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Article · September 2024

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INVESTIGATION OF ANALGESIC, ANTI-INFLAMMATORY AND ANTIDIABETIC EFFECTS OF *PHYLLANTHUS BEILLEI* LEAVES H.

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Abstract

The current study was carried out to explore the analgesic, anti-inflammatory and anti-diabetic potential of methanol extract of *Phyllanthus beilei* H. The analgesic activities were determined by acetic acid induced writhing test in mice. The oral administration of doses 500 mg/kg of methanol extract of *Phyllanthus beilei* H. inhibited 42.22% of writhing movements compared to standard drug diclofenac-Na 94.28% writhing movement inhibition induced by acetic acid. Anti-inflammatory effect of ethyl acetate extract was determined after oral administration of 1% Carrageenan, paw edema in mice. Mice treated with ethyl acetate extract of *Phyllanthus beilei* H. (500 mg/kg) moderately decreased in paw volume at 180 min and 240 min compared with mice of control group. Here, pronounced effects were observed in extract group 34.36% inhibition of paw edema compared to that of Standard Group 55.13% inhibition of paw edema. In the Oral glucose tolerance test the control group of mice exhibited higher blood glucose levels whereas, mice treated with extract (500 mg/kg) showed significant decrease in blood glucose level after 30 mins and 120 mins compared with control group of mice.

Key words: *Phyllanthus beillei, Analgesic, anti-inflammatory, antidiabetic*

Introduction

The history of drug from natural sources is very significant and well known. Medicinal plants play a major source of therapeutic agents. Pain is an unsound counterpoint to many medical problems and one of the most important therapeutic priorities is the control of pain. [1] Despite current traits in ache treatments, the scientific community still desires secure, effective, and potent analgesic capsules for the remedy of various painful conditions in particular the continual ache [2]. Thousands of patients with excessive pain, inclusive of that due to most cancers or excessive injury, should depend on contemporary regimes (peripheral or centrally performing) like morphine, aspirin, and nonsteroidal anti-inflammatory drugs [3, 4].

Studies have shown that opiates purpose bodily dependency, tolerance, and addiction at the same time as NSAIDs usually motive gastrointestinal issues [5, 6]. For that, the invention of different options to deal with pain is vital [7]. Natural herbal therapy might be a foremost option for the treatment of opioid dependence or addiction and discontinuation [8].

A study have proven that infection is normally elicited by way of damage to living tissues on account of infectious agents (Bacteria, virus, fungi, Protozoa), Allergic conditions (Allergic rhinitis, Allergic asthma) , Trauma(Blunt and Penetrating injuries), Physical agents (Burn, Radiation), Chemical agents (Corrosives like acids, alkalis) and faulty immune response.[9, 10] The indispensable persistence of infection is produced through numerous anti-inflammatory mediators and presence of monocytes [11].

Chronic infection plays a role in the burdens related to pathological situations such as development of obesity-associated diabetes caused by insulin resistance. [12,13]. Diabetes mellitus is a persistent metabolic sickness characterized through high degree of glucose within the blood due to lack of insulin motion [14] and also affects a population of about nine million adults (elderly 20-79) global in 2017 [15]. This disease is related to micro- and macrovascular headaches which result in the improvement of incapacity and existence-threatening medical conditions [16]. Hyperglycemia, hyperlipidemia, and oxidative stress are the primary crucial characters of diabetes mellitus and constitute a main risk aspect for the development of headaches of diabetes [17, 18]. Now a days, diabetes can be managed by insulin and some oral antidiabetic agents but still now the scientists are searching the permanent remedy of diabetes [18, 19].

The active constituents found in the plant sources are used as a vital source for the preparation of herbal drug as well as of modern medicine. Thus, we need to be more aware of searching a large number of medicinal plants, active constituents and their properties to treat various diseases for the wellbeing of the human beings [20, 21].

Methods

Plant material: Leaves were collected from *Botanical Garden, Dhaka,* Bangladesh. This was then separated from other plant parts, dried in the sun, cutting into small pieces and finally grinded into coarse powder by using grinder. The powdered leaves was kept in an sealed container and stored for further use.

Preparation of crude extract: The powdered leaves of plant parts was taken in a clean, bottle and saturated in methanol for 10 days with infrequent shaking and stirring. It was then filtered by cotton and finally by using Whatman filter paper. The filtrate was the subjected to evaporate the solvent to obtain desired crude extract.

Drugs and Chemicals:

Metformin hydrochloride was used as the standard drug for diabetes management Alloxan monohydrate and Carrageenan was purchased from LobaChemie, India and purchased from Otto Chemika, India respectively. Glucometer meter (Hsinchu, Taiwan) was used for test of glucose level. Acetic acid was used from the laboratory and the Diclofenac-Na was obtained from a pharmaceutical company in Bangladesh named Square Pharmaceuticals Limited.

Experimental Animals:

Healthy Swiss albino mice (21-30g) of 8 weeks old were collected from the animal house of Jahangirnagar University, Dhaka, Bangladesh

and kept under appropriate conditions (12/12 hrs of light/dark cycle). The mice were given with standard pellet diet as food. The animals were cared according to the guidelines of our institute.

Analgesic activity test:

In order to perform the experiment, the animals were subdivided into three groups. The writhing was induced by intraperitoneal administration 1% acetic acid. The test samples, reagent or extracts were given to test animals as follows:

Group No.	Group name	Number of animals (n)	Administration of test samples/reagent
Group-1	Control group	(n=5)	0.5% Methyl cellulose
Group-2	Standard group	(n=5)	Diclofenac-Na (10 mg/kg)
Group-3	Extract group	(n=5)	Plant Extract (500 mg/kg)

The effect of control group and standard group was compared with control group.

Anti-inflammatory activity test:

The anti-inflammatory activity test was performed by inducing paw edema in the left hind paw of each mouse through the uses of 1% Carrageenan dissolved in normal saline. The test samples, reagent or extracts were given to test animals as follows:

Group No.	Group name	Number of animals (n)	Administration of test samples/reagent
Group-1	Control group	(n=5)	0.1% Carboxy Methyl cellulose
Group-2	Standard group	(n=5)	Diclofenac-Na (10 mg/kg)
Group-3	Extract group	(n=5)	Plant Extract (500 mg/kg)

The paw volume was measured at 60, 120, 180, 240 minutes by using a micrometer screw gouge. The effect of control group and standard group was compared with control group.

Antidiabetic effect test by Oral Glucose Tolerance Test (OGTT):

For the Oral Glucose Tolerance Test (OGTT) the test animals are divided in three groups. The test samples/reagent or extracts were given to test animals as follows:

Group No.	Group name	Number of animals (n)	Administration of test samples/reagent	
Group-1	Control group	(n=5)	Glucose 2gm/kg glucose	-
Group-2	Standard group	(n=5)	Glucose 2gm/kg glucose	Metformin (100 mg/kg)
Group-3	Extract group	(n=5)	Glucose 2gm/kg glucose	Plant Extract (500 mg/kg)

The blood samples were collected at 30, 90- and 120-minutes after glucose ingestion and blood glucose level were estimated Gluco meter (Hsinchu, Taiwan).

Statistical Analysis

All values were measured as mean ± Standard error of mean (SEM). Statistical analysis was accomplished by One-way analysis of variance (ANOVA), followed by using student-t test. Results were measured as significant if p values less than 0.05 ($p<0.05$).

Results

Phytochemical test results of leaves extract of *Phyllanthus beillei* H.

This test exhibited the presence of different group of constituents such as tannin, alkaloid, glycoside, Saponins and Flavonoid, in methanol extract of *Phyllanthus beillei* H. that have pharmacological properties. The results of chemical tests of the plant extract are given in the table 1.

Analgesic activities of leaves extract of *Phyllanthus beillei* H.

In this study, the methanolic extract of *Phyllanthus beillei* H. leaves exhibited analgesic activity showed in the table-2. This result of plant extract (500 µg/disc) exhibited a promising result of analgesic effect by showing a result of % of Acetic acid-induced writhing inhibition about 57.14 %. This result ensures the presence of analgesic activity of methanol extract of leaves of *Phyllanthus beillei* H.

Result of anti-inflammatory of leaves extract of *Phyllanthus beillei* H.

In this study, the methanolic extract of *Phyllanthus beillei* H. leaves exhibited anti-inflammatory activity showed in the table-3. This result of plant extract (500 µg/disc) exhibited a promising anti-inflammatory result on Carrageenan induced paw edema in mice. From this experiment it is assumed that the methanolic extract of leaves of *Phyllanthus beillei* H. may possesses some compounds having anti-inflammatory effect.

Anti-diabetic activities of leaves extract of *Phyllanthus beillei* H.

This study was performed through Oral Glucose Tolerance Test (OGTT) methods by ingestion of glucose (2gm/kg body wt.) into the mouse orally. In this study, the Control Group received glucose & 0.5% Methyl cellulose whereas Standard Group was given glucose & 100mg/kg Metformin. Extract Group was given glucose and treated with 500 mg/kg body weight (p.o) of the crude extract of *Phyllanthus beillei* H. From this experiment it was observed that the methanolic extract of leaves of *Phyllanthus beillei* H. have promising glucose reducing effect which was confirmed by comparing with the normal control group and standard group in the experiment.

Discussion

Plants possesses a lot of groups of chemical compounds. The available phytochemical test results of leaves extract of *Phyllanthus beillei* H. showed presence of Tannins, Alkaloids, Glycosides, Saponins & Flavonoids but Steroids are absence. The screening results of constituents is shown in the Table 1.

The oral administration of doses (500 mg/kg) of extract *Phylanthus beillei* H. promisingly inhibited 57.14% of writhing activities, whereas diclofenac-Na induce standard group exhibited 85.71% writhing movement inhibition in compared to the control group shown in the table-2. Thus, this results expressed a prominent analgesic effect of *Phylanthus beillei* H.

After oral administration of 1% Carrageenan, paw edema in mice of both control and experimental groups were significantly shown in Table-3. In control group the highest intensification in paw volume was observed after 60 min and retains for the next hour. Mice treated with the extract of *Phyllanthus beillei* H. (500 mg/kg) strongly decrease in paw volume at 180 min and 240 min compared with mice of control group. Here highly pronounced effects were observed with extract (500 mg/kg) 34.36% and inhibition of paw edema respectively and this effect is closely similar that of Standard Group 55.13% inhibition of paw edema.

Both the diabetic control and experimental groups of mice exhibited significantly high blood glucose levels after oral administration of glucose, as shown in Table-4. The diabetic control group showed an increase in blood glucose level after 30 min and continued over the next hour. Mice treated with plant extract showed substantial decrease in blood glucose level at 90 min and 120 min compared with diabetic control mice. Thus, prominent effects were observed with Extract Group 500 mg/kg compared to that of standard group and normal control group.

Conclusion

A plenty of plants are used for medicinal purpose due to having active chemical compounds and plenty of studies have attempted to prove scientifically on these medicinal plants. *Phyllanthus beillei* H. is one of the important medicinal plants among them. In this study, the plant exhibited a promising effect regarding analgesic, anti-inflammatory and glucose reducing activities. Hence, further studies are required to find out the active chemical compounds having the pointed activities as well.

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Table-1. Results of chemical group tests:

Tested groups	Methanol extract of *Phyllanthus beillei* H. Leaves
Tannins	+
Alkaloids	+
Glycosides	+
Saponins	+
Steroids	-
Flavonoids	+

(+) indicates presence and (-) indicates absence of the components

Table-2: Analgesic effects of the methanol extract of *Phylanthus beillei* H. on writhing on experimental mice.

Animal Group	Writhing Counting (Mean ± SEM)	% of Writhing Inhibition
Control Group	35±0.22	-
Standard Group(100mg\kg)	5±0.11	85.71*
Extract Group (500 mg/kg)	15±0.36	57.14 *

The values were expressed in Mean ± SEM. In each experimental group encompassed 5 animals (n=5) and the results were compared to the Control Group (n=5). * Designates significant change compared to control group ($p<0.05$).

Table-3: Anti-inflammatory effects of the methanol extract of *Phyllanthus beillei* H. extract on 1% Carrageenan induced paw edema on mice.

Time	Control Group (mm)	Standard Group (10 mg/kg) (mm)	*Phyllanthus beillei* H. Extract (500 mg/kg)
0 min	5±0.075	4±0.058	4.2±0.002
60 min	4.5±0.065	3.36±0.025	3.93±0.004
120 min	4.2±0.075	3.03±0.065	3.45±.005
180 min	4.06±0.055	2.17±0.045	3.10±0.004
240 min	3.90±0.045	1.75±0.065	2.56±0.002
% of Paw Volume Inhibition	-	55.13%*	34.36%*

The values were expressed in Mean ± SEM. In each experimental group encompassed 5 animals (n=5) and the results were compared to the Control Group (n=5). * Designates significant change compared to control group ($p<0.05$).

Table-4: Effect of the methanol extract of *Phyllanthus beillei* H. on oral glucose tolerance test in mice

Time	Control Group Glucose level (mM/L)	Standard Group Glucose level (mM/L)	Extract Group (500 mg/kg)
0 min	5.3	5.6	5.7
30 min	19.8	14.4	16.23
60 min	23.4	16.3	18.83
90 min	22.5	11.5	16.13*
120 min	19.3	9.4	13.53*

The values were expressed in Mean ± SEM. In each experimental group encompassed 5 animals (n=5) and the results were compared to the Control Group (n=5). * Designates significant change compared to control group ($p<0.05$).