive compounds promote apoptotic pathways, autophagy and inhibits invasion of malignant tumor along with promotes immune response of body by increasing natural killer cells (Alexander Chota et al.,2020).

Apples are the most common fruits consisting of sugars, minerals and fiber content. Apples are rich source of bioactive compounds including vitamin C, phenols and flavonoids. They consist of anti-oxidants and best source of phytochemicals in diet. Apples consist of phenols as secondary metabolites which gives them their distinct color, flavor, astringency and aroma. Not only positive side but they are responsible for discoloration of apple as well due to oxidative deterioration. Apple consist of health promoters such as almost about 1700 mg of vitamin C and phenolic content ranging from 110 to 357 mg/100 g. Phenols exhibit high anti-oxidant and anti-proliferative property thus present greater amount in skin to protect it from UV radiations. Along with this apple also consist of chlorogenic acid, epicatechin, procyanidin B2, phloretin and quercetin. Phytochemicals in apples help against oxidative stress due to free oxygen radicals. They are the stimulants of immune system and help in regulation of gene expression and normal apoptosis balancing the hormone metabolism. Due to these, apples have carotenoids, flavonoids, isoflavonoids, phenolic acids, lignans and triterpenes which helps to protect against mammary cancer, breast cancer. They act as chemotherapeutic agents. Phenolics from apple help to protect from colon carcinogenesis. The skin of apple can treat human liver-tumor HepG2 cells and inhibit oxidative stress induced membrane damage in neuronal cells (González et al., 2008).

Cranberries are wholesome fruit that make contributions coloration, flavor, nutritional value, and capability. They may be one of most effective three fruits local to the United States. over the past decade, public interest for the North American cranberry (Vaccinium macrocarpon) has been rising with reports of their capacity health advantages related to the

numerous phytochemicals present within the fruit—the anthocyanins, the flavanols, the flavan-3-ols, the proanthocyanins, and the phenolic acid derivatives. The presence of those phytochemicals seems to be answerable for the cranberry belongings of stopping many illnesses and infections, including cardiovascular illnesses, diverse cancers, and infections regarding the urinary tract, dental health, and Helicobacter pylori-triggered stomach ulcers and cancers. Latest years have seen vital breakthroughs in our expertise of the mechanisms thru which these compounds exert their beneficial biological outcomes, but these stay to be scientifically substantiated (J. Côté. Et al., 2010).

Berries are small fruits that grow in cold damp weather regions such as North America and Europe, and some high-altitude locations of southern countries, during the summer to early Autumn (late June to early October). They are small in size and dark and bright in color. Berries include fruits of the genus Vaccinium spp (blueberry, bilberry), Fragaria (strawberry), Rubus (raspberry, blackberry, marionberry, boysenberry), Ribes (red currant, black currant, gooseberry), among others. Berries are enriched with wide range of flavonoids, anthocyanins, procyanidins and phenolic acid derivatives (hydroxycinnamic, ellagic) that possess antioxidant activity. The type and concentration of phenolic compounds depends on harvesting, storage and sun light exposure and temperature of processing conditions. Berries consist of phenolic compounds and anthocyanins, hydroxycinnamate derivatives and flavanols. Berries are beneficial against high reactive oxygen species (ROS) values with DNA damage, heart diseases, cancer, and other chronic and degenerative diseases. Berries exhibit potential protection against cancer due to its chemo preventive properties, anti-inflammatory action, cardiovascular disease preventing features as well as intestinal and urinary infection, reducing properties, among others (González et al., 2008).

Scutellarin is a phytochemical that helps to fight against breast, colon, lung, prostate, renal, and tongue cancers. They work by inducing apoptotic cell death through multiple pathways. They can also destroy cancer cells by cell cycle arrest and proliferative inhibition pathways. Scutellarin induces tumor suppression in prostate cancer upregulation of caspase 3, 9, G2/M-phase cell cycle arrests and Bax/Bcl-2 ratio. They activate caspase-3 enzymes and STAT3 signaling pathway initiating apoptotic activities in liver cancer cell line HepG2. It also suppresses metastasis of hepatocellular carcinomas thru inhibition of Akt-STAT3/Girdin activities. scutellarin inhibits tumor proliferation and inversion via upregulation of Hippo/Yap signaling pathways reducing the risk of breast cancer (Alexander Chota et al., 2020).

Cirsimaritin belongs to flavonoid and exhibit antioxidant, anti-inflammatory, antimicrobial, anticancer, and enzyme inhibitory activities. Cirsimaritin belongs to 7-O-methylated flavonoid possessing anticancer activities which have been observed using different cancer

cell lines, such as breast, lung, and gallbladder. This phytochemical works by inhibition of angiogenesis by the downregulation of p-Akt, p-ERK, and VEGF in MDA-MB-231 breast cancer cells. It also inhibits growth of gall bladder tumor by mitochondrial apoptosis. Moreover, β-farnesene is one of the important sesquiterpenes which is used in the treatment of tumors of breast, lung, and prostate. They work by suppressing tumor by apoptotic pathways in which cytochrome c is release which work with Apaf 1 to create apoptosome that activates caspase cascade to induce cell death. (Alexander et al., 2020).

Another essential bioactive compound is β-sitosterol, which is used in the treatment of different cancers as it possesses anti-inflammatory, antioxidant, antidiabetic, antifertility, antimicrobial, immunomodulatory, and anticancer properties. It prevents tumor cell proliferation and activates the apoptotic pathway of various cancer cell lines. These compounds induce endoreduplication in HL60 and U937 cell lines via PI3K/Akt and Bcl-2 pathways inhibiting tumor cell growth, inducing G0/G1-phase cell cycle arrest, and apoptotic activities, downregulates NF-kB activities, upregulates the expression of Bax, and downregulates the expression of Bcl-2 protein. A-Humulene is a naturally occurring bioactive compound that is extracted isolated from Eupatorium odoratum L exhibiting various anticancer properties. This compound uses multiple pathways to induce tumor cell death by increased production of ROS and inhibition of Akt activation (Alexander et al., 2020).

2.6.3 Cancer and Required Bioactive Compounds

Breast cancer has persisted to purpose high most cancers demise rates amongst women international. Plant based products have validated anticancer potential thru special organic pathways which include modulation of the immune machine. Immunomodulatory features of medicinal plants were proven to mitigate breast tumor cell increase. exceptional immune cell types participate in this procedure especially cytotoxic T cells and natural killer cells, and cytokines which includes chemokines and tumor necrosis factor-α. Medicinal flora which includes Glycyrrhiza glabra, Uncaria tomentosa, Camellia sinensis, Panax ginseng, Prunus armenaica (apricot), Allium sativum, Arctium lappa and Curcuma longa were reported to preserve robust ability in breast cancer treatment. These immunomodulatory compounds consist of ajoene, arctigenin, β-carotene, curcumin, epigallocatechin-3-gallate, ginsan, glabridin and quinic acid (Shu'aibu ,Wong, Keng, Yaacob & Soriani, 2017).

Lung cancer was shown a positive result when given with β-carotene supplementation in non-smoking adults. A diet rich in carotene-rich diet (for example, α-carotene, lutein, lycopene, β-cryptoxanthin, and β-carotene) reduces the risk of lung cancer in non-smokers. Another important cancer which is prostate cancer. Different researches proved that carotene helped to reduce the risk of prostate cancer. Lycopene from tomatoes have been really effective as it enhances oxidation stress defense system. According to research

studies, β-carotene has been shown to play a crucial role in preventing against cancers of breast, head, mouth, pharynx, and larynx and lungs. These studies have further reported that consumption of high fruits and vegetables in diet could reduce the risk of head and neck cancers by as much as 50%. Similarly, observational research data have also proved correlations between the consumption of fruits and vegetables and the incidence of esophageal, colon, and other gut cancers, as well as an inverse relation between serum concentration of carotene and risk of cancer and tumors (Aanchal Walia et al., 2019).

2.7 Bioactive Compounds as Cancer Therapies

Plants are rich with anticancer agents that are being extracted and used ad medicines to treat various cancer along with health diseases. These novel agents have less side effects as compare to other therapies of cancer such as chemotherapy. They act as natural defense against malignant tumors. WHO (World Health Organization) reports that countries such as middle East, Europe and Asian countries uses herbs in past and is approved for cancer treatments due to its miraculous effects on tumors. About 80,000 medicinal plants are used with anticancer properties which have not only prevent the cancer but also reduce the number of cancer patients that were increasing in statical scale (Alexander et al., 2020).

These natural agents are more of interest due to its limited side effects. Chemotherapies causes resistance against cancerous agents and kills the normal cells also. Scientist approached these anticancer agents due to their potent mode of action on cancerous cells. With the help of modern research, now two-thirds of cancer treatments are done from plan based bioactive compounds. Thymoquinone is plat based reactive oxygen species inducer extracted from Nigella Sativa which is activator and transducer of factor 3(STAT3) path way. Similarly, in lung cancer, Petroselinum crispum has major role as it contains Apigenin. Apigenin is bioactive agent which attacks the apoptotic pathways leading to inhibition of cancer cells. In colon cancer, Baicalin which is extracted from Scutellarin baicalinase's promotes apoptosis and growth suppression (Alexander et al., 2020).

The scientific reports suggest that phenolic acids are more effective against cancer metastasis. The bioactive compounds have oncogenic properties along with teratogenic and mutagenic features which have effective anticancer effect and cell-mediated immune responses. Compounds which effects breast cancer are curcumin along with punicalagin and fucoxanthin. Triterpenoids and saponins are anticancer agents which help to fight the lung cancerous cells. Anthocyanin is asl effective against lung cancer. Blood cancer is prevalent cancer which is now treated with Epigallocatechin gallate inducing apoptosis and Rosavin which is profound anticancer compound. Corilagin, gallic acid and ellagic acid are effective for women reproductive system. Prostate cancer can be treated with Gallic acid and apoptosis inducing agents which are Neobavaisoflavone, psoralen and

Rhodioflavonoside. Anti-proliferative compounds such as garcinol and Limonoids treats pancreatic cancer. Genistein and Crocin are also effective in pancreatic cancerous tumors. To treat colorectal cancer cells Carotenoids, saponins, genistein and B-sitosterol are potential anticancer agents (Subramaniam S et al., 2019).

Bioactive compounds, often produced as secondary metabolites such as alkaloids, sugars, steroids, terpenoids, peptides, and polyketides which are produced for protection against diseases and may be used by individual as antibacterial, antifungal, antiviral, antitumor, and immunosuppressive among other methods of drug treatments. The production of secondary metabolites includes complex molecular structures and biochemical pathways. No ribosomal peptides and polyketides are bio compounds synthesized by using different types of enzymes: the no ribosomal peptides synthetases (NRPS) and polyketide synthases (PKS), respectively. these enzymes are liable for many secondary metabolites that exhibit a crucial biological ability and can be useful for medicine and drugs. Different bioactive compounds are detailed as below; (Graça Ana P et al., 2016)

2.7.1 GERANIIN

Geraniins isolated from geraniums and is a d dehydroellagitannin. It is present as potent bioactive compound in many plants. High anti - oxidative, antimicrobial, anti-hyperglycemic, antiviral, and anticancer interaction is attained by Geraniin. Gallic acid, Corilagin, and ellagic acid are the hydrolyzed components that were extracted from Geraniin. Galloyl groups, which have a strong propensity to scavenge nitrogen oxide (NO), have an additional hydroxyl structure. The antioxidant properties of Geraniin are additionally enhanced by Corilagin and Gallic acid. (Subramaniam et al., 2019).

2.7.1.1 Chemical Structure of Geranin

Geranium sibiricum L. contains ellagitannin known as Geraniin has proven to serve as bioactive residences consisting of , anti-hyperglycemic, antihypertensive, and antitumor activities as they cause apoptotic reaction in cancers cells, which includes breast most cancers, lung adenocarcinoma, and melanoma cells, suggesting its potential anti-cancer capacity (Ren et al., 2017). Geraniin has molecular formula of C41H28O27.7H2O indicating as an ellagitannin a molecular weight of 952 g/mo. Corilagin (CO), ellagic acid (EA), and gallic acid (GA) have been shown to be the major important metabolites of Geraniin. Geraniin possess anticancer, antimicrobial, antiviral, and anti-hyperglycemic activity (Sumita Elendran, Wang, Prankerd & Palanisamy, 2015). (FIGURE 1.2 IN APPENDIX)

2.7.1.2 Sources of Geraniin

Ellagitannin geraniin was extracted from Geranium thunbergia. In mid 1970s the component was known as Tannin 1. Geraniin has now been found to exist in at least 71

different plant species from 26 genera and across 9 families since its initial isolation. The nine groups of Geraniin-producing plants include Euphorbiaceous, Geraniaceae and Phyllanthocin including highest amount of geraniin. Geraniin are abundant in the genus Geranium such as Euphorbia spp. and Phyllanthus spp. Plants that produce Geraniin can be found in both tropical and temperate climates. Both herbaceous and woody plants, including the complete plant, leaf, herbaceous stem, tree bark, root, fruit skin, and seed, have been found to contain Geraniin; nevertheless, the leaf is the plant portion that is employed the most frequently. The Indian gooseberry's fruit flesh contains Geraniin as well (P. emblica) (Cheng et al., 2017).

2.7.1.3 Impact of Geraniin on Cancer

Ellagitannin, which are hydrolysable tannins found in raspberries, strawberries, blueberries, pomegranates and nuts demonstrates antioxidant, antiviral, anti-mutagenic, antimicrobial, and antitumor effect. Geraniin is made up of acyl units including galloyl, hexahydroxydiphenoyl, along with dehydrohexahydroxydiphenoyl groups (Antonio et al., 2013). Free radical scavenger activity was present in both Geraniin and Corilagin, indicating that the compounds served as hydrogen atom donors.; consequently, free radicals had been stronger. large number of free radicals could result in infection. consequently, geraniin and Corilagin reduces free radical activity which ought to prevent inflammation. Further, due to their anti-inflammatory properties, Geraniin and ellagic acid can also protect atherosclerosis caused by hypercholesterolemia. Additionally, Corilagin serves as a hepatoprotectant, enhancing liver tissues by reducing oxidative stress and preventing tissue damage. (Lusi et al., 2020).

2.7.1.3.1 Breast Cancer

On human MCF-7 breast cancer cells, Geraniin has an inhibitory impact. Geraniin was found to inhibit the proliferation of MCF-7 human breast cancer cells with an IC50 value of 13.2 g/mL, according to research employing murine splenocytes. Pro-apoptotic effects of Geraniin isolated from Phyllanthus urinaria Linn on MCF-7 (Subramaniam, 2019). The ellagitannin Geraniin exhibits strong anti-proliferative effects on MCF-7 human breast cancer cells. After 72, 48, and 24 hours of treatment, the IC50 values were 9.94, 17.98, and 42.32 M; this substance can disrupt the potential of the mitochondrial membrane and halt the S phase of the cell cycle. In MCF-7 cells, Geraniin can also cause the anti-apoptotic protein Bcl-2 to be phosphorylated. It can also cause the cleavage of the caspase-3 and poly (ADP-ribose) polymerase enzymes (p38 MAPK). With p38 inhibitor therapy, Geraniin induces apoptosis in MCF-7 cells and generates intracellular reactive oxygen species by pretreatment with N-acetyl-l-cysteine (Jia-Wen et al., 2016).

2.7.1.3.2 Ovarian Cancer

Different concentrations of Geraniin were administered for 48 hours to demonstrate its

effects on gene expression, apoptosis, mitochondrial membrane depolarization, and viability. According to results, Geraniin minimized cancer cell viability. Geraniin functions by inhibiting NF-B p65 binding to the mcl-1 promoter and downregulating Mcl-1. In ovarian cancer cells, geraniin-induced apoptosis was reversed by increase production of Mcl-1. Geraniin reduced the ovarian tumor and decreases phospho-p65 and Mcl-1. Geraniin suppresses expression of NF-B and Mcl-1. Geranin is potential for its anti-cancer effect (Xue Wang et al., 2017).

2.7.1.3.3 Oral Cancer

Geraniin is comprised of endless biological characteristics such as antiviral, antihypertensive, anti-hyperglycaemic, liver protective, antidiabetic, and apoptotic activities and anti-migration on oral cancer. Geraniin works against oral cancer by invasion of cell lines SCC-9 and 14. By analysis of Western blot assays it is concluded that the expression of matrix metalloproteinase-2 is reduced. Geraniin exhibit anti-tumor effect by reducing phosphorylation of extracellular signal-regulated kinase. It has no effect on p38 mitogen-activated protein kinase. Geraniin inhibits MAPK/ERK pathway reducing risk of oral tumors (Chia et al., 2019).

2.7.1.3.4 Lung Cancer

Geranin triggers the action of apoptosis by initiating p38 MAPK pathway. Epithelial–mesenchymal transition is reported to play an important role in cancer malignancy and tumor. Geraniin works to reduce EMT by inhibiting growth factor beta-1 in cancer cells and lung tumor and increases the production of E-cadherin. Geraniin inhibits all the factor the lead to formation of EMT. Geraniin plays role in decreasing metastasis by inducing TGF-β-1-induced signaling pathway. Thus, they play important role in reducing lung cancer (Subramaniam et al., 2019).

2.7.1.3.5 Colorectal Cancer

Geraniin is isolated from Phyllanthus amarus having notable contribution against colorectal cancer. They work by inhibition of growth of SW480 and HT-29 colorectal cancer cells and the development of clones. Geraniin is known to increase the expression of Bax, caspase-3, and caspase-9, while decreasing the amount of Bcl-2, and to cause death of SW480 and HT-29 cells in a dose-dependent manner. Geraniin significantly inhibits tumor growth by lowering levels of phosphor (p)-phosphatidylinositol 3-kinase and p-Akt. Geraniin inhibits the Akt/phosphatidylinositol 3-kinase pathway, which promotes the growth of colorectal cancer cells. (Zhou LA, Liu TB & Lü HN., 2020).

2.7.1.3.6 Bladder Cancer

Bladder transitional cell carcinoma is seen high rated cancer. Geranin works against bladder cancer by its anti-tumor effect inhibiting growth of T24 cells, decreasing viability. Geraniins also have effect on cessation of S phase in the cell cycle. It downregulates the

receptor proteins cyclin D1 and p21, and induces cell apoptosis in T47 cells. The PI3K/AKT pathway regulates cell. Geraniin down-regulates PI3K/AKT signaling pathway. It regulates cell growth by inhibiting viability and promoting apoptosis in T24 cells (Junwei, Qin, Yao, Chen & jiang, 2020).

2.7.1.3.7 Glioma Cancer

By impairing STAT3 phosphorylation and lowering the expression of downstream target genes Bcl-xL, Mcl-1, Bcl-2, and cyclin D1, Geraniin inhibits the growth of gliomas. In glioma tumor, Geraniin reduces cell viability and boosts apoptosis. Geraniin inhibits STAT3 phosphorylation and has pro-apoptotic effects on glioma cells, which decrease tumor size. (Ren et al., 2017).

2.7.2 TOCOTRIENOLS

Tocotrienols belongs to Vitamin E and is fat soluble bioactive compound. Vitamins are made up of eight dietary components called tocopherols and tocotrienols. Tocotrienols have several properties such as they are able to lower blood cholesterol level, have cardioprotective effects and are efficient antioxidant anti-cancer and neuroprotective agents (Subramaniam et al 2019). Tocopherols and tocotrienols are 2 subgroups that make up the vitamin E, but only tocotrienols exhibit anticancer activity. Tocotrienols have potent anti-tumor effect by down-regulation of carrier transporter systems that display saturation (Paul W Sylvester et al., 2010).

The discovery of vitamin E (α-tocopherol) started out in 1922 as an essential aspect required in reproduction. vitamin E is amazing essential antioxidant, which possess ability of neutralizing free radicals at once through donating hydrogen from its chromanol ring. Tocopherol is considered to be the most powerful form of vitamin E as α-tocopherol has ability to shift protein within the liver binding it and stopping its degradation. Tocotrienols had been proven to own advanced antioxidant protects over α-tocopherol. specially, inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase to decrease cholesterol, attenuating infection through downregulation of transcription factor NF-κB activation, and effective radioprotectant in opposition to radiation damage are a few properties possessed by tocotrienols. Aside from most cancers, vitamin E is recognized for its defensive abilities in bone, cardiovascular, eye, nephrological and neurological diseases (Hong et al., 2015).

2.7.2.1 Chemical Structure of Tocotrienol

Vitamin E consist of tocopherols and tocotrienols. Alpha-tocopherol was first vitamin E to be isolated from subgroups known as alpha, beta, gamma and delta –tocopherols and α, β, γ and δ-tocotrienols. The saturated form of vitamin E is termed as tocopherols whereas unsaturated forms are termed as tocotrienols with an isoprenoid side chains. Tocotrienols are a type of natural compound that can be obtained from several varieties of nuts, grain

products, wheat germ, and vegetable oils. Vegetable and bran oil and palm oil are highest producing tocotrienols source. According to Bunyan et al., tocotrienols are tocopherols with isoprenoid side chains. A primary substance called Tocol (2-methyl-2-(4,8,12-trimethyltridecyle)-chroman-6-ol) is the source of tocotrienol. With side chains at the 3, 7, and 11 positions, tocotrienols are unsaturated. The position and quantity of attached methyl groups on 6-chromanol rings determine the differences between the subgroups of tocotrienols. For example, -tocotrienol is 5,7,8-trimethyl, -tocotrienol is 5,8-dimethyl, -tocotrienol is 7,8-dimethyl, and -tocotrienol is 8-monomethyl, all of which share the same methyl structure and notation but Tocotrienol receives a single unit stereoisomeric carbon due to the tail's unsaturation. The methylation of α-form gives the vitamin activity of tocotrienols (Ahsan, H., Ahad, A., & Siddiqui, W. A., 2015).

(FIGURE 1.3 IN APPENDICES)

2.7.2.2 Sources of Tocotrienols

Vitamin E is naturally found in leafy vegetables, nuts and fish oil. Annatto is major source of tocotrienols, extracted from the seeds of achiote tree (Bixaorellana L.). Tocotrienols, which are also found in palm oil and are extracted from the rich reddish pulp of the palm tree's fruits (Elaeis guineensis), are mostly composed of 46% tocotrienol and 22% tocotrienols (Kabir et al., 2017). Tocotrienols are abundant in foods like palm kernel oil, coconut oil, barley germ, wheat germ, and annatto, although they are found in almost larger concentrations in foods like rice bran oil and annatto. Other sources of tocotrienols include grape fruit seed oil, rye, hazelnuts, maize, olive oil, Buckthorn berries, flax seed oil, poppy seed oil, and sunflower oil. (Ahsan, H., Ahad, A., & Siddiqui, W. A., 2015).

Tocotrienols from palm oil protects against various diseases such as Alzheimer's, deficiency of vitamin A and cardiovascular diseases. Barley flour, oats and rye flour also contain small amount of tocotrienols. About 0.33 mg of tocotrienols is present in cranberries and 0.08 mg in blue berries per 100g. Plum, coconut and kiwi and berries include tocotrienols. (Kabir et al., 2017).

2.7.2.3 Impact of Tocotrienols on Cancer

Tocotrienols are potent anti-cancer with pharmacological role towards ageing, health, inflammatory diseases. Ageing is process in humans in which capability of organs and tissues decreases gradually over the time. This insufficient delay in cellular activity leads to death. Tocotrienols are antioxidants work synergistically with ageing biomarkers and delay the process. Tocotrienols prevent lipid oxidation and work antagonist to free radicals exhibiting neuro-protective, anti-inflammatory, anti-osteoporotic and cellular protective features. Experimental research states that tocotrienols decreases Alzheimer disease improve cognitive function preventing cell death and neuro degeneration. Tocotrienols are active anti-cancer exerting their action on cellular metabolism, proliferation, and survival

rate (Kabir et al 2017).

Cancers of the prostate, chest, epidermis, colon, gut, pancreatic, liver, and lung can be reduced by tocotrienols. They work by mediating apoptosis and immunoregulation inhibiting breast cancer line cells. The order in which they destroy cells are αT3 < TRF < γT3 < δT3. CD59 glycoprotein precursor gene is active for immune regulation in human body. According to reports 1 mg TRF daily can minimize tumor progression by increasing the expression of the Interleukin 24 gene and decreasing levels of vascular endothelial growth factor. δT3 is known to reduce the cell metabolism and metastasis of cancer. Reduction of IL-8 and vascular endothelial growth factor genes reduced the tumor progression (Subramaniam et al., 2019).

2.7.2.3.1 Apoptotic effect against Cancer

In cervical cancer cells and hepatoma cells, T3 and tocopherol cause apoptosis and anti-proliferative effects. By increasing IL-6 transcription and lowering of cyclin D3, p16, and CDK6 in HeLa cells, T3 inhibits the growth of human cervical cancer. They increase DR5, which is reliant on JNK and p38 MAPK activation, to cause apoptosis in breast cancer cell lines. Human lung adenocarcinoma A549 and glioblastoma U87MG cells undergo apoptosis when exposed to T3. By inhibiting STAT3 pathway, tocotrienols prevented growth of bladder tumor (Aggarwal et al., 2019).

2.7.2.3.2 Anti-Inflammatory effect against cancer

Tocotrienols have anticancer and anti-inflammatory effect on health. They mediate by affecting transcription factors, namely, NF-B along with STAT3. They down regulate the genes and promoter of inflammation reducing survival of cancerous tumors. Factors that are responsible for inflammation in bladder cancer such as Src kinase and Janus kinase are inhibited by tocotrienols by downregulating STAT3 activation in tumors. Thus, they are potent anti-inflammatory agents (Aggarwal et al., 2019)

2.7.2.3.3 Inhibition of tumor metastasis

Tocotrienols are anti-mutagenic and anti-cancer compounds. δ-T3 is known to increase the regulation of tumor in cells such as A549 and H1299 cells. By inhibiting the protease activity of MMP-9/urokinase-type plasminogen activator the size of tumor is reduced. γ-T3 is used to down regulate NF-κB/p65 pathway reducing impact of human colorectal cancer cell lines HCT-116, HT-29 and Caco-2. Tocotrienols from nuts and fish and oils are used to induce apoptosis, anti-

inflammatory effects, anti-oxidant, regulation of Non-coding RNA`s, suppression of metastasis, Angiogenesis Inhibition and Cell Cycle Arrest. They have significant effect on modulation of cancer-related signaling pathways demonstrating therapeutic effect on cancer (Aggarwal et al., 2019)

2.7.3 CURCUMIN

Curcumin a phytochemical is present in turmeric. Turmeric is a spice used in India and Asian countries as their potent spices. Extracted from curcumin they exhibit oxidative activity with anti-inflammatory effect. It is used to treat cancer, metabolic syndrome, rheumatoid arthritis, stress, hyperlipidemia, inflammation brought on by exercise, and discomfort of the muscles. Turmeric powder belongs to rhizomatous *Curcuma longa* with major bioactive compound known for its medicinal properties. Potent antioxidant, anti-inflammatory, anti-proliferative, antibiotic, and anticancer qualities, curcumin has been used as a medicine for centuries in Asian nations. (Hewlings, S. J., & Kalman, D. S., 2017). Turmeric, named as curcuma long L, is cultivated in tropical regions used for remedy for different diseases at different age groups. According to environmental conditions, turmeric can contain from 2% to 9% of curcuminoids indicating curcumin, desmethoxycurcumin and bisdemethoxycurcumin and cyclic curcumin. First scientific extraction was reported in 1815, followed by solvent extraction and column chromatography. Lampe in 1918 used carbomethoxy feruloyl chloride and ethyl acetoacetate for extraction along with inert organic amide solvents to improve the yields of extraction of curcumin (Priyadarsini KI, 2014).

2.7.3.1 Chemical Structure of Curcumin

Curcumin is scientifically named as Di feruloyl methane with a symmetrical molecular chemical formula $C_{21}H_{20}O_6$, and molecular weight of 368.38. Curcumin consists of dual aromatic ring structures containing o-methoxy phenolic groups. Curcumin consists of diketone group and dipole moment of 10.77. They exhibit a hydrophobic structure. Curcumin is readily soluble in polar solvents like methanol, ethanol, acetonitrile, chloroform and sparingly soluble in hydrocarbon solvents like cyclohexane and hexane. (Priyadarsini KI, 2014).

It is a derivative with anti-inflammatory, anti-cancer, and hepatoprotective properties, flavor, a biological pigment, a nutraceutical, an antifungal property. It is polyphenol an aromatic ether derived from ferulic acid. It functions as a pigment, a ligand, an extreme scavenger, an inhibitor of histone deacetylase, an immunomodulator, an iron chelator, a chemo preventive agent, a flavoring, an inhibitor of aldehyde reductase, an inhibitor of shikimate dehydrogenase, an inhibitor of IMP dehydrogenase, an inhibitor of NAD(P)H dihydrogen. (National Center for Biotechnology Information 2022).

(FIGURE 1.4 IN APPENDIX)

2.7.3.2 Sources of Curcumin

Curcumin is extracted by solvent extraction of turmeric plant which is rhizome used as spices in India named as curcuma longa and curcuma domestica. It is known for its medicinal and therapeutic properties with combination if anti-oxidant and anti-inflammatory. Curcumin is rich source of anti-viral, anti-bacterial and outstanding anti-cancer activities widely cultivated in India, China, and Indonesia (Stanić & Zorka, 2017). Curcumin is yellow-orange turmeric crystalline powder. It is also present in oils and resin but in small quantities. The constituents predominant in resins and oils are αturmerone, β-turmerone, curlon, zingiberene, ar-turmeron, turmerol A, turmeronol B etc. The dried root of rhizome curcuma longa is grounded to powder, washed with solvent that extracts its coloring compound. Oleoresin is yield after distillation with solvent, along with volatile oils and resinous compounds. curcumin is extracted from oleoresin by further washing with selected solvents. The final product is a colored powder with minute volatile oil and dry matter of natural origin. This is used as domestic and industrial level (Stankovic, 2004).

2.7.3.3 Impact of Curcumin on Cancer

Medicinal properties of turmeric are famous in ancient history and is increasingly recognized as anti- antioxidant, antiviral, antibacterial, and antitumor activities. Curcumin modulates transcription factors, cytokines, protein kinase along with inhibiting signaling pathways involve in tumor progression and inflammation. The chemical composition of curcumin has effects such as inhibition of oxidation and transcription of those genes that are linked to oxidative stress and inflammatory responses of cells (Stanić & Zorka, 2017).

Curcumin is made up of curcuminoids with low bioavailability increased with combination of nanoparticles, piperine, phospholipid complexes and liposomes. Curcumin is used as it shows inhibitory effect on mushroom tyrosine and inhibits prostate, pancreas and colon cancer cells. Curcumin inhibits cancer cell proliferation, angiogenesis and limit metastasis combating mutated cancer cells and reducing chronic inflammation in tissues and cells (Stanić & Zorka, 2017).

Liver cancer cells proliferations are reduced by CUR3d responsible for cancer cell growth. It also has cytotoxic effect on prostate and breast cancer cells. Curcumin via the expression of p53 induces apoptosis in MCF-7 of human breast cancer cells. According to a study supplementation of 1g per kg of curcumin inhibited metastasis and proliferation of colorectal cancer cells liver cells, papillary thyroid carcinoma. High dosage of curcumin prevented the migration of K1 papillary thyroid cancer cells by downregulating metalloproteinase-9 expression (Shonia et al., 2019).

2.7.3.3.1 Anti-inflammatory effect against cancer

Curcumin is potent anti-oxidant increasing of superoxide dismutase according to evidence.

Curcumin is known to modulate the activity of GSH, catalase, and SOD enzymes inhibiting reactive oxygen species-generating enzymes such as cyclooxygenase and xanthine oxidase. Curcumin is termed as chain breaking antioxidant due to is lipophilic hydrophobic nature which makes it essential scavenger. Curcumin suppresses inflammation by suppressing inflammatory mediators (Hewlings, S. J., & Kalman, D. S., 2017).

2.7.3.3.2 Effect of curcumin against glioma cancer

Curcumin is anti-tumor compound working against glioma cancer cells. According to this report by Jie-Xiang, Chen, Ma, Wang, Yang, Cui 2019, effect of Curcumin were studied on H19 cells , miR-675 factors , and VDR. According to results curcumin downregulated their expression along with Vitamin D. The levels of VDR expression increase as H19 reduced messenger RNA and protein levels. It is also target gene miR-675. By this curcumin decreases tumor intensity (Xiang et al., 2019).

2.7.3.3.3 Effect of curcumin against breast cancer

By causing cell cycle abnormalities and p-53-induced apoptosis, inhibiting tumor growth and angiogenesis, reducing transcription factors, and changing the expression of signaling proteins like RAS, phosphatidylinositol-3-kinase (PI3K), protein kinase B (Akt), mammalian target of rapamycin (mTOR), and Wnt/-catenin, curcumin prevents the growth of breast cancer Through inhibiting the interaction of cyclin D1 and CDK4, curcumin inhibits cell cycle. By halting cells in the G phase, promoting the proteasomal breakdown of cyclin E, and upregulating the CDK inhibitors p53, p21, and p27, it prevents the growth of MCF-7 breast cancer cells. (Song, X., Zhang, M., Dai, E., & Luo, Y., 2019).

2.7.3.3.4 Effect of curcumin against Lung cancer

Curcumin works against lung cancer by prevention of NF-κB in and by action on the JAK2/STAT3 signaling pathway. Curcumin is also known to inhibit cell damage and induced apoptosis by the upregulation of microRNA-192-5p and suppression of the PI3K/Akt signaling pathway. Curcumin suppresses neutrophil elastase-induced tumor proliferation via upregulating α1-antitrypsin expression. Curcumin works by its proapoptotic activity in lung tumor cells by suppressing the expression of *COX-2*, EGFR, and extracellular signal-regulated kinase (ERK) 1/2 activities. This reduces survival of lung adenocarcinoma cells. Thus, strong anti-oxidant activity of curcumin makes it best to prevent cancer (Giordano, A., & Tommonaro, G., 2019).

2.7.4 MYRICETIN

Belonging from group of flavonoids, myricetin (3,5,7,30 ,40 ,50 -hexahydroxy flavone cannabis cetin) was initially extracted from plant Myrica Nagi Thunb. Myricetin from Myricaceae is therapeutic phytochemical known for its effect in cancer, diabetes Miletus and cardiovascular disease. Myricetin is lipophilic and hydrophobic solubilized in organic

compounds such as dimethylacetamide, tetrahydrofuran, acetone and dimethylformamide. Myricetin is known for its extra-ordinary pharmaceutical properties of being an anti-carcinogen, chemoprotective, and anti-tumor against liver, skin, colorectal, ovarian, cervical and breast cancers (Shonia et al., 2019).

Myricetin is isolated from nuts, fruits, berries, wine, tea and plants. Myricetin availability depend on factors such as genetic, environmental condition, seed germination, ripeness, seasonal variation, climate change, storage conditions, cooking and processing technique. Myricetin also possess antimicrobial property such as disruption of membrane. They inhibit cellular DNA and RNA polymerases of bacterial cells. Moreover, this it can inhibit intracellular reactive oxygen species production protecting cells from toxicity of peroxide. (Taheri, et al., 2020).

2.7.4.1 Chemical Structure of Myricetin

Myricetin belongs to flavone (Hexahydroxy flavone substituted by hydroxyl groups. It is extracted from Myrica Rubra leaves and bark of Myrica Nagi Thunb. It works as cyclooxygenase 1 inhibitor and consisting of antioxidant, antineoplastic properties. It has role as plant metabolite, a component of food, neuroprotective activity. Myricetin has conjugated acid as well named as hexahydroxy flavone and a 7-hydroxyflavonol (National Center for Biotechnology Information 2022).

Myricetin is stable compound at pH level of 2. Degradation of Myricetin depend on Temperature and pH levels. As myricetin is hydrophobic, microemulsion formulation improves solubility by 1225 time greater than water enhancing its anti-proliferative activity against cancer cells (Shonia, Selvaduray & Radhakrishnan, 2019).

Myricetin is glycosidially bonded free molecules. Its antioxidant property exists due to presence of hydroxyl groups. This catechol group forms semi-quinone radicals giing nyricetin its protective effect against oxidative stress, tissue injury of lungs and hyperglycemia (Muhammad Imran et al., 2021).

(FIGURE 1.5 IN APPENDIX)

2.7.4.2 Sources of Myricetin

Myricetin is poly hydroxyflavonol having light yellow crystals along with methanol, acetonitrile, and other polar solvents. The molecular mass of myricetin is 318.24 with chemical formula of $C_{15}H_{10}O_8$. Myricetin is extracted from plants such as Vitaceae, Primulaceous, Rosaceae and are readily found in fruit berries, green vegetables, honey, tea and other daily foods as important ingredient to health sector and works as additive in foods as well (Xia minting et al., 2021). It is also present in high amounts in *Trigonella foenum-graecum* L. gamma-modified, *Euphorbia tirucalli* L, rhizomes of *Cyperus rotundas* L. and seed extract of *T. foenum-graecum*. Strawberries, black currant, honey, grapes wine, spinach *C. rotundus* gemmo-modified extracts, Species

of *Anacardium* and *Mangifera* (Anacardiaceous) are rich in myricetin, gallic acid, proanthocyanins and flavanols (Taheri et al., 2020).

2.7.4.3 Impact of Myricetin on Cancer

According to cell studies, reports suggest anti-cancerous, anti-tumor, anti-proliferation activities of Myricetin. Myricetin can inhibit proliferation and growth of T24 Bladder cancer tumor. This is done by prevention of cyclin B1 and cyclin-dependent kinase pathways. Myricetin also exhibits anti-mutagenic and anti-metastatic effect on breast cancer cells by downregulating MMP2 or MMP9 cells (Shonia, Selvaduray & Radhakrishnan, 2019). Furthermore, Myricetin inhibits invasion, migration of cancer cells reducing expression of azoxymethane and colorectal tumorigenesis along with factors such as TNF-α, IL-6, NF-B, and PCNA (Muhammad Imran et al., 2021).

2.7.4.3.1 Effect of Myricetin on Skin Cancer

Myricetin shows anti-tumor effect on skin cancer cells by inhibiting NF-κB pathway. It also prevents tumor inhibiting MEK kinase activity by binding to it and deleting its mutants. UVB induced skin tumors are also prevented by myricetin as it suppresses MAPK, Akt, Fyn, and JAK1/STAT3 pathways. Myricetin also reduces benzene hydrocarbons that causes skin tumors (Naam Ju , Jung, Won Lee & Lee, 2011).

Myricetin is well known against skin cancer due to its anticancer promoting activity. it inhibits mitogen activated kinase and signaling to ERK/p90RSK/AP-1 pathway that inhibits MEK1 activity. These kinases regulate the activity of cancer line cells by multiple signaling pathways. Myricetin also prevents epidermal growth factor cell and promotes apoptosis skin cancer cells. (Taheri, Y., Suleria, H et al 2020).

2.7.4.3.2 Effect of Myricetin on T24 Bladder Cancer cells

Myricetin contributes anti-cancer effect against bladder cancer by its chemo-preventive mechanism. The MTT assay experiment used in this article demonstrates that myricetin reduces T24 cell proliferation in a dose- and time-dependent manner. Through DNA fragmentation analysis, downregulation of cyclin B1 and cyclin-dependent kinase cdc2, and cell cycle arrest during G2 phase, it triggers apoptosis. Akt phosphorylation inhibition and activation of p38 MAPK significantly reduces T24 cell migration, decreasing MMP-9 expression. Myricetin thus has potential anti-tumor activity against this bladder cancer (Fang Sun, Zheng, Ye, Wu, Wang & Chen, 2012).

2.7.4.3.3 Effect of Myricetin on Ovarian Cancer cells

Myricetin's anti-angiogenic action inhibits the angiogenesis of ovarian carcinoma cells. Angiogenesis is the phenomenon of new vessels of blood emerging that contributes to cancer. Myricetin massively reduces the angiogenesis that OVCAR-3 cells cause. In SKOV3 human ovarian cancer cells, myricetin is known to diminish viability and initiate apoptosis through endoplasmic reticulum stress and DNA double-strand breaks. According

to Tavian and Kayali's findings, myricetin has the potential to treat ovarian cancer since it inhibits cell invasion, induces apoptosis, arrests the cell cycle, and slows the proliferation of ovarian cancer cells. (Taheri et al., 2020).

2.7.4.3.4 Effect of Myricetin on Colon Cancer cells

By increasing the BAX/Bcl2 ratio and triggering apoptosis in the HCT-15 cell line, myricetin has cytotoxic action. Based on inhibitory mechanisms and cancer cell-based assays, myricetin has a therapeutic impact on colon cancer by inhibiting the hFEN1 protein. This endonuclease is a protein that interacts with the amino acids Arg100 and Lys93 by hydrogen bonds; this interaction is widely known for its crucial role in the activity of hFEN1 during human colon cancer. (Taheri et al., 2020).

2.7.4.3.5 Effect of Myricetin on lung Cancer cells

Myricetin is metabolite of flavonoid possessing anticancer activity by reducing proliferations of A549 lung cancer cells. The cancer cell growth is inhibited by promoting G1 phase aggregation and decreasing fraction of S phase cells. The expression of P53 is increased by Myricetin and relegation of the expression of EGFR in A549 cells. The cytotoxic potential is induced by preventing growth of cell cycle along with A549 lung cancer cells. Thus, in this way it shows anticancer therapy (Rajendran P et al., 2021).

2.7.5 SAPONINS

Saponins are bioactive compounds with glycosides and a foaming in nature. They are extracted from soapwort plant (Saponaria), marine animals and bacteria. the roots of Saponaria consist of saponins. Saponins exhibit high foaming ability due to the combination of hydrophobic and hydrophilic sugar. Saponins consist of glycon and aglycone, classified as neutral and acid type. Saponins is known to show anti-microbial or anti-insect activity (Sapna D. Desaia, Dhruv G. Desai & Harmeet Kaur, 2009).

Saponins are triterpenoid with active glycosides causing hemolysis of red blood cells (RBC's), exhibiting anti-inflammatory, antibacterial, antifungal, antiviral, insecticidal , anticancer, cytotoxic and molluscicide action. They form soapy foams when shaken with aqueous solutions. Saponins are also known to act on cholesterol by cholesterol-lowering action. Thus, saponins are used for prevention of metabolic and vascular disorders (**El** Aziz MMA, Ashour AS & Melad ASG, 2019).

(FIGURE 1.6 IN APPENDIX)

2.7.5.1 Structure of Saponins

The hard framework of saponins, which is made up of at least four hydrocarbon rings, is joined by groups of one or two sugars, which are further separated into triterpenoid and steroid glycosides. Their two primary structures, spirostan (16,22,22,26-diepoxycholestan) and furostan (16,22-epoxycholestan), each include 27 carbon atoms (Dorota Kregiel,

Berlowska, Witonska, Antolak, Proestos, Babic, Babic & Zhang 2017). Saponins are glycosides consisting of sapogenin sugar as the aglycone moiety distributed in plants. The saponin may be a steroid or a triterpene and the sugar could be six carbon sugar, galactose, or a methyl pentose (National Center for Biotechnology Information 2022).

Sapogenins are polycyclic aglycone containing several unsaturated C-C bonds. The oligosaccharide chain is normally attached at the C3 position (monodesmosidic) or C26 or C28 position (bidesmosidic). They also have steroidal amines along with containing six carbon glucose, galactose, glucuronic acid, xylose, rhamnose or methyl pentose, linked to a hydrophobic aglycone which may be triterpenoid or steroid in nature. The foaming ability of saponin is due to association of the nonpolar sapogenin and the water-soluble side chain making saponins bitter. The pathway of sapogenins involves the joining of acetate units with occurrence of the cyclic triterpenoids (Sapna D. Desaia, Dhruv G. Desai & Harmeet Kaur, 2009).

2.7.5.2 Sources of Saponins

There are 100 families of plants, including marine sources, from which saponins are derived. saponins can be found in numerous parts of dicotyledonous plants, including the seeds of Hippocastani, the roots and flowers of Primulae, the leaves of Hedrae, the roots of ginseng, the Glycyrrbizae, the roots of Senegae, the leaves of Polygalae Amarae, the roots of Saponariae, the seeds of Triterpenoid saponins can be found in abundance in legumes including peas, beans, and soybeans. (Dorota et al., 2017).

A lot of saponins is also taken from agricultural plants like ginseng, yams, alliums, asparagus, fenugreek, and yucca. Diosgenin is a steroidal aglycone obtained from the bulbs of Dioscorea villosa by hydrolyzing dioscin (wild yam). Commercially, steroidal saponin is also employed as a precursor in the production of steroids such cortisone, progesterone, and pregnenolone. Species of the Family solanaceae, such as tomato, potato, aubergines, and capsicum, contain steroidal glycoalkaloids, but cereals and grasses lack saponins. In *Avena* species (oats) have low amount containing both triterpenoid and steroidal saponins (Dorota et al., 2017).

Saponins are also taken from legumes, mainly red beans, kidney or black beans and pulses, onion, garlic, leaves of asparagus, oats, spinach leaves, sugar beet, tea and sweet potatoes. Saponins used for medicinal purpose are extracted from bark and leaves of soap bark tree, Mojave yucca, licorice, *Panax* species, fenugreek, horse chestnut, soapwort, gypsophila genus and sarsaparilla (Dorota et al., 2017).

2.7.5.3 Impact of Saponin on Cancer

Saponins are known to be able to lower risk of cancer by lowering the levels of cholesterol. Saponins are said to prevent dental caries, aggregation of platelet, treatment of

hypercalciuria, as an antidote against acute lead poisoning, renal stones, Molluscoid, Antiulcerogenic, Anticancer, Antioxidant, Immunomodulatory, Anti-malarial, Anti-bacterial, Eczema, Analgesic, Anti-nociceptive and as a hepatoprotective agent (Sapna D. Desaia, Dhruv G. Desai & Harmeet Kaur, 2009).

2.7.5.3.1 Effect of saponins on breast cancer cell

Saponins have great anti-tumor properties. Avicins D and G, two pure physiologically active derivatives of triterpenoid saponins derived from Acacia victoriae, have been shown to suppress the growth of tumour cell lines as well as the proliferation of immortalised breast epithelial cells and human foreskin fibroblasts in mice and humans. The human MDA-MB-453 breast cancer cell line's cell cycle (G1) is arrested by the saponins, and the Jurkat (T cell leukaemia) and MDA-MB-435 (breast cancer) cell lines undergo apoptosis. Saponin controls the activity of phosphatidylinositol-3-kinase in Jurkat T cells as well as phosphorylation in the downregulation of protein Akt. Additionally, it causes mitochondrial disruption, chemoprevention, and nuclear Factor-B inhibition. (Mayank, Melzig, Fuchs & Weng, 2011).

2.7.5.3.2 Effect of cycloartane on cancer cells

Cycloartane belongs to group of saponins which are chemotherapeutic possessing anticancer activity against cancerous xenografts and colon cells. Saponins downregulates production of the HCC tumor marker α-fetoprotein along with Hepatic G2 cell growth by inducing apoptosis and modulating NF-κB signaling pathway. (Dorota., et al 2017).

2.7.5.3.3 Anti-tumor effect of saponins

Additionally, synthetically altered saponins are used to treat malignancies. Examples include the synthetic triterpenoid 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid methyl ester (CDDO-Me) and the rexinoid LG100268 for the treatment of estrogen receptor-negative mammary carcinogenesis. Saponins were also effective against PC3 and DU145 cancer cell lines, which were both androgen-responsive and non-responsive, respectively. Nano molar and low micro molar quantities of CDDO-Me caused cell death. To halt the spread of cancer cells, saponins from the triterpene group also hinder cell development and promote apoptosis. To improve membrane transfer, saponins are frequently used with chemotherapeutic drugs. As, transportation of medicines to the tumor place is difficult, saponins works efficiently as transporter to tumor therapy (Mayank, Melzig, Fuchs & Weng, 2011).

2.7.6 CUCURBITACIN

Cucurbitacin’s belongs to group of compounds known as triterpenoids. They are isolated in cucurbitaceous plants. cucurbitacin were first reported in 1932 and in 1981 they were dictated as highly toxic compound. Cucurbitacin are bitter in taste was found in zucchini

squash canned in California. The first cases of food poising were found in 1981-1982 produced from zucchini in Australia when eaten in excessive amounts. The tetracyclic terpenes, cucurbitacin are steroidal structures extracted from family Cucurbitaceous such as pumpkins pie, green gourds and cucumbers. Cucurbitacin have toxic properties but are recognized as medicinal in emetics, narcotics and anti-malarial (Jorn Gry, Soborg & Andersson 2006).

Cucurbitacin are common in species of the Bryonia. Different tissues of plants vary in the quantity of cucurbitacin, most concentrated in fruits and roots of plant. Fruits contain highest amount of cucurbitacin whereas it is vice versa in seeds. In some plants such as Iberis species and Lepidium sativum also contain cucurbitacin in seeds. As cucurbitacin are in variety due to derivates in sidechain giving cucurbitacin its pharmacological nature. Cucurbitacin's give the cucurbitacin its bitter taste named as α-elaterin. Cucurbitacin's have anticancer, anti-diabetic, anti-proliferative effect (Kaushik et al., 2015).

2.7.6.1 Structure of Cucurbiatacin

Cucurbitacin is tertiary alpha-hydroxyl ketone compound well known for being antineoplastic agent and role as plant metabolite for treatment of various diseases (National Center for Biotechnology Information 2022). Cucurbitacin are tetracyclic nucleus skeleton and formula of $C_{32}H_{46}O_8$, molecular weight 558.712 g/mol found in the plants of Cucurbitaceae and Brassicaceae. It is classified as most bitter which protects against parasites, inflammation and toxicity along with cell adhesion and leukemic disorders, immune mediated and angiogenic disorders (Garg, S., Kaul, S.C., & Wadhwa, R. 2018).

Cucurbitacin G and H varies from each other in the attachment of the hydroxyl group and aldehyde group (Kaushik, U., Aeri, V., & Mir, S. R. 2015).

(FIGURE 1.7 IN APPENDIX)

2.7.6.2 Sources of Cucurbitacin

Cucurbitacin's are isolated from cucurbitaceous mostly in Bryonia, cucumber, melons, squash, pumpkin, angled gourd, Echinocytes, bottle gourd, watermelon, colocynth cucumber, Ecballium elaterium. They are also found Momordica charantia levels varying between tissues. Majorly are present in roots and stems rather leaves and flowers. Mostly, the roots are the most bitter tissue in plants species. Roots which are bitter are prerequisite. Mostly cucurbitacin in fruits have economic importance (Jorn Gry, Soborg & Andersson, 2006).

2.7.6.3 Impact of Cucurbitacin on Cancer

Cucurbitacin is an anti-cancer bioactive chemical that targets cancer cell lines by inhibiting cell growth, stopping the cell cycle at the G2/M phase, and causing cancer cells to undergo apoptosis. Cucurbitacin inhibits pathway of Signal Transducer Activator of Transcription 3 signaling pathway, which is necessary for cell growth and maintenance. This induces

anti-cancerous potential. They work by inhibition of only JAK2 and STAT3 or acting as inhibitor of tumor angiogenesis by preventing expression of JAK-STAT3 and mitogen activated protein kinases (MAPK)- signaling pathways.

Cucurbitacin E and B interfere with actin cytoskeleton contributing towards anti-proliferation by the disruption of the F-actin cytoskeleton. Cucurbitacin B is known to suppress STAT3 in patients with laryngeal cancer when used in combination with docetaxel augment. The chemotherapeutic effects of cucumber fruits have anti-tumor effects rich in Cucurbitacin C (Kaushik et al 2015).

2.7.6.3.1 Effect of Cucurbitacin on Breast Cancer Cells

In acute promyelocytic and myeloid leukaemia, Cucurbitacin B is known to cause cell cycle arrest and cellular differentiation. It also causes S phase growth arrest, swollen cell morphology, altered cytoskeleton due to rapid and haphazard polymerization of filamentous actin into globular aggregates, and decreased clonogenicity in immature blasts. Cucurbitacin upregulates monocytes-/granulocytic-specific CD11b, signifying cell differentiation in cancer cells. Cucurbitacin promotes anticancer activity by suppressing the activation of MAPK/ERK pathway and inhibition of STAT3 activation in various human chronic myeloid leukemia cells. the activation of STAT3, RAF, MEK and ERK inhibits protein expression whereas STAT3 activation modulation resulted into G_2/M arrest and apoptosis by experimental research. Cucurbitacin B known to protect against metastasis of cancer (Garg, S., Kaul, S.C., & Wadhwa, R., 2018).

Cucurbitacin compounds exerts antiproliferative potential on various human tumor cells and tumor xenografts, including tissues of breast, prostate cell linings, lung cells, tissues of uterine cervix, liver cells, dermis, and brain cancer cells. The subgroups under cucurbitacin have been reported to possess anticancer effect against HCT-116, breast (MCF-7), lung (NCI-H460) and brain (SF-268) cancer cell lines. Cucurbitacin, I help in reducing growth in breast and prostate carcinoma cell lines. Treatment with cucurbitacin B and E achieves anticancer effect by cell cycle arrest and apoptosis in MCF-7 and MDA-MB-231 breast cancer cells (Alghasham A. A., 2013).

2.7.6.3.2 Effect of cucurbitacin on lung cancer

Cucurbitacin (Cucurbitacin B) is a highly oxygenated bitter triterpene that protects the essential redox regulators for mitochondrial apoptosis, cell cycle progression, cytoskeleton remodeling, and the control of redox sensitive signal transducers and transcription activators. The thiol anti-oxidant NAC pretreatment, which attenuated all of Cucurbitacin B's cytotoxic effects, exacerbated the effects of the GSH synthesis inhibitor BSO on lung cancer cells. Thiols are intermediate compounds between Cucurbitacin B and lung cancer cells. Cucurbitacin B inhibits STAT3 phosphorylation to produce growth arrest and death in a dose- and time-dependent manner, which inhibits the development of lung cancer cells.

Cyclin B1 and BCL2 downregulation blocks the STAT3 pathway. (Garg et al., 2018)

Cucurbitacin works by downregulation of cMYC/kRAS, DNMTs, HDACs and SIRT and upregulation of CBP and PCAF. Treatment with Cucurbitacin delays cell migration and growth of tumor. Along with this, the upregulation of E-cadherin proteins is effective as anti-angiogenic treatment of Cucurbitacin B (Garg et al., 2018).

2.7.6.3.3 Effect of cucurbitacin on cervical cancer

Cucurbitacin, in particular Cucurbitacin D, is known to affect cervical cancer cells. These cells' expression and growth are inhibited by the induction of apoptosis. When Cucurbitacin D is used to treat cervical cancer cells, the cell cycle is stopped in the G1/S phase, inhibiting the constitutive expression of E6, Cyclin D1, CDK4, pRb, and Rb and inducing the levels of the proteins p21 and p27. Phosphorylation of STAT3 at Ser727 and Tyr705 are hindered along with dysregulation with gene expression c-Myc, and MMP9 enhancing the utterance of oncogene microRNAs (miR-145, miRNA-143, and miRNA34a) in cervical cancer cells (Sikander *et al*, 2016).

2.7.6.3.4 Effect of cucurbitacin on ovarian cancer cells

Cucurbitacin also show effects on blood, brain, lungs, pancreatic and ovarian cancer. In ovarian cancer tumor rapid growth is determined by resistance to cisplatin treated with chemotherapeutic agents. Cucurbitacin B is known to demonstrate beneficial anti-cancer activity against ovarian cancer cell line and cisplatin-resistant cell line of A2780CP. Cucurbitacin B causes a hypersensitivity impact that is reliant on total glutathione depletion, an increase in Radicals caused by a drop in the level of dual-specificity tyrosine-regulated kinase (Dyrk1B), a drop in the level of pERK1/2, and a drop in the level of pSTAT3 (El-Senduny et al., 2016). (SEE TABLE 1.1 IN APPENDIX)

2.7.7 FLAVONOIDS

Flavonoids belongs to polyphenols widely isolated from fruits, vegetables and certain beverages as secondary metabolites, used against cancer, Alzheimer's and vessel clotting. They are vital in a wide range of nutraceutical, pharmacological, medical, and cosmetic applications due to their outstanding biochemical and anti-oxidant nature. Because of their anti-oxidative, anti-inflammatory, anti-mutagenic, and anti-carcinogenic properties as well as their ability to modulate important cellular enzyme functions, flavonoids have health-promoting effects on the body. These include inhibiting several enzymes like xanthine oxidase, cyclo-oxygenase, lipoxygenase, and phosphoinositide 3-kinase. (Panche, A. N., Diwan, A. D., & Chandra, S. R. 2016). Flavonoids, a class of 4000 naturally occurring polyphenolic food compounds, are found in vegetation as water-soluble glycosides and frequently as acyl glycosides; in contrast, acrylate, methylated, and sulphate moieties occur less frequently and in smaller amounts. Plants have flavonoids mostly in their intracellular

vesicles, which are further split into subclasses based on the carbon atoms in the C ring that the B ring is linked to as well as the degree of unsaturation and oxidation. Flavonoids consist of anthocyanins, flavones, flavanols, flavanones, flavanonols, and flavanols or catechins. (Nicola Tazzini, 2014).

They are extracted from plants and they are used for growth, nourishment and defense against plaques. These compounds are distributed in fruits, herbs, vegetables, tea and cocoa Flavonoids have important biological activity giving distinct color, aroma to flowers, promoting pollination and fruit dispersion which helps in spore germination and nourishing of seedlings. They not only have protective effect on human body but also in plants protecting from biotic or abiotic injuries, stress, hardiness, drought resistance, heat acclimatization and freezing tolerance. They are UV filters to plants functioning tumors and microbes. They are used as chemo preventive and neuro preventive and as a disease therapy (Panche, A. N., Diwan, A. D., & Chandra, S. R., 2016).

2.7.7.1 Structure of Flavonoids

A 15-carbon framework, two aromatic (A & B) rings, and a (C) hetero ring make up the composition of flavonoids. The formula for the carbon skeleton is C6-C3-C6. According to the IUPAC, flavonoids may be divided into three different groups: bioflavonoids, isoflavonoids and neoflavanoids. Flavanols (such as quercetin and rutin), flavanones (such as naringenin and hesperidin), flavanols (such as epicatechin and Gallo catechin), flavones (such as luteolin and apigenin), anthocyanins (such as pelargonidin as well as malvidin), and isoflavonoids are additional subgroups that have been categorized (genistein and daidzein). This classification is based on difference in heterocyclic ring (Waheed Janabi et al., 2020).

Flavonoids are divided into aglycones, glycosides, and methylated derivatives. With the position of the benzene ring differentiating the flavonoid into flavonoids (2-position) and isoflavonoids, its six-member ring condensed with the benzene ring is either a -pyrone (flavanols and flavanones) or its dihydroderivative (flavanols and flavanones) (3-position). Flavanols and flavanones are distinct from one another by having hydroxyl groups in the 3-position and a C2-C3 double bond. The hydroxyl positions of flavonoids are at 3, 5, 7, 2, 3′, 4′, and 5′. The alcoholic group in structure are often Methyl ethers and acetyl esters whereas the linkage of glycoside is located

at positions 3 might be 7 with other carbon compounds (Shashank & Pandey, 2013). (FIGURE 1.8 IN APPENDIX)

2.7.7.2 Sources of Flavonoids

According to NHANES, US individuals (older 19 years) consume an estimated 200–250 mg of flavonoids per day on average, with flavan-3-ols accounting for 80% of this amount, flavanols for 8%, flavanones for 6%, anthocyanins for 5%, and is flavones and flavones for 1%. However, foods that contain flavonoids in dietary form include tea, citrus, tropical fruit juice drinks, berries, beverages, apple juice, grapes, mixed berries, red onion, kale, lettuce, tomatoes. Other examples of flavonoids include herbal tea extracts, black tea extracts, and oolong tea extracts. A number of factors, including farming techniques, ambient conditions, fruit ripening, storage, and food processing, affect the quantity and quality of flavonoids. (Jane, Drake, Delage & Crozier, 2016).

2.7.7.3 Effect of Flavonoids on Cancer

Flavonoids are dietary compounds playing crucial role against cancers. Fruits and vegetables are rich in flavonoids with chemo preventive agents such as intake of onions or berries, inhibits the activity of prostate, lung, stomach, and breast cancer as they contain quercetin. Wine in moderation prevents against the progression of lung, endometrium, esophagus, stomach, and colon (Shashank, Pandey 2013). Dietary flavonoids are important effectors in atherogenesis, LDL oxidation and inflammation. (Sarah, Rimbach 2011). Through suppression of mutated p53 protein, apoptotic, protein tyrosine inhibition, inhibition of temperature shock proteins, inhibition of estrogen receptor binding capacity, and inhibition of Ras protein expression, flavonoids have influenced a variety of hormonal activities and cancer prevention. (Shashank & Pandey, 2013).

Nuclear acids and proteins are oxidatively damaged by exposure to industrial chemicals, air pollutants, ionizing radiation, or UV light, which can result in tumour growth and a number of degenerative disorders. With regard to skin, pancreatic, lungs, prostrate, kidney, gut, colorectal, and thyroid cancers, flavonoids from cabbage, broccoli, sprouts, or sauerkraut, strawberries, spices, carrots, stalks, coriander, herbs, bulbs, citrus, turmeric, tomatoes, peppers, and whole grains are tumor-protective. Because isoflavones work as an estrogen antagonist and lower the incidence of estrogen-sensitive cancers, soybeans contain isoflavone genes that offer protection against prostate and breast cancer. Tomatoes work similarly as a chemo preventive for prostate cancer. (Waheed Janabi, A. H et al., 2020)

2.7.7.3.1 Effect of flavonoids on breast cancer

Genetic abnormalities causing malignant tumors are due to Mutations of p53. Cancerous

growth is inhibited by preventing the visibility of p53 arresting it in the G2-M cell phase. P53 cells are downregulated in breast cancer. Flavonoids inhibits tyrosine kinase activity as they are implicated in the transmission of growth factors to the nucleus, in tumor genesis through an ability to override normal regulatory growth control. The chemotherapeutic flavonoid, Quercetin was the first to act as inhibiting compound protecting against cancer. Heat shock proteins improves the progression of cancer cell by preventing themselves from cell cycle arrests. Flavonoids prevents the production and activity of heat shock proteins treating against breast cancer (Shashank, Pandey, 2013).

2.7.7.3.2 Effect of cancer on colorectal cancer

Flavonoids protects against cancer not only with early stages, but also with increase in development of tumor and spread into other organs and tissues and neuro damage. Crucial regulatory agencies of the epithelial-mesenchymal transition or regulatory molecules like MMPs, uPA/uPAR, TGF-, and other contributors to the complex process of metastatic spread are activated by regulation of key signaling pathways involved in the migration and invasion of tumour cells and metastatic progression. (Liskova et al., 2020). Flavonoids protects against colorectal cancer cells by intake of Isoflavones, anthocyanidins, flavones and flavanols (Marta Rossi 2006). Quercetin is known to possess chemo preventive by reduction of hepatocellular carcinoma HepG2 cells and inducing apoptotic cell number in colon rectal cells and human breast cancer MCF-7 cells (Kopustinskiene, Jakstas, Savickas, & Bernatoniene, 2020).

2.7.7.3.3 Effect on other cancers

Dietary compound, flavone epigallocatechin-3-gallate minimizes the growth of fatty acid-based synthase and lipogenesis in Men. They arrest the tumor growth factors. Lymphoid cells proliferation is observed by action of quercetin by inhibition of leukemia cells, gastric cancer cell, MKN-2, COLON 320 DM, human breast cancer cells, human squamous and gliosarcoma cells, and ovarian cancer cells. Genistein, daidzein, and biochanin protects against mammary carcinogenesis without reproductive or endocrinological toxicities (Shashank, Pandey, 2013). Kaempferol is a flavonoid with cytotoxic effects through ROS-mediated mitochondrial targeting. Ovarian cancer cells are protected by apigenin and luteolin. (Kopustinskiene et al., 2020).

2.7.8 ANTHOCYANIDINS

Anthocyanidins or anthocyanins are colored bioactive pigment in plants mainly of blue, red, or purple pigments. They are isolated from plants, in flowers, fruits, and tubers. Anthocyanins are known as flavylium ion, molecular structure depending on physical conditions such as pH, light and temperature for its stability (Khoo et al., 2017). Belonging to group of flavonoids, anthocyanins are colored secondary metabolites. They have

glycosylated polyphenols and water-soluble nature. They are isolated from cell vacuoles of plants; however, their color depends on the surroundings. Nature consists of many anthocyanins, in which 600 are identified and proven in researches divided into subgroups of anthocyanidins, pelargonidin, cyanidin, delphinidin, peonidin, petunidin, and malvidin having a potential role against biotic and abiotic stresses in plants. Anthocyanins are strong antioxidants with attractive colors and endless benefits to human health (Liu, Yury, Rob E., Leo, Richard, Arnaud 2018).

These unique pigments propagate, protects the physiology of plants in which they are present. Anthocyanins protects from any foreign material to plant such as herbivores and parasites, attracts pollinators and seed dispersers such as honey bees and protecting plants against biotic and abiotic stresses. Not only they guard the plants body but also have effectivity in treatments against diseases due to its anti-diabetic, their antioxidant, anti-inflammatory and neuroprotective properties. These flavonoids have solid structure belonging to polyhydroxy and polymethyl derivatives, with possibility of attached sugar groups or acylated moieties at different positions. Anthocyanins are extracted from flowers and the fruits such as red anthocyanins from of many plants red flowers, blue color anthocyanins from cornflower and blue chicory etc. These are used as herbal remedies for folk medicine, as coloring agents, and as food for prevention of diseases (Khoo et al., 2017).

2.7.8.1 Structure of Anthocyanins

Anthocyanins are vibrant giving life to the beauty of flowers and fruits. These fascinating colors have attracted mankind for centuries. Anthocyanin can give different colors to different species of plants such as yellow to sunflower or red/pink to roses. According to older books it suggested that colors are due to the pH of cell sap, but this concept died due to discovery of anthocyanins. The pigmentation, self-association and presence of aromatic rings are what makes anthocyanins colorful and interesting to study (Luis et al., 2021). The name anthocyanins are given because of glycosides of anthocyanidin which are origin of three basic colors such as the red, violet, and blue. Only few species packed themselves with versatility of colors. They can switch their color by fluctuations of pH, such as strongly acidic environment gives orange to red, whereas a reddish violet to violet color appears in weakly acidic or neutral solutions while in alkaline solution anthocyanidins gives blue color to plant (Joana Oliveira et al 2021).

Anthocyanidins include pelargonidin, anthocyanins, peonidin, delphinidin, petunidin, and malvidin; however, important anthocyanins are formed from the anthocyanidins' 3-glucosides and 3,5-diglucosides as well as residues of galactose, rhamnose, xylose, and arabinose in some species. (Joana Oliveira et al., 2021). It consists of phenols with fifteen carbon atoms composed of dual benzene with a three-carbon chain. They also have

flavylium nucleus which is highly reactive (Aanchal, Gupta & Sharma, 2019). To produce coloration, anthocyanins undergo different pathway induced by different ionization states and electronic rearrangements in the molecules depending on protonic concentrations in the environment (Mattioli, Francioso, Mosca, Silva, 2020).

2.7.8.2 Sources of Anthocyanins

Fresh fruits are appealing due to its bright appearance due to water soluble pigments, Anthocyanins. These are used as traditional medicine with wide range of characteristics. Anthocyanins are found in red peel of Apple (*Malus pumila* L.), dried apricots (*Prunus armeniaca* L), black bilberry extract, Blackberry, Blueberry, Cherry, Cranberry *V. oxycoccus* L. and American Cranberry, Redcurrant and Blackcurrant, Grape, and Haskap Berry (*Lonicera caerulea* L.). They are also present in Mulberry., Orange, Peach (Prunus *persica* L), Pear (*Pyrus* spp.), Plum (*Prunus domestica* L. and Other *Prunus* Species), Pomegranate (*Punica granatum* L.), Rosehip (*Rosa canina* L. and Other *Rosa* Species), Saskatoon Berry, Strawberry. (J. Zhang, G. B. Celli and M. S. Brooks 2019). Other foods that also include anthocyanins are Asparagus (*Asparagus officinalis* L.) Black, red, and kidney beans, Cabbage, Carrot (*Daucus carota* L.), Cauliflower, Eggplant: *Solanum melongena* L., Ginger: *Zingiber officinale* Roscoe, Lentil: *Lens culinaris* Medic., Peas, Peanuts, Pepper, Potato, Onion., Radish., Rhubarb, Soybean., Sweet Potato, Turnip, Barley, Corn, Rice, Rye, Sorghum and Wheat (J. Zhang et al 2019). (FIGURE 1.9 IN APPENDIX)

2.7.8.3 Impact of Anthocyanins on Cancer

Anthocyanins are free radical scavengers in nature that have antioxidant properties that protect against various pathogens, draw pollinators for pollination and predators for seed dispersal, as well as the new projected modulation of signaling cascades. They are also thought to have antioxidant capacity to protect plant cells from ultraviolet (UV) radiation and high light intensity, cold temperature, water stress, wounding, and to defend against microbes and phytophthora. Anthocyanin is produced in the vegetative and fruit tissues of plants, including pear, apple, citrus, Chinese bayberry, and peach, which are rich sources of vitamin C, flavonoids, carotenoids (provitamin A), and other nutraceutical compounds. Anthocyanins have anticancer, antioxidative stress, and anti-heart disease properties. (Tariq, Songtao, Faghihi, Haider & Fang, 2017).

2.7.8.3.1 Effect of Anthocyanins on Colon Cancer

Antioxidants and chemo protectants, anthocyanins have the capacity to stop the spread of colon cancer cells. Experimental studies employing a human colorectal adenocarcinoma (HT29) cell line revealed that anthocyanin from purple foods such as purple maize, chokeberries, bilberries, purple carrots, grapes, radish, and elderberries significantly influenced the growth inhibition (GI50) of tumour. Through chemoprotection and interactions with other phenols, anthocyanins function to inhibit the development of HT29

cells. Anthocyanins containing pelargonidin, triglyceride, and/or acylation with cinnamic acid demonstrated the least effect on HT-29 cell growth, but nonacylated Mon glycosylated anthocyanins had a larger inhibitory effect. (Pu, Bomser, Schwartz, Jian, Magnuson & Giusti, 2008).

Within 24 hours of exposure, anthocyanins from blueberry pyruvic acid adduct extracts inhibited the development of human HT-29 colon cancer cells, increased the expression of the tumour suppressor genes (p21WAF1 and p27KIP1), and decreased the expression of the cyclooxygenase-2 gene. Similar to anthocyanin, which has a preventive effect against colorectal cancer by causing cell-cycle arrest, anti-proliferative, and through apoptotic mechanisms, acute myeloid leukaemia cells were made to mature by TNF-related apoptosis-inducing ligand. In a cancer investigation, anthocyanin from berries and vines was found to have anti-invasive properties in human hepatoma Hep3B cells. (Khoo et al., 2017).

2.7.8.3.2 Effect of Anthocyanins on Breast Cancer;

cancer in breast cells was treated by anti-tumor drugs along with bioactive compounds which shows great potential in inhibiting the cells. According to research by P. Suganya Devi, Kumar, Das 2008, the use of red sorghum associated to bran anthocyanin induced growth inhibition of MCF-7 cells dose dependently. The formation of apoptotic bodies was observed along with fragmentation by anthocyanins on DNA to oligonuleosomal-sized fragments reducing the effect of MCF-7 cells. Luca et al 2019 investigates effects of strawberry anthocyanin extract on murine breast cancer cell lines, detecting a specific pathway (AMP-activated protein kinase or AMPK) of anticancer activity. Strawberries block cell viability and apoptosis, intracellular ROS rates, and cell oxidative damage in N202/1A (which has high levels of the HER2/neu oncogene) and N202/1E (which has low levels of the HER2/neu oncogene). Strawberry anthocyanins stimulated the expression of various proteins involved in apoptosis, autophagy, metastasis, oxidative state, mitochondrial activity, and the AMPK pathway, which in turn had an antiproliferative impact on cancer cells. (Devi et al., 2008)

2.7.9 PHYTOESTROGEN

Phytoestrogens are phytochemicals found in plant diets that have estrogenic and anti-estrogenic actions and have an activity comparable to that of oestrogen. Phytoestrogen-rich diets prevent estrogen-deficiency symptoms in postmenopausal women and have protective effects against bowel, prostate, and breast cancers as well as cardiovascular disease. (Gorzkiewicz, 2021). They function as estrogen-like substances that have a structure with 17-estradiol. Isoflavones, stilbene, coumestan, and lignan make up phytoestrogens. Soybeans and other legumes, especially red clover, contain isoflavones as phytoestrogens

in the form of genistein, daidzein, glycitein, formononetin, and biochanin A. Two isomers of the phytoestrogen resveratrol, known as cis and trans, are derived from grapes and peanuts. In terms of reproductive health, heart health, weight reduction, hormone-dependent cancers, bone and skin health, and immune system function, phytoestrogens are helpful substances. (Desmawati, D., & Sulastri, D. 2019).

Isoflavones belongs to flavonoids with important effect of scavenging of free radicals. They are most researched phytoestrogens including genistein and daidzein. They possess anticarcinogenic properties, antiallergic, antiviral and anti-inflammatory effect binding to estrogens receptors acting as phytoestrogens. Similarly, lignans are extracted from plants, such as grains, pulses, vegetables and seeds (Flax seeds). Metabolites of lignan include Enterolactone and enter diol, metairesinol e secoisolariciresinol. Coumestan are present in legumes with highest estrogenic activity. Stilbenes include resveratrol as a phytoestrogen produced by grapevines, peanut and Polygonum cuspidatum roots. They act anticancer, antioxidant and protection against atherosclerosis and cardiovascular diseases (Bacciottini, et al 2007).

2.7.9.1 Chemical Structure of Phytoestrogens

As seen in the image, phytoestrogens include isoflavones, lignans, coumestan, stilbenes, and the flavonoids quercetin and kaempferol. Similar to estrogens, they spread to the caveolae region of the membrane, allowing it to interact with other signaling molecules. They are phytoestrogens because when 17-estradiol (E2) binds to cell surface proteins, downstream signaling cascades are activated, causing calcium to flow, adenylate cyclase to become active and produce cAMP, phospholipase C (Moutsatsou,2006).

The three main families of phytoestrogens—flavonoids, lignans, and stilbenes—are a sizable and heterogeneous group that consists of a phenolic ring and two hydroxyl groups that can bind to the oestrogen receptors (ER). The two aromatic rings (benzene A and B) are connected by a chain of three carbons that is cycled by an atom of oxygen in the flavonoid's structure, which is C6-C3-C6. The 3-phenylchroman skeleton of isoflavonoids is split into isoflavones and coumestan. Genistein, daidzein, formononetin, and biochanin A are among those that have the B ring connected to the heterocyclic ring at the C3 position rather than the C2 position. Coumestan are flavonoids composed of the structure 1-benzoxolo(3,2-c) chromen-6-one. The potent stilbene is resveratrol made up of two phenolic rings connected by a styrene double bond. They occur in cis and trans form exerting anti-cancer effects (Torrens-Mas M, Roca P., 2020). (FIGURE 1.10 IN APPENDIX)

2.7.9.2 Sources of Phytoestrogens

Phytoestrogens in human body are breakdown and metabolized in intestine by bacteria. The final step occurs in liver as they conjugate there and then excreted from urine. Soybeans are the richest source of phytoestrogens. Isoflavones from liquid texture are absorbed at high rate in form of aglycones (Desmawati, D., & Sulastri, D. 2019). Estrogens are used in several events of body specially in target tissues such as uterus, breast, pituitary gland and hormone responsive tumors. Phytoestrogens are compounds that mimic the role of estrogen in human body isolated form plum, pear, apple grape berries, vegetables, beans, sprouts, cabbage, spinach, soybeans, grains, hops, garlic, onion, sweet potatoes, wine, tea along with botanical dietary supplements. Isoflavones are compound of beans, soy, lignans are extracted from flax seeds, grains, clover, alfalfa and soybean sprouts mainly, while stilbenes are extracted from the skin of grapes. Coumetarol are reported in Brussel sprouts and spinaches, while the highest concentrations are isolate from clover and in soybean sprouts. Soybeans are main compounds for phytoestrogens following kidney bean, American ground nut, chickpea, lentils, flaxseeds, sunflower seeds, peanuts, wheat bran, barley, rye bran, strawberry, cranberry, blueberry, raspberry, red cabbage, broccoli, garlic zucchini, carrot, green tea, beetroot and black tea (Bacciottini, L. et al., 2007).

2.7.9.3 Impact of Phytoestrogens on Cancer

Phytoestrogens have key role in protection against malignant tumors as the expression of estrogens beta type prevents cancer. Alpha estrogen is expressed in toxins related to ovarian cancer in epithelial and stomal regions while beta estrogens are dominant in granulosa cell-derived tumors. Phytoestrogens act in body to promote ERβ production in ovarian cancer cells which leads to inhibition of proliferation and enhancement of apoptosis acting as tumor-suppressor role in ovarian carcinogenesis. Phytoestrogens include daidzein, glycitein, equal and biochanin A, enter lactone, genistein, enter diol, coumetarol, quercetin, kaempferol, resveratrol and zeranol (Moutsatsou, 2006).

Cancer can also occur due to hormone changes due to diets and environmental conditions along with diseases epigenetics. The alter in hormone production may lead to cancer. Intestinal bacteria transform phytoestrogens from soy products, whole grain cereal foods, seeds, and possibly berries and nuts into hormone-like compounds with weak estrogenic but also antioxidative activity, preventing cancer. These phytoestrogens are composed of diphenol structure (lignans and isoflavonoids). The biological activity of sex hormones, intracellular enzymes, protein synthesis, growth factor action, malignant cell proliferation, differentiation, angiogenesis, and naturally occurring cancer-protective chemicals are all

influenced by phytoestrogens. Additionally, phytoestrogens are crucial for preserving estrogen-sensitive organs including the uterus, ovary, cervix, liver, and kidney by acting as an antioxidant, antimutagen, antiangiogenic, pro-apoptotic, and anti-cancer. (Zmejkoski et al., 2018)

2.7.9.3.1 Effect of phytoestrogens on breast cancer

By acting on oestrogen receptors, cell signaling pathways, regulating the cell cycle, apoptosis, steroid production, and epigenetic processes, phytoestrogens have an impact on target cells, including the epigenome of the formation and progression of breast cancer. Some of these phytochemicals have a preferential affinity for ER, which can inhibit the transcriptional growth-promoting activity of Er. Saturating doses of phytoestrogens, stimulating both ER and, exhibit growth inhibitory effects on breast tumour. These phytochemicals bind weakly to oestrogen receptors (ERs), and some have a preferential affinity for ER. Along with the suppression of cyclin D1 expression and the upregulation of cyclin-dependent kinase inhibitors (p21 and p27) and the tumour suppressor gene p53, signaling.

They function by activating or inhibiting kinases, which may change the ligand-independent transcriptional activity of oestrogen receptors or other transcription factors like AP-1 and NF-B. They also respond to growth factors. The creation of tyrosine kinase inhibitors is inhibited by substances such the isoflavones genistein and resveratrol, which change the expression and activity of the PI 3-Akt pathway and extracellular regulated kinase (ERK). In breast cancers, genistein in concentrations of 10-8 mol/L downregulates the expression of the MEK 1/2 and PI-3K/Akt pathways, which has been shown to enhance the efficacy of ER activation and decrease proliferation. Additionally, it guards against cancer in postmenopausal women (Bilal, I., Chowdhury, A., Davidson, J., & Whitehead, S. 2014).

2.7.9.3.2 Effect of phytoestrogens on prostate cancer

With the advancement of health problems, prostate cancer is one of most rising cancer. Phytoestrogens works to control prostate tumors. According to research and experiment from 3H-estradiol ligand binding assay using mouse uterine cytosol, 2.5 μM quercetin, baicalein, genistein, epigallocatechin gallate (EGCG), and curcumin displaced > 85% of estradiol binding along with apigenin and resveratrol displaced > 40%. This concentration proved that growth inhibition in LNCaP cells prevented progression of prostate cancers. Revestrol arrested the S phase cell cycle inhibiting cell growth by Inducing apoptosis. Other estrogens promoted the growth of PC-3 cells that prevented the growth of tumor of prostate cancer (Nader, Zhou, Browning, Ansell, Sakla, Lubahn & MacDonald, 2004).

2.7.10 PHYTOSTEROLS

Phytosterols are bioactive phytochemicals which occurs as cholesterol structure except for an extra hydrocarbon chain at the C-24 position in structure. They were biochemically described and reported in 1922. The sterols phytosterols are made of are Campesterol, *β*-sitosterol, and stigmasterol (Jiang et al., 2019). Phytosterols are crucial micronutrients and bioactive compounds. they are just like cholesterol, 250 in nature found as sterols and stenols. Phytosterols are phytochemicals they are present in cellular membrane and act as modulating membrane permeability and fluidity. They are present in fruits, green herbal vegetables, beans, nuts, legumes, whole grains, tubers and seeds proving to be great attraction for human health as antioxidant, anti-cancer and cholesterol-lowering mediators along with putative effect on preventing cardiovascular diseases. Since hyperons are not produced by the human body, they must be obtained through dietary sources. As a result, they can act either directly by interfering with specific proteins in the redox signalling pathways involved in various bodily physiological actions to affect immune response, mitochondrial dysfunction, oxidative stress, dyslipidemia, and gut dysbiosis. (Teresa et al., 2020).

By preventing cell growth, metastasis, and the triggering of apoptosis, phytosterols found in food can shield the body from cancerous tumours. Phytosterols have been shown to act as host systems and perform anticancer effects by enhancing the immune system's detection of cancer, inhibiting the growth of hormone-dependent endocrine tumours, and controlling the production of sterols. (Jiang, L., Zhao, et al., 2019). Phytosterols are absorbed when dietary cholesterol incorporates into micelles in enterocytes. Intestinal serum cholesterol mediates transport of enterocytes across apical membrane producing Niemann Pick C1-Like 1 (NPC1L1), which uptakes phytosterols. By using intestinal acyl-coenzyme A (CoA) cholesterol acyltransferases, which have been isolated from the liver, cholesterol binds to esters in enterocytes. These chylomicrons, which are pro-inflammatory mediators, are then released into the intestinal lymphatics. Blood enters through the lymphatic system after that. Chylomicron leftovers are ingested by the liver when circulating chylomicrons are depleted of triglycerides. Following this, cholesterol in chylomicron remnants is converted back into other lipoproteins for circulation or it might be secreted into bile and discharged into the small intestine. They are strong bioactive substances as a result (Susan B. Racette, 2017). (FIGURE 1.11 IN APPENDIX)

2.7.10.1 Structure of Phytoestrogens

Phytosterols are cholesterol like molecules but built with a slightly different structure. It acts like cholesterol in nature involving side chain and a double methylated or ethylated bond. Dietary phytosterols are divide into β-sitosterol (SIT), Campesterol and stigmasterol

(Atif B. Awad, Carol S. Fink 2000). These fatty compounds are natural steroids with unsaponifiable plant lipids. A saturated bond is present in phytosterol structure at C-5 to C-6 bond along with aliphatic side chain. This aliphatic chain is attached to C-17 bond of carbon along with hydroxyl group to C-3 group. There are non-esterified and esterified forms of cinnamic acid/fatty acids (FA) or as glycosides of plant sterols. The bound form of phytosterols is hydrolyzed by pancreatic enzymes in small intestine estimated of 50% absorption in depending on types, structure and molecular weight of phytosterols (Salehi Bahare et al., 2021).

Vegetable and fruit extracts include phytosterols with a C-5 double bond and a 3-hydroxyl group, but the C-24 side chain has undergone structural changes. They are created by phytosterols being saturated at the C-5 position, as opposed to ergo sterol, brassica sterol, and stigmasterol, which are phytosterols having a side chain that is C-22 unsaturated (Alpe Berdiel & Francisco, 2010). Phytosterols are recognized into following classes;

The stenols group which doesn't have any double bond in its sterol. Stenols include sitosterol and Campesterol. Several dietary compounds include these stenols such as seeds, nuts and several fruits. Sterols are phytosterols consisting of a double bond in its sterol ring including β-sitosterol, Campesterol, and stigmasterol abundantly present in fruits vegetables and legumes along with nuts and seed oils. (Susan B. Racette, 2017).

2.7.10.2 Sources of Phytosterols

Phytosterols are bioactive compounds that are analogous to cholesterols. According to scientific researches, two hundred and fifty phytosterols have been isolated till now, Phytosterols helps in modulating membrane permeability and fluidity present in fruits, vegetables, beans and pulses, nuts, legumes, whole grains and barley, tubers, wheat germ, vegetable oils, and sunflower seeds. They are extracted from Various food compounds such as Refined olive oil, Virgin olive oil , Argan oil , Sunflower oil, Artichoke, Green asparagus, Green beans, Broccoli, Cabbage, Carrot, Cauliflower, Celery, Chard, Cucumber, Eggplant , Endive, Escarole, Garlic , Leek , Lettuce Marrow, Onion, Parsley, Potato, Green pepper, Red pepper, Spinach, Tomato, Rice, White wheat, Wheat grain, Wheat bran, Wheat flour, Barley, Rice bran, Corn bran, Oat bran, Legumes Chickpea, Lentil, White bean, Peanuts, Fruit Apple, Apricot, Banana, Cherry, White grape, Kiwi, Melon, Olive, Orange, Peach, Pear Plum, Strawberry, Watermelon, Avocado, Pineapple, Apple, Custard apple, Raspberry Almond, Hazelnut, Peanut, Pistachio, Sunflower seed and Walnut (Teresa, Francisco, Marañón, Bañuls, Rocha & Víctor 2020.)

2.7.10.3 Impact of Phytosterols on Cancer

Phytosterols are dynamic phytochemicals that mimic the action of cholesterol against

several cancers. These plant sterols initiate anticancer response by effecting host system and promoting one`s immunity to recognize and compete tumors. Along with delaying cell cycle progression, inducing apoptosis, and inhibiting tumour spread, they have an impact on the hormonally dependent development of endocrine cancers (Peter Bradford , Awad, 2007). Phytosterols inhibit proliferation, induce apoptosis, and prevents metastasis of tumor. High intake of sitosterol is proved by observational studies that they promotes the reduction of growth of cancer cells of breast and prostate cancer. According to control group of experimental studies in Uruguay, that intake of dietary phytosterols were less in the blood of cancer patients than in serum of cancer free patients. Similarly experimental study done in USA reported that breast cancer women were have extremely low phytosterols in their plasma serum than non-cancer patient. However, several studies indicated its anti-inflammatory, anti-tumor response in cellular pathways and as anti-oxidants. (Susan B. Racette, 2017).

2.7.10.3.1 Effect of Phytosterols on Colorectal Cancer Cell

Phytosterols are robust anti-cancer bioactive phytochemicals. Beta-sitosterol, a phytosterols, interacts with colon cells in a dose-dependent manner. It was tested on colon cells in rats given 1,2-dimethylhydrazine (DMH) without toxic effects, and it also attenuated the expression of ß-catenin and proliferating cell nuclear antigen (PCNA) in malignant tumours of the human colon. When combined with 5-fluorouracil, phytosterols had an impact on colorectal malignant cells, namely Caco-2 and HT-29 cell lines, causing S-phase cell cycle arrest, apoptosis, and increasing caspase activation. (Saleh Bahare, Quispe Cristina et al 2021). Although the precise mechanism by which phytosterols work has not been established, it has been suggested that they do so through a number of different mechanisms, including the reduction of angiogenesis, the inhibition of carcinogen production, the reduction of cancer cell growth and multiplication, invasion and metastasis, and the induction of cell cycle arrest and apoptosis, as well as the production of reactive oxygen species. (Vanu Ramkumar et al., 2015).

2.7.10.3.2 Effect of Phytosterols on Breast Cancer Cell

By causing apoptosis and enhancing Fas protein expression, caspase 8, and tumour necrosis factor-related apoptosis-inducing ligand change of structure and function of cancer cell membranes, ß-sitosterol supplementation has substantial effects on MCF-7 and MDA-MB-231 breast cancer cells. Phytosterols induced MDA-MB-231 breast cancer cells' apoptosis through an estrogen-signaling-independent mechanism. Hyperplastic lesions of mammary glands in women were reduced by

preventative lipoprotein and oxidation prevention. (Salehi Bahare, Quispe Cristina et al 2021). Phytosterols when incorporated in membranes they alter their structure regulating cellular phosphorylation cascades and changes in signal transduction. (Woyengo, T., Ram Prasath, V. & Jones, 2009)

2.7.10.3.3 *Effect of Phytosterols in Lung and Cervical Cancer*

ß-sitosterol and daucosterol induces arresting of tumor in G2/M phase cell cycle mainly by apoptotic death of A549 lung cancer cells and by reducing proliferation of tumors. *ß*-sitosterol reduces cervical cancer cells (HeLa), interfering on DNA fragmentation, dephosphorylation, mitochondrial depolarization, and intracellular Ca^{2+} influx and ROS level raise, cell cycle arrest in phase G0/G1 and cell necrosis in Caco-2 cells (Salehi Bahare, Quispe Cristina et al., 2021)

2.7.11 CAROTENOIDS

Carotenoids were isolated from archaebacteria as lipids of cell membranes. They are most abundant natural bioactive compounds classified into α-carotene, β-carotene, γ-carotene, lycopene, phytoene, phytofluene, lutein, zeaxanthin, β-cryptoxanthin, astaxanthin, and fucoxanthin according to function, structure, source and end groups. They are known as isoprenoids units as they are made up of 8 isoprene joined together in head tail structure (Riaz M., Zia-Ul-Haq M., Dou D., 2021). Carotenoids have several biological functions such as coloration patterns in plants and animals, screening from excessive light and spectral filtering such as of vitamin A, defense of egg proteins from proteases in some invertebrates; the direct carotenoid derivative--retinal--acts as visual pigment in all animals and as chromophore in bacteriorhodopsin photosynthesis, retinoic acid in animals and abscisic acid in plants serve as hormones along with anti-cancer and anti-oxidants properties. Carotenoids have various properties of oxidation, hydrogenation, isomerization, cyclization, and halogenation which helps to perform their functions (Riaz M et al. 2021).

Salmon, birds, and other living things like birds and animals have bioactive pigments called carotenoids. -carotene, -cryptoxanthin, and -carotene all have vitamin A activity. Children's blindness is mostly caused by vitamin A deficiency in poor nations like Tanzania, India, Niger, etc. Carotenoids are potent antioxidants that serve as singlet oxygen scavengers, capturing the excitation energy of these reactive oxygen species and dissipating it as heat. They can also inactivate singlet oxygen chemically by reacting with it in a way that renders it irreversibly inactive. Therefore, they protect from cancers and other inflammatory diseases. The common carotenoid, β-carotene reduces the effect of cardiovascular disease risk, while α-carotene helps to fight cancer. Another important carotene is Lycopene with

exceptional biological efficiency to scavenge singlet oxygen and protect protective against malignant tumors while Lutein and zeaxanthin are also antioxidants that uses blue light filters of high energy however, they are yellow pigments by nature. β-cryptoxanthin is also a carotenoid demonstrating antimutagenic, osteosynthesis and immunomodulatory effect (Alan Giovanni de Oliveira Sartori et al., 2014).

2.7.11.1 Structure of Carotenoids

There are now 700 known carotenoids, which may be distinguished by the orange, yellow, and red hues of poly-isoprenoid hydro-carbons linked to prokaryotic cells, higher plants, and concentrating in animal lipids (Ola Tunde, Ahmed et al 2020). Carotenoids are composed of a trans-configured linear chain of 10 to 11 conjugated C=C bonds. The double bonds serve as auxiliary light-harvesting pigments in all plants, absorbing light where chlorophyll fails to do so. They are able to transfer excitation energy from carotenoid excited states to chlorophyll in the light-harvesting complex as well as (ii) from triplet chlorophyll or singlet oxygen to carotenoid in photosynthetic reaction centers, protecting against light damage. (Muhammad Zia-Ul-Haq, 2021)

Carotenoids are made up of 15 conjugated double bonds divided into carotene and xanthophylls according to structures. Carotene such as β-carotene are hydrocarbons in nature whereas xanthophylls are oxygenated compounds. they are hydrophobic organic solvents and non-Saponi able fats with antioxidant functions present in fruits and vegetables (Ola Tunde., et al 2020). C30, C40, C45, and C50 are doubly bonded with carotenoids. Carotenes are hydroaromatic rings with four isoprene molecules attached to both ends. These rings, which have three ionone rings with -, -, and pseudo-ionone rings, are referred to as ionospheric rings. Vitamin A is created from carotenoids. The yellow-colored isomers known as xanthophylls, including as lutein, zeaxanthin, -cryptoxanthin, astaxanthin, and fucoxanthin, are discovered interacting covalently with fatty acids. They are not stereoisomers, and some of them have a hydroaromatic structure with an OH group in one of their ionic rings. Others are carotenoids alcohol. Thus, this structure makes them unique Oguz Merhan (2017). (FIGURE 1.12 IN APPENDIX)

2.7.11.2 Sources of Carotenoids

Throughout the form of an oily solvent, carotenoids are extensively disseminated in plants. They are also esterified with fatty acids, proteins, and carbohydrates, which control their biological roles including energy transmission, light absorption during photosynthesis, and defense against the damaging effects of light on the cells. Fresh broccoli, butter, egg yolks, veggies, carrot, potatoes, pumpkin, tomatoes, red peppers, dark-colored vegetables, greens, citrus, banana, pumpkin, and lettuce are all off-limits to them. Zeaxanthins are colored chemicals that break down picrocrocin to produce the color, flavor, and scent of saffron. (Oguz Merhan, 2017). β-carotene are carotenes which are abundant in Canarium

monophylum, apricots slices, cantaloupe juice, carrots chops, pumpkin and sweet potato. Phytoene also belongs to carotenes isolated from watermelon, grapefruit and tomatoes whereas lutein can be found in mangoes, oranges, papaya, peaches, prunes, spinach and squash. Another carotenoid, β-cryptoxanthin is associated to citrus fruits, papaya and peach whereas pigmented dehydroxylated form of xanthophyl Zeaxanthin is found in whole grain corn, vegetables, alfalfa, wolf-berry and marigold (Ola Tunde et al., 2020).

2.7.11.3 Impact of Carotenoids on Cancer

Yearly 10 million cancer cases occurs and numbers are nonstop. Hence consumption of foods such as mangoes and pulp, legumes and beans, peaches, cantaloupes, persimmons, apricots, papayas, carrots, sweet potatoes, arugula, water-cress, broccoli, pumpkins, tomatoes fulfill the body requirement of carotenoids preventing the risk of cancer such as prostate, brain, eye, breast and lung cancer. The carotenoids -carotene, astaxanthin, and -cryptoxanthin exhibit anti-cancer effects, as well as immune system activation, suppression of cancer cell growth, and promotion of connexion43 expression. The gap junction protein is upregulated by the Connexion43 gene, which stops the growth of tumour cells. Human plasma contains the dietary antioxidants cryptoxanthin, lutein, and zeaxanthin, which prevent age-related diseases like cancer, cataract development, macular degeneration, and cardiovascular disorders. They also induce apoptosis in the human HL-60 cancer cell by fragmenting DNA and preventing cell division. (Ola Tunde, Ahmed & Tijani et al 2020).

Beta-carotene is a cancer preventive bioactive compound while beta-cryptoxanthin showed anti-tumor effects by Stimulation of the expression of RB gene, an anti-oncogene, and p73 gene helping in human cancer prevention (Nishino H, Tokuda H, 2000). Dietary carotenoids with biotherapeutic potential for chemoprevention of breast, colorectal, lung, and prostate cancers include astaxanthin, fucoxanthin, siphonoxanthin, -cryptoxanthin, -carotene, and lycopene. These compounds have cytotoxic, antiproliferative effects that modulate oxidative stress and redox balance, mitogen-activated protein kinase. (Ramesh, Young, Keum, Maria, Rengasamy 2020).

The primary factor in cancer that makes it challenging to cure is the spread of malignant cells. Additionally, carotenoids inhibit the migration and invasion of cancer cells as well as the progression of metastasis by modulating regulatory molecules and important regulators of the epithelial-mesenchymal transition, such as matrix metalloproteinases (MMPs), tissue inhibitors of metalloproteinases (TIMPs), urokinase plasminogen activator (uPA) and its receptor (uPAR), and hypoxia-inducible factor-1. (Koklesova L, Liskova A, 2020).

2.7.11.3.1 Effect of carotenoids on Breast cancer

In Breast cancer cells, lycopene and beta-carotene have greater role as they effect the cell cycle and cell viability in cancer cell lines (Koklesova L, Liskova A 2020). β-carotene helps to stimulate expression of breast MCF7 cancer along with functioning as growth inhibition

and apoptosis. They also promote production of reactive oxygen species and liberation of cytochrome C which is responsible for the anti-cancer and anti-tumor activities. Carotenoids also down-regulates cyclin D1 expression and upregulates cyclin-dependent kinase inhibitor p21 expression and showcasing inhibitory effects of carotenoids on K562-cell proliferation is supported by rosiglitazone. In this way carotenoids helps in inhibiting breast cancer (Ola Tunde., et al 2020).

2.7.11.3.2 Effect of carotenoids on liver cancer

Carotenoids prevents the proliferation of liver cancer cells by preventing expression of murine embryonic liver cells and human hepatoma cells inhibiting malignant tumor (Ola Tunde et al., 2020).

2.7.11.3.3 Effect of carotenoids on prostate cancer

Lycopene from tomato inhibited the expression of survival and growth-associated genes in PC3 cancer cells and regulated the activation of apoptosis, whereas lutein caused cell cycle arrest, apoptosis, and growth-associated biological marker genes to be expressed. (Ola Tunde et al., 2020).

2.8 Remedies to Treat Malignant Tumors

Cancer is the most effective and life taking disease which is caused by various factors and mutations on oncogenes. In the last 15 years, there has been a noticeable rise in chronic diseases including cancer, type 2 diabetes, Cardiovascular, certain neurological problems, etc. Cancer is a major cause of mortality that affects the world's health and is challenging to control if not detected and treated promptly. Global figures for 2018 show that there were 9.6 million cancer deaths and 18.1 million new cases. According to the research, 1 in 5 men and 1 in 6 women will get cancer or a tumour throughout their lifetime, and 1 in 8 men and 1 in 11 women will pass away from a malignant tumour. The cases are unstoppable and will continue to rise exceptionally in the next decade. To treat it, essential steps and remedies are needed before onset of tumors and moving it to fourth stage which is the last and cannot be treated then (Aanchal Walia, Amit Kumar Gupta & Vatsala Sharma, 2019).

Cancer is the uncontrollable division of cells which thus forms tumors and disturbs the functions of normal cells, nutrients intake and damage tissues organs and blood supply. W H O (World Health Organization) observed a fact report stating the number of cancers. It concluded that cancer is a devastating cause of deaths around the world with mortality of 8.8 million deaths in 2015 resulting in 1 per every 6 deaths being cancer while the latest reported that 140,690 cancer cases are reported in 2019. There is majority number of cases fighting this disease lifelong while some are successful in this battle and some lost their lives unfortunately. The prevalence is also observed in Pakistan, when a study was taken place in 2012. This research reported almost 63,415 males and 85,590 females cancer

patients with most common lung cancer, while breast cancer in women continues to top the list with the maximum reported deaths in Pakistan with wide range of causes such as including hormonal, hereditary, metabolic, autoimmune, smoking cigars, alcohol consumption, dietary imbalance (malnourished or obese), radiation or infections like Human Papilloma Virus (HPV), Hepatitis B Virus (HBV), Human Immunodeficiency Virus (HIV), H Pylori and many more (Saeed et al., 2019).

Cancer being the leading causes of morbidity and mortality globally while cardiovascular disease being second leading cause responsible for one in eight deaths worldwide while — more than AIDS, tuberculosis, and malaria together are less in stats data. The cancer prevalence of cancer is more in America, Australia, New Zealand and Western Europe, India and Pakistan as compared to the rest of the world (Desai, A. G. et al 2008). Radiotherapy, hormone immunotherapy, heat stress, immunization, photodynamic therapy, chemo and radiation, transplantation of stem cells surgery, and targeted therapy are some of the current therapies. (National Cancer Institute 2021). While chemotherapy is most used treatment with side effects. Cancer cells are deficient to many normal cells function and they divide to vast number of cells thus are susceptible to chemotherapeutic drugs along with radiations. Chemotherapeutic agents are now being discovered after 5 decades of hard work and research but they come with several toxicity of body as well such as 5-fluorouracil, is most widely used chemotherapeutic agent but can myelotoxicity, cardiotoxicity act as a vasospastic agent. Similarly, doxorubicin is chemotherapeutic drug which is associated with cardiac toxicity, renal toxicity, and myelotoxicity while bleomycin causes pulmonary toxicity, cutaneous toxicity. The toxicity of drugs doesn't stop here. Cyclophosphamide treats tumors along with causing bladder toxicity and cardiotoxicity in the form of hemorrhagic cystitis, immunosuppression, alopecia. (Desai, A. G. et al., 2008). Biomarker testing is also done for malignant genes which observes genes, proteins, and other substances of tumor markers which gives unique pattern tumors. These biomarkers help to identify which organs is affected and which treatment should one doctor go for. These biomarkers include tumor testing, tumor genetic testing, genomic testing or genomic profiling, molecular testing or molecular profiling, somatic testing and tumor subtyping. When this is paired with a treatment the biomarker testing is then known as companion diagnostic test (NIH 2021). Another therapy known as hormone therapy is a treatment to treat cancers and shorten the size of tumors by blocking hormones that have direct or indirect influence on cancer. This hormonal therapy is mostly used to treat breast and prostate cancers. Neoadjuvant therapy works by shrinking the tumor before a radiation therapy or surgically removing it, while adjuvant therapy is a hormonal therapy that the lowers that risk of cancer again in life. Hormonal therapy can also destroy cell that have returned again completely. It comes with side effects such as hot sweating and flashes, loss

of interest (cognitive weakness) in or ability to have sex, weakened bones, diarrhea, nausea, enlarged and tender breast, fatigue and vaginal dryness (NIH 2015).

Another method to treat cancer is Hyperthermia which uses heat at 113 °F on body tissues with cancer. This not only damage the tumors but also kills the onco-cells. This thermal therapy uses methods to generate heat, including probes that generate energy from microwaves, radiofrequency, lasers, and ultrasound, heating fluids with the perfusion technique, including blood or chemotherapy drugs, and submerging the entire body in a hot water bath or heated blankets. Appendix, bladder, brain, breast, cervical, esophageal, head and neck, hepatic, pulmonary, malignant, mesothelioma, sarcoma, and rectal cancers are all treated with hyperthermia. (NIH 2021). Immunotherapy is cancer prevention treatment which boosts the immune system to works against tumors. Tumor-infiltrating lymphocytes or TILs are promoted by immune therapy which are natural regulators to cure cancer preventing or slowing the growth of cancer. The types of immune therapy are Immune and checkpoint inhibitors**,** T-cell transfer therapy**,** Monoclonal antibodies and Immune system modulators (NIH 2019). Photodynamic uses the light activation through drugs such as photosensitizing agent which destroys the tumor. The side effects include Coughing excessively, trouble swallowing, stomach/gut pain, painful breathing, shortness of breath and skin problems, such as redness, stinging, swelling, or itching (NIH 2021).

These treatments come with side effects as well (Aanchal Walia, Amit Kumar Gupta & Vatsala Sharma, 2019) reported the need of natural plant-based compounds with minimum or no side effects at all. They stated that fruits and vegetables are enriched with anti-cancer phytochemicals which body is in need to boost its immune system and targeting the disease area. Carotenoids for example are associated to decrease the chances of breast cancer, head and thyroid cancer and prostate cancer. A risk assessment to control lung cancer concluded that intake of Alpha-Tocopherol, Beta-Carotene, α-carotene, lutein, lycopene, β-cryptoxanthin, and β-carotene in non-smoking patients helps to control the progression of cancer due to their pro-oxidant effects. This was proved by Beta-Carotene and Retinol Efficacy Trial. Lycopene helps in treating prostate cancer by enhancement of the oxidation stress defense system. Bioactive chemicals also help to treat cancers of tissues of breast, head, mouth cells, pharynx, and larynx with bronchioles, gut, ovarian, and uterus cancer. (Aanchal Walia, Amit Kumar Gupta & Vatsala Sharma 2019). Following are some Chinese remedies used to treat cancers or promoting chemotherapies;

Due to its anti-proliferative, pro-apoptotic, anti-metastatic, anti-angiogenic, autophagic, reversal multidrug resistance, balancing immunity, and enhanced chemotherapeutic effects, Chinese herbal medicine is the oldest traditional medication used globally to treat cancer. These drugs include triptolide, turmeric, epigallocatechin, berberine, artemisinin, ginsenoside Rg3, ursolic acid, silibinin, emodin, ginsenoside Rh2, cucurbitacin B,

and dihydroartemisinic, etc. These medicines work by immunomodulation and therapeutic effect on body. These herbal medicines are used for a long time now as they exhibit anti-inflammatory effect by cytotoxic effects and inhibition of tumor microenvironment and improving chemotherapy. As per reports, Epigallocatechin gallate targeting laminin receptor effected prostate cancer while ginsenoside Rh2 inhibited P-glycoprotein (P-gap) activity to reverse multidrug resistance. (Luo et al., 2019).

Curcumin is a traditional herb extracted from turmeric known as diferuloylmethane. This a traditional Indian medicine which exerts properties such as antiangiogenic, antitumorigenic and antioxidant, negatively regulating growth factors, protein kinases, transcription factors, cytokines, receptors, and other oncogenic proteins to treat tumors. Curcumin works by arresting phases to reduce cell growth in cell cycle. They help to treat breast cancer by multidrug resistant cells and inhibition of ornithine decarboxylase activity. They help to reduce he proliferation of breast cancer cells via the EGFR pathway while they inhibit Fatty acid-binding protein 5 that negates the effects of retinoic acid via the FABP5/PPAR β/δ pathway. It promotes the expression of RA-resistant TNBC cells to RA mediated growth suppression to treat cancer (Amol, Singh, Nobre, Kirolikar, 2016).

Berberine is herb found in Oregon grape, tree turmeric, and other plant. They are extracted from *Coptidis chinensis*, *Mahonia bealei* and *Phellodendron chinense* Schneid. This herb is used along with food or as supplements or in the form of paste. They exert anti-tumor effects over ovarian cells, breast, thyroid cancers, leukemia, multiple myeloma, nasopharyngeal carcinoma, and neuroblastoma, and esophageal by inducing apoptosis and inhibiting or movement of tumor to other organs and tissues preventing angiogenesis. They work by promoting cell phases such as G1 and M phase arrest in murine prostate cancer cells. It is effective in treating breast cancer as they arret cell cycle in human estrogen receptor positive breast cancer cells but not in estrogen receptor negative cells. Not only breast cancer they are also used to treat human colorectal cancer cells by inducing apoptosis of HCT-8 cells. Autophagic cancer cell death is induced by berberine by enhancing GRP78 levels and the metastasis of cancer is reduced by up-regulation of plasminogen activator inhibitor-1 (Luo *et al.*, 2019).

A recipe to use berberine from barberry (Summit Malhotra, 2021) Table 1.2
Ingredients; 1 cup Water 2 Teaspoon of barberry fresh
Instructions; Heat your water in a saucepan. Heat it until steam starts to evaporate. Chop your berries into smaller pieces. Dried berries could be crushed. Add these into hot water and oil it for 15 minutes This tea 3- 4 times a day helps to regulate your body.

Another Chinese herb Artemisinin is isolate form wormwood (*Artemisia annua* L.). Through the induction of apoptosis and cell cycle arrest, inhibition of cell proliferation and growth, metastasis, and angiogenesis, artemisinin has an anticancer effect on cancers of the lung, liver, pancreas, colorectal, esophageal, breast, ovarian, cervical, head and neck, and prostate. They cause the release of cytochrome c and caspase-9 cleavage, which increases apoptosis in human breast cancer MCF-7 cells and inhibits the cancer cell through mitochondrial-dependent pathways. they also promote death via Bcl-2 down-regulation in female cervix cancer HeLa and CaSki cells and Bim-dependent intrinsic pathway in human hepatocellular carcinoma HepG2 and Huh7 cells (Luo *et al*, 2019). It can also be used in fresh or dry form to make an infusion or tea. From following way tea can be made (Annie Price, CHHC, 2020).

First take one teaspoon of fresh wormwood and boil it in 1 cup of boiling water for 15-20 minutes.

They are strong and bitter in taste so not more than 1 teaspoon is desirable.

It can also be taken in powdered form and added your foods.

Black seeds**,** are extracted from Ranunculaceae family known as black cumin of Indian spices. Black cumin is commonly used as protective remedy for several disorders including cancer. According to Islamic Religion, black cumin is treatment for all ailments accept aging or death. Black cumin is also accepted in Holy Bible written as Malathion by Hippocrates and believed to be exceptional seeds to aid the disease. Black seeds have several properties such as anti-allergic, non-diabetic anti-

hypertensive, immunopotentiation, anti-inflammatory, and antimicrobial activities. These seeds consist of quinone a bioactive compound indicating several chemo preventive activities against cancer and reducing the toxicity of antineoplastic drugs. By use of croton oil black seed inhibits skin carcinogenesis by two stage initiation-promotion. The components of black seed such as thymoquinone induces cytotoxic effect on cancer cell lines such as parental and multidrug-resistant phenotype expressing cells. The cancer cells are reduced by triggering of apoptotic cell death Nd arresting of G1 cell cycle. (L. Ait Mbarek et al., 2007).

Mushrooms, vegetable food group but is biologically different. They consist of array of protective features as they consist of filamentous fungi becoming the source of macromolecules, lipids, potassium, calcium, Vitamin D and fibers. This healthy food is consisted of polysaccharides which contributes to prevent the growth of tumor cells and metastasis of cells. they exhibit anti-angiogenesis and anti-cancer effect. Mushrooms source Ganoderma lucidum has anti-tumor effect as they reduce NO mediated endothelial cell invasion whereas Antrodia cinnamomea from Taiwan exhibits anti-cancer effect by In vivo method. China and Japan are the source of Grifola frondose which inhibits the expression of VEGF dependent angiogenesis. They work by downregulation of tumor signaling accompanied with reduction of oxidative stress serving as anti-oxidants (Anindita Deb Pal 2017).

Radix Astragali is also known to exhibit immunomodulatory effect by increasing the activity of lymphocytes cells and macrophages and promoting the secretion of interleukin-6 (IL-6) and tumor necrosis factor (TNF) which helps to fight against cancer. They exhibit anticancer activities against, breast and colorectal cancers reducing chemotherapy side HB toxicity, nausea and vomiting (Ye, L., Jia et al 2015).

Garlic, is known as Allium sativum and is the best affordable herb used world widely as culinary spice in foods and medicinal herb to treat cancers. Garlic helps to decrease the cholesterol levels and triglyceride in blood. They exhibit anti-cancer effect along with the alteration of blood thickness by promoting platelet growth and promoting fibrinolysis. They are used for treating gastrointestinal tumors sickle cell anemia, atherosclerosis, peptic-ulcer disease, chronic candidiasis, hypertension, hyperlipidemia, hypertriglyceridemia, and peripheral vascular disease. The anticancer effect is exhibited by allicin from alliin which exerts inhibitory effect on CYP2C91, CYP2C19, CYP3A4, CYP3A5, and CYP3A7 metabolism. They are

also known to decrease HIV protease inhibitors saquinavir70 and ritonavir protecting from HIV disease (Alex Sparreboom et al., 2004).

Blood root, is ornamental plant belong to the family-Papaveraceous, genus Sanguinaria, species-Sanguinaria Canadensis which exerts antineoplastic activity in emetic, respiratory aid and other treatments. Similarly, Milk Thistle is isolated from family-Asteraceae, genus-Silybum, species-Silybum marianum used as treatment for liver diseases and cancer (Supriya Korrapati, Kurra & Puttugunta, 2016). Melissa officinalis L. Essential Oil named as lemon balm found in Europe and Mediterranean region. They are used for their digestive, antispasmodic, sedative, antiviral, and antioxidant properties, as well as their antibacterial, antifungal, spasmolytic, and antitumoral effects. They are also used to treat cancer. According to the results of the MTT assay, lemon balm oil had a cytotoxic effect on human cancer cell lines from the heaptic, colon, breast, and leukaemia (HL-60 and K562) subtypes. In human glioblastoma cell lines apoptosis was induced demonstrated by the presence of DNA fragmentation and activation of caspase-9 and caspase-3 thus preventing from cancer. This oil reduces the expression of MRP1 in GBM cell cultures that express an active form of the transporter in the treatment of tumor. Thyme is herb of Lamiaceae family which is traditionally used for several diseases. The essential oil of thyme exhibits antioxidant and anticancer activities against human prostate carcinoma A549 cancer, and MCF7 breast cell lines. The cytotoxic effect of thyme oil was observed in 2007 against ovarian adenocarcinoma cell line resistant to three chemotherapeutic drugs. the use of this oil exhibited its anti-cancer effect in 30 days by inhibition of tumor proliferation, reduced tumor volume, and delayed the mortality. (Rossella Russo, 2015).

Dang shen root is also an herb to improve appetite by mixing off other herbs. They are extracted from family-Campanulaceae, genus Codonopsis, species-Codonopsis pilosula. They are also used to improve immunity and boost energy. Ginger root belongs to family-Zingiberaceae, genus Zingiber, species-Zingiber officinale used for nausea. They are also used as neuro-protective, gastroprotective, anti-emetic and hepato-protective agents. Another herb, Cinnamon is isolated from family-Lamiaceae, genus Rosmarinus, species-Rosmarinus officinalis and use as flavoring agent as it is enriched with proanthocyanins and cinnamaldehyde. Rosemary is sued as herb and oil. They are extracted from Lamiaceae, genus Rosmarinus, species-Rosmarinus officinalis. And is favorite ingredient of Italian cuisine used against

cancer. Saffron is widely used herb in sweet desserts of Asian cooking and contain carotenoids. Saffron gives food a distinct yellow golden color and is used as anti-tumorigenic agent. Similarly, Broccoli is a vegetable which contains lutein and zeaxanthin as bioactive compound. Broccoli is having various functions and is anti-oxidant and anti-cancer use to treat bladder and colorectal cancers. (Supriya Korrapati, Kurra & Puttugunta, 2016).

St. John`s wort is herb use to treat symptoms of menopause and depression. They belong to Hypericum perforatum. Specie. (Supriya et al., 2016). St. John`s Wort is diuretic compounds used for treatment of neurologic and oncologic disorders. It is a mixture of various compounds such as tannins, proanthocyanins, flavonoids (mainly hyperoxide, rutin, quercetin, and kaempferol), bioflavonoids (e.g., apigenin), phloroglucinol derivatives like hyperforin, phenolic acids, volatile oils, and naphtodianthrones, including hypericin and pseudohypericin. They are antidepressants inhibiting the reuptake of neurotransmitters in synapses by hypericin and hyperforin. St John`s wort exerted impact on LS-80 intestinal carcinoma cell by induction of P-glycoprotein in a dose-dependent manner. P-glycoprotein increases with St John`s wort in peripheral blood lymphocytes. However, it can interact with anticancer drugs and stops its absorption so testing and research is still needed (Alex Sparreboom 2004).

Beverages made from natural compounds have key role against cancer. This includes tea, coffee, dairy products such as smoothies' milk, yogurt etc. they have anti-angiogenic effect if made from herbs of bioactive compounds. Tea is most taken beverages in world and is cheapest and of great varieties. Black tea, green tea, barberry tea, ginger tea, turmeric tea and Oolong tea helps to treat inflammation, promotes digestion and remove toxins from body. Tea extracts consist of polyphenols which effects VEGF moderated angiogenesis. Green tea is enriched with epigallocatechin 3- gallate which inhibits tumor production by decreasing VEGF and iNOS expression. Similarly leaves from Origanum onites L. have anti-mutagenic effect by cell migration assay. Cafestol is present in unfiltered coffee extracts. It exhibits anti-inflammatory, anti-tumorigenic by blocking the signaling induced processes of cell proliferation. Milk from camel treats chronic diseases and prevents cancer by decreasing the expression of VEGF cancer cells decreasing the rate of neo-vascularization during tumorigenesis. Lactoferrin in milk promotes the

chemoprevention by apoptosis, reducing cell cycle progression, angiogenesis and altering tumor signaling pathways (Anindita Deb Pal, 2017).

Flax Seeds**,** are isolated from flax plant. They are brown and golden with active components and rich source of fiber, omega 3 fatty acids, and lignans. Lignans gives flax seeds its estrogenic activity as it is involved in metabolism of enterodiol and enterolactone in digestive tract. These are phytoestrogens involved in elimination of 2-hydoxyesterone exhibiting powerful anti-cancer activity. secoisolariciresinol diglycosidic in flax seeds helps to fight malignancies. Similarly, Black cohosh from *Cimicifuga racemose is used to treat cancers. This is sued while chemotherapy and radiotherapy to shrink the size of tumor and treatment of* menopausal signs and symptoms. It is used for women who don't want to use Hormonal Replacement Therapy (HRT). This herb is effective in women as it contains triterpene glycosides, resins and caffeic, isoferulic and fukinolic compounds exhibiting estrogenic and anti-estrogenic properties and synergistic effects for breast cancer patients. Ginseng from *Panax ginseng* is widely used China, Korea, Japan and Russia as roots in treating cancer. Studies in Korea concluded that fresh Ginseng instead of dried roots used in juice or tea are more effective in cancer (Shareef et al., 2016).

Following contains table of some foods that are used as anti-cancer compounds Table 1.3

Plant	Source	Effect on cancer	Reference
Astragalus	Beans, legumes	Immune booster, all cancers	Supriya et al. 2016
Echinacea	Sunflowers, rag weeds	Colon, brain, pancreatic	Supriya et al. 2016
Curcumin	Turmeric	Breast cancer, colon	Supriya et al. 2016
Golden seal	H. canadensis species	Different cancers	Supriya et al. 2016
Red clover	Trifolium pratense, peas and beans	Breast and prostate	Supriya et al. 2016
Ginger	Ginger roots	Colon, ovarian, prostate	Supriya et al. 2016
Garlic	Allium sativum	Colorectal cancer	Supriya et al. 2016

Turmeric	Turmeric spice	Lung, breast, prostate,	Michael et al 2020
Saffron	Crocus sativus L	Colon, skin, cervical, breast, liver, pancreatic	Samarghandian et al 2014
Oil of nutmeg	Myristica fragrans	Hepatoma cancer cell	Mickus R et al 2021
Soy	Cereals, soymilk, soybeans	Breast cancer, lung colon	Supriya et al. 2016
Cranberry	Vaccinium macrocarpon	prostate, lung, esophageal, ovarian, bladder, prostate	Andrea S. 2017
Salvia oil	Sage leaves	Renal, breast, prostate	Rossella Russo 2015
Thyme oil	Lamiaceae family	Prostate, lung, breast	Rossella Russo 2015
Lemon grass oil	Cymbopogon flexuosus	colon, neuroblastoma, liver, cervix	Rossella Russo 2015
Cardamom	Zingiberaceae family	Breast, ovarian and prostate cancer	Supriya et al. 2016
Kava	Piper Methysticum	Lung, bladder	Agarwal, R 2008
Grapes	Fruit	Lung, prostate, colon and breast cancer	Supriya et al. 2016
Aloe vera	family-Asphodelaceae	Prostate and lung	Supriya et al. 2016

CHAPTER 3

DISCUSSION

Cancer is disease effecting globally and is considered for its more than 7.6 million deaths worldwide which comprises of 13% of deaths. The numbers are unstoppable expected to cross 13.1 million by 2030. The research on cancer has outgrown various advancements but still developed and under developing countries are in rage this deadly malignancy. With the number of increasing cancers, the discovery and experiments are still under consideration. Anti-cancer therapeutic agents and compounds are now being extracted and used successfully due to its rich abilities to shrink tumor and treating comorbidities related to it. These natural compounds are high in their activities and chemical structures which makes them suitable for modern natural drug design and to be used directly for treatment of cancer. The experimental evidence of the bioactivity of these compounds are evident by in vitro/vivo experiments including oncogenic assays, fractionation, target bases therapeutic drug, and evaluating their mechanism of action on cancer cell line (Manu Mangal et al., 2013).

Cancer is now known as epigenetic malfunction influencing dietary habits and depends on role of lifestyle and nutrition of a person along with environmental and social factors. Behaviors, depression, hormonal changes and toxins can disturb the cell line production damaging organs and tissues leading to physiological and cancer development. In particular, plant-derived bioactive nutrients are profound agents used to induce normal cell growth promoting proliferation and differentiation decreasing the activity of cancer. Bioactive compounds are used to decrease tumorigenesis by prevention of malignancies and reducing metastasis. The cancer is defined by its cancer stem cell (CSC) subpopulations. They differ due to hypoxic and acidic microenvironments along with various niches. The cancer cells can vary and can be resistant towards tumor relapse and treatments. Thus, bioactive compounds are used as natural substance to counteract the effect of cancer metabolism in tumor micro environment (Pistollato et al., 2015).

Different cancer stem cells have surface marker which interacts with bioactive constituents such as flavones, Geraniin, curcumins, saponins and others. The Signal transduction pathways which promote cancer are being studies and evaluated. The epidemiology of these compounds such that green tea used leaves of plants are effective along with used as flavoring compounds or spices. Teas have great effect on minuting cancerous tumors. Clinical trials are still undergoing and need experimental data of mechanism of action of

these compound on tumor cell. This research demands a potential investigation in pharmacokinetic indicators, interaction, metabolism, toxicity, drug interaction and polymorphism and drug mechanism. The issues to study the importance and impact of all plant based bioactive compounds on cancer requires the development of complete model for cancer stem cells along with test for mechanism and amount of dose (Nyamdavaa et al., 2020).

By clarification and confronting the issues better treatments can be developed for use of these compounds and incorporating into diet. By assessing biological activities of all pathways, we can have significant reduction in most prevalent cancer such as lung, prostate and ovarian cancer. Use these compounds solely for treatment have slower effect. But using them by combination with other therapies can have solid determined results. They can reduce the self-renewal along with metastasis of cancer if used wisely (Nyamdavaa et al., 2020). Thus, more clinical trials are needed in this field and advancements can lead to safe healthier future with sustainable natural treatment.

CONCLUSION

Natural sources are the best sources to treat malignant tumors as they have potent features of chemotherapeutic and chemo preventive agents. They are now widely used to treat cancers. The prevalence of cancer is increasing day by day which demanded a need of therapeutic agents to forecast its action. Bioactive compounds and phytochemicals are possible source to treat malignant tumors and resistant cancer cells such as Curcumin and tocotrienols, flavonoids, tannins, anthocyanins, phytoestrogens, phytosterols have shown a diverse chemo preventive and are therapeutic agents to fight against cancer due to their anticancer activities. Fruits and vegetables are enriched with agents possessing oxidative resistant properties along with anti-inflammatory and anti-mutagenic credentials and anti-carcinogenic agents. Berries are enriched with polyphenols such cranberries, citrus fruits, elderberries, raspberries and strawberries all exhibiting anti-oxidant effect by reducing hydrogen peroxide as well as TNF-αinduced angiogenesis through downregulation of the expression of pathways. Proanthocyanin are coloring compounds present in cranberry extracts preventing tumor in endothelial cells by blocking migration. Revestrol is isolated from grapes preventing skin cancer. Lyceum barbarum is flavonoids which act as anti-tumor. Psidium Guajava is rich source of minerals and vitamins to prevent the expression of NFkβ, COX-2 and NOS mediated pathways. Gallic acid is used to treat ovarian cancer while tomatoes consist of lycopene and a source of phytonutrients and chemicals reducing prevalence of cancer.

Not only fruits and vegetable but cereals, beans legumes and essential oils also consist of anti-carcinogenic activity as they have polyphenols known as hydroxycinnamic acids and ferulic acid. Cereals are known to exhibit anticancer effect by targeting EGFR mediated VEGF signaling pathways, MMPs and NOS. Legumes are known to have dietary inositol which decreases VEGF expression and inhibits the migration of endothelial cells. Similarly, rice bran is filled with nutritional compounds inhibiting migration of cancer cells. Soybeans consist of soy compound. Soy is a source of fatty acids, proteins, fibers and carbohydrates preventing from tumors. There are many bioactive compounds against cancer and to determine its effect the pathogenesis of that cancer is required. There are several studies that have reported treatment against malignant tumors but exact target remains elusive and need more experimental researches. The working mechanisms of some of compounds is unknown yet but they exhibit therapeutic effect and used to target cancer. Targeted therapy and stem cell therapy which used this plant based bioactive compounds have replaced current synthetic treatments due to their wider and diverse actions. Many compounds are undergoing clinical trials in which some are proven anticancer agents and some have unknown efficacy towards tumor.

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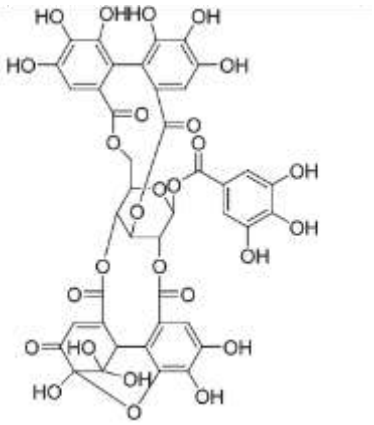
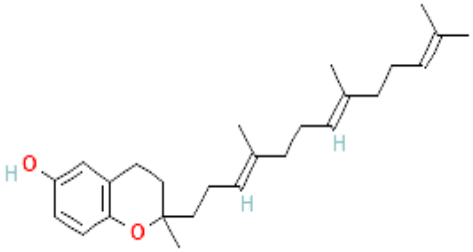
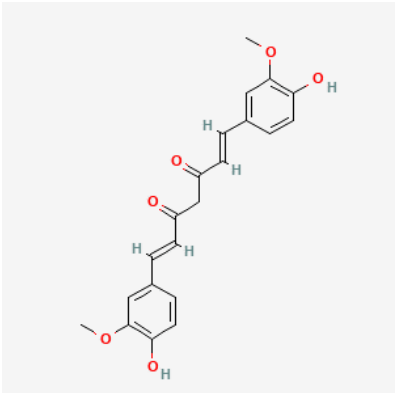
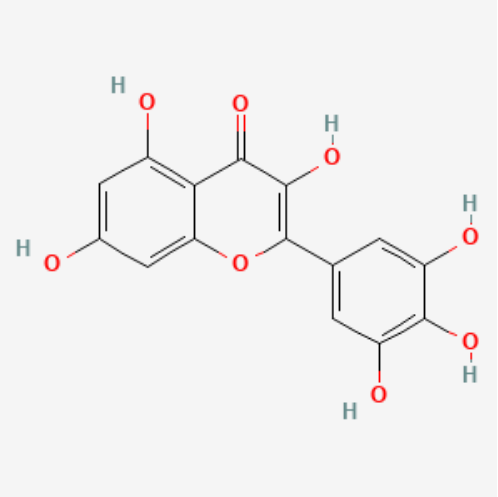
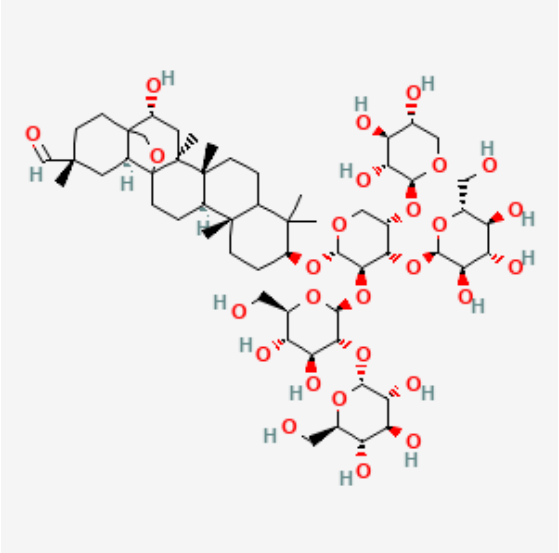
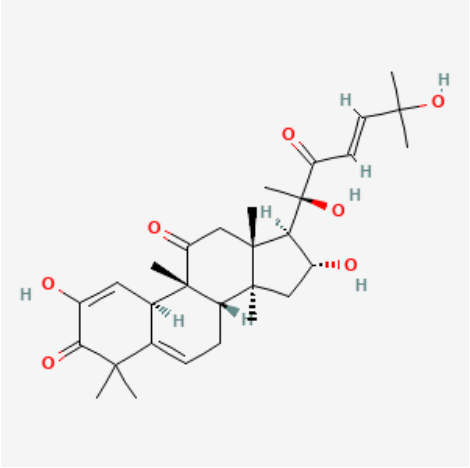
APPENDIX

FIGURE	COMPOUND	REFERENCE
Figure 1.2	Geranin	Perera et al., 2012 
Figure 1.3	Tocotrienols	National Center for Biotechnology 2022 
Figure 1.4	Curcumin	National Center for Biotechnology Information (2022). 
Figure 1.5	Myricetin	National Center for Biotechnology Information (2022)

		
Figure 1.6	Saponins	National Center of Biotechnology 2022 
Figure 1.7	Cucurbitacin	National Center for Biotechnology Information (2022) 
Figure 1.8	Flavonoids	National Institute of biotechnology 2022

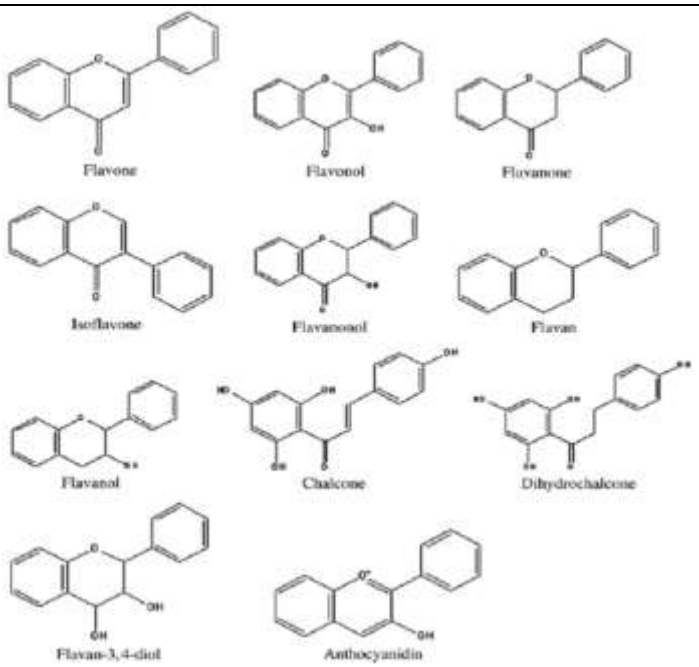
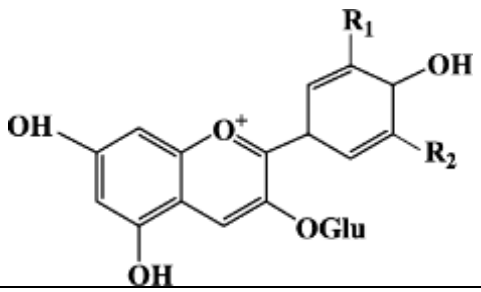
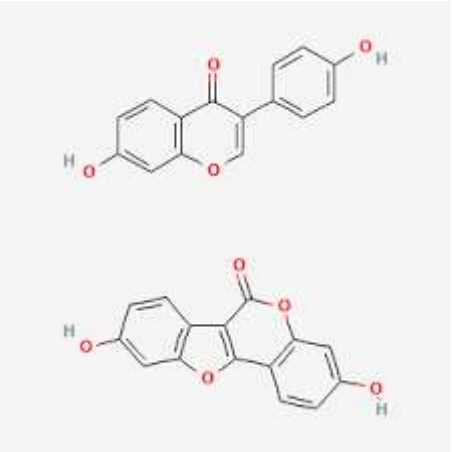
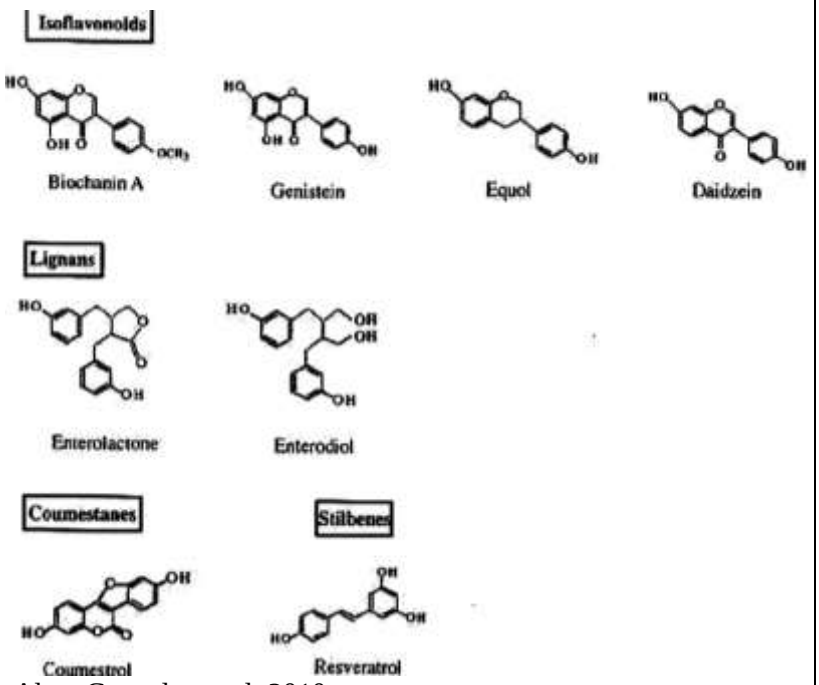
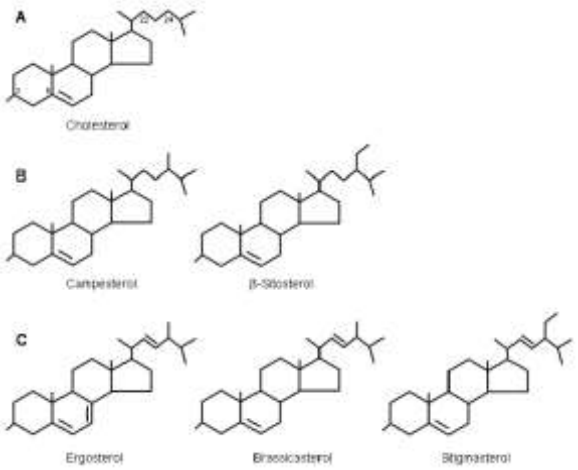
		
Figure 1.9	Anthocyanidins	Tadesse 2012 
Figure 1.10	Phytoestrogens	Moutsatsou 2006 

Figure1.11	phytosterols	 Alpe, Gonzalez et al. 2010
Figure 1.12	Carotenoids	Zielinska-pukos et al. 2017 

Tables

TABLE 1.1; Source through Alghasham A. A. (2013)

Types Of cucurbitacin	Plants source	Effect on cancer
Cucurbitacin A	*Trichosanthes cucumerina*	Lung A549 cell lines
Cucurbitacin B	*Cucurbita andreana* *Wilbrandia ebracteate*	Leukemia (HL60, U937, THP1, NB4, K562, BALL1)
Cucurbitacin D	*Trichosanthes kirilowii* *Cucurbita andreana*	Hepatocellular: Hep-2, HL60, Breast: MCF-7, Colon: HCT-116
Cucurbitacin E	*Bacopa monnieri* *Cucurbita andreana*	M5076, HCT-116, MCF-7, NCI-H460, SF-268, PC-3, HepG2
Cucurbitacin I	*Momordica balsamina L* *Cayaponia tayuya*	HCT-116, MDA-MB-231, MDA-MB-468, NCI-H460. SF-268
Cucurbitacin Q	*Cayaponia tayuya*	Lung: A549, A549, MDA-MB-435, and v-Src/NIH 3T3
Cucurbitacin R	*Cayaponia tayuya*	Colon: HCT116 and Hke-3