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RESEARCH ARTICLE

Evaluation of Anti-inflammatory and Anti-diabetic activities of *Actinodaphne madraspatana* bedd leaves

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ABSTRACT:

The present study was carried out to find out the *in-vivo* anti-inflammatory and anti-diabetic activities of ethanol extract (200 and 400mg/kg) of leaves of *Actinodaphne madraspatana* (*A. madraspatana*) on Swiss Albino rats. The anti-inflammatory activity was investigated in carrageenan induced rat paw edema model which was compared with standard drug indomethacin at a dose level of 10mg/kg and the parameter measured being the paw volume by mercury displacements at 0, 15, 30, 60, and 120 minutes. The edema was induced in rats by administration of 1 % w/v solution of carrageenan in normal saline solution (1%w/v). The anti-diabetic activity was investigated in streptozotocin induced diabetic rat, which was compared with standard drug glibenclamide at a dose level of 4 mg/kg and the parameter measured being the blood glucose level on 0, 7, 14, 21 days. Diabetes was induced in rats by administration of streptozotocin (60mg/kg) in ice cold citrate buffer (pH 4.3). Results of pharmacological activities revealed that the ethanol extract of the plant leaves showed the significant ($p<0.001$) anti-inflammatory and anti-diabetic activities in a dose of 200mg/kg and 400 mg/kg body weight. The ethanol extract of leaves of *A.madraspatana* possess the anti-inflammatory and anti-diabetic activities.

KEYWORDS: *A.madraspatana* Leaves, Acute toxicity study, Ethanol extract, *In-vivo* pharmacological activities.

INTRODUCTION:

The use of medicinal plants and traditional medicines in developing countries as therapeutic agents for the maintenance of good health is well known in the literature. Medicinal plants containing various phytoconstituents are used to treat animal and human diseases and are considered as a rich resource of pharmacologically active ingredients which can be used in the development and synthesis of new drugs[1].

Medicinal plants play a critical role in the development of human cultures and moreover, medicinal plants, considered as a source of nutrition, and are rich in fiber and antioxidants. Antioxidants compound possesses anti-atherosclerotic, anti-inflammatory, anti-bacterial, anti-viral, anti-carcinogenic, and anti-tumour activities to greater or lesser extent[2]. Medicinal plants have a promising future because there are about one million of plants around the world and most of their biological activities have not investigated yet and their biological activities could be decisive in the treatment of present or future studies[3].

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A.madraspatana is one the most used herbal remedy in the natural medicine. It belongs to the family Lauraceae in the major group of angiosperms (flowering plants). It is commonly known as 'Putta Thali' in Tamil, 'Ray Laurel' in English, 'Irolimarom', 'Mungali' in Malayalam, 'Kovangutti' in Telugu[4]. It is a medium-sized evergreen tree and Shrub, widely distributed on the Rock Hill slopes at higher elevations, Aruku Valley, Vishakhapatnam District, Talakona, Dharmagiri, Microwave station, on the way to Thumburu Theertham. Leaves, flowers and fruits of *A.madraspatana* constitute the phytoconstituents. It is a precursor of vitamin A. The benzene extract of the Heartwood was reported to contain 5,7,8-Trimethoxyflavone[5]. The Leaves of the plant are used traditionally to cure wounds, cure mania, fickle minded behavior and diabetes[6]. Literature survey revealed that there's no scientifically proved report on the anti-inflammatory and anti-diabetic activities of *A.madraspatana*. Hence, the purpose of the current study had been designed to evaluate the anti-inflammatory and anti-diabetic activities of ethanol extract of leaves of *A.madraspatana* experimentally by *in-vivo* methods such as carrageenan-induced rat paw edema model for anti-inflammatory activity and streptozotocin induced diabetic in rats for anti-diabetic activity.

MATERIALS AND METHODS:

Collection and authentication of plant material:

The leaves of *A.madraspatana* were collected from Talakona forest near to Tirupathi and were authenticated by Dr. K. Madavachetty, S. V. University, Tirupati, Andhra Pradesh. A voucher specimen (ACD) has been kept in the Herbarium.

Drugs and chemicals:

Streptozotocin (STZ) was purchased from sigma Aldrich Chemicals, Germany. Carboxymethyl cellulose (CMC) was purchased from M/S Hi-media Ltd, Bombay. Glibenclamide and indomethacin were obtained as gift samples from Accent Pharma, Pondicherry, India. All other chemicals and reagents used in the study were of analytical grade.

Preparation of Plant Extract:

The fresh leaves of *A.madraspatana* were washed thoroughly with tap water and then in distilled water. The washed leaves were a shade dried at room temperature and powdered by the electronic grinder. About 200g of dry powder was extracted in the ethanol by continuous hot percolation using soxhlet apparatus. The extraction was continued for 72 h. The ethanol extract was filtered and concentrated to a dry mass by using rotary evaporator.

Experimental Animals:

Swiss Albino rats (190-250gms) of either sex used for this study. The animals were housed in polypropylene cages in a controlled room temperature 22±10°C and relative humidity of 60-70%. They were kept under standard conditions of 12/12 h light and dark cycle. The animals were maintained with standard pellet diet (Kamadenu Enterprises, Bangalore) and water *ad libitum*. The animals were acclimatized to laboratory condition for seven days before commencement of the experiment. The experimental protocol was subjected to the scrutiny of the Institutional Animal Ethical Committee (Reg.No. 1558/PO/a/11/CPCSEA) and was cleared by the same before starting the experiment.

Acute toxicity study:

Acute toxicity study of ethanol extract of *A.madraspatana* was carried out in Swiss Albino rats of either sex (190-250g) according to OECD (Organization for Economic Cooperation and Development) guidelines No. 423. Extract at different doses upto 2000mg/kg p.o. was administered and the animals were observed for behavioral changes, toxicity, and mortality upto 48 hours[7,8,9].

Evaluation ofanti-inflammatory activity:

Rats of either sex were randomly divided into four groups (I-IV) with six animals in each group (n = 6) and treated as follows. Group I, received a 1ml of 0.5% CMC; Group II, received an ethanol extract (200mg/kg); Group III, received an ethanol extract (400mg/kg); Group IV, received a standard drug indomethacin (10mg/kg). Thirty minutes after drug administration, edema was induced by the injection of 0.1ml of 1% carrageenan solutions in normal saline into the subplantar tissue of the right hind paw. The hind paw volume of the rats was measured using a plethysmograph before injection and at 0 min, 30min, 1 h, 2 h, 3 h, 4 h, 5 h, and 6 h after carrageenan injection[10,11,12,13]. The difference between the initial and subsequent paw volume reading gave the actual edema volume. The percent inhibition of inflammation was calculated using the formula

$$\text{Inhibition (\%)} = \frac{\text{Control - Test}}{\text{Control}} \text{ X } 100$$

Experimental induction of diabetes:

Rats were fasted for 24h prior to the induction of diabetes and diabetes was induced by a single intraperitoneal injection of a freshly prepared solution of streptozotocin (60mg/kg) in ice cold citrate buffer (pH 4.3). 5% Dextrose solution was administered orally for 24 h to prevent mortality due to initial hypoglycemia. After 72 h, fasting blood levels was tested using glucose oxidase-peroxidase reactive strips (One Touch, Life

Scan India, Mumbai, India). Rats showing the fasting blood glucose more than 250mg/kg were considered as diabetic and used for further study[14,15,16,17].

Evaluation of antidiabetic activity:

The diabetic rats fasted overnight and were randomly divided into five groups (I-V) with six animals in each group (n =6) and treated as follows. Group I rats served as normal control and received a citrate buffer (pH 4.3); Group II, received a citrate buffer (pH 4.3); Group III, received an ethanol extract (200mg/kg); Group IV, received anethanol extract (400mg/kg); Group V, received a standard drug glibenclamide (4mg/kg). After administration, anti-diabetic activity was evaluated by collecting blood samples on 0, 7, 14, 21st day of study respectively. Blood samples were collected from snipping tail of rat with the help of sharp razor and each time the tail of the rat was sterilized with spirit. Blood glucose levels were determined using glucometer (One Touch, Life Scan India, Mumbai, India).

Histopathological study:

After the study, rats were sacrificed under anesthesia. Their pancreas was excised immediately, washed in ice-cold normal saline (0.9%w/v) and fixed overnight in 10% formalin solution. Pancreas section was made by microtome, dehydrated in graduated ethanol (50-100%), cleared in xylene and embedded in paraffin. The sections (4-5µm) were stained with hematoxylin and eosin dye and examined with a photomicroscope.

Statistical analysis:

The data are expressed as the mean ±SEM. The statistical analysis was carried out using one-way analysis of variance (ANOVA) followed by Dunnett's test for the multiple comparisons using prism GraphPad version 5.0. The p values less than 0.001 were considered statistically significant.

RESULTS AND DISCUSSION:

Acute toxicity study:

The oral administration of ethanol extract of *A.madraspatana* did not show any behavioral changes, toxicity, and mortality even after 48 hours. The extract was found to be safe at the dose of 2000mg/kg. From the dose response curve, 1/10th and 1/5th of LD_{50} value showed good therapeutic efficacy. Hence 1/10th and 1/5th of doses were selected for the present study[18,19].

Evaluation of anti-inflammatory activity:

Anti-inflammatory activity of ethanol extract of leaves of *A.madraspatana* on on carrageenan induced rats paw edema model were tabulated (Tables 1 and 2). Carrageenan induced rat paw edema is a widely used animal model to screen the anti-inflammatory activity. Carrageenan induced rat paw edema model is used for evaluation of pain at the site of inflammation without any damage or injury to the inflamed paw. There are several mediators involved in inflammation. Serotonin, bradykinin, and histamine are the mediators in the early phase of carrageenan induced inflammation. Prostaglandins (PGs) are the mediators in the late phase of inflammation. Local and systemic inflammation is associated with enhanced levels of the pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6)[19].

Table 1: Anti-inflammatory activity of ethanol extract on carrageenan induced paw edema

Groups	Initial Paw volume	Mean Paw volume after induction in ml						
		30 minutes	1 Hour	2 hours	3 hours	4 hours	5 hours	6 hours
I	0.09±0.007	0.22 ±0.006	0.29 ±0.009	0.42 ±0.010	0.59 ±0.008	0.63 ±0.008	0.69 ±0.009	0.72 ±0.010
II	0.10±0.006	0.18 ±0.008*	0.22 ±0.010*	0.30 ±0.006*	0.37 ±0.009*	0.36 ±0.007*	0.37 ±0.009*	0.33 ±0.007*
III	0.10±0.007	0.16 ±0.006*	0.20 ±0.006*	0.26 ±0.007*	0.33 ±0.007*	0.33 ±0.004*	0.32 ±0.007*	0.30 ±0.010*
IV	0.11±0.007	0.13 ±0.004*	0.17 ±0.004*	0.20 ±0.010*	0.26 ±0.006*	0.25 ±0.006*	0.26 ±0.006*	0.25 ±0.007*

All values are expressed as mean ± SEM for six animals; p<0.001 compared to negative control; statistically significant

Table 2: Percentage inhibition of paw edema of ethanol extract on carrageenan induced paw edema

Group	Dose in mg/kg	Percentage inhibition of paw edema						
		30 minutes	1 hour	2 hours	3 hours	4 hours	5 hours	6 hours
II	200	18.18	24.14	28.57	37.29	41.27	46.38	54.17
III	400	27.27	31.03	38.10	44.07	47.62	52.66	58.33
IV	10	40.91	41.38	52.38	55.93	58.73	62.80	65.28

The present study revealed that the significant (p<0.001) reduction of paw edema was observed in rats after the administration of both doses of ethanol extract (200 mg/kg and 400mg/kg) and the standard drug indomethacin compared to carrageenan treated rats. The potential mechanism for the anti-inflammatory activity will probably due to the inhibition of release of mediators like Serotonin, bradykinin, histamine, and

prostaglandins. A previous research study with some other plants like *Aegle* marmelo[11], *Trigonella foenum-graecum*[19] and *Zhumeria majdae*[19] also showed the same activity in this model.

Evaluation of antidiabetic activity:

To induce diabetes in animals, streptozotocin is commonly used which produces moderate hyperglycemia with similar clinical symptoms of to type 2 diabetes mellitus. Streptozotocin causes alkylation of pancreatic DNA strands by entering to the islet β-cell *via* low affinity glucose transporter 2 and induces activation of poly (ADP-ribosylation) that causes depletion of cellular adenosine triphosphate, and nicotinamide adenine dinucleotide. As a result, the generated free radicals cause pancreatic β-cells necrosis[20,21].

Table 3 reveals the blood glucose levels of normal, diabetic control, ethanol extract, and drug treated rats. The present study revealed that the administration of streptozotocin to rats significantly ($p<0.001$) increased the blood glucose level when compared to normal control rats due to pancreatic β-cells necrosis. A significant ($p<0.001$) reduction of blood glucose level was observed in diabetic rats after the administration of both doses of ethanol extract (200mg/kg and 400mg/kg) and the standard drug glibenclamide from first to third week compared to diabetic control rats due to regeneration of damaged pancreatic β-cells. The variations in blood glucose level in normal and experimental groups were also recorded. The body weight of the rats was reduced after the streptozotocin administration significantly ($p<0.001$) than normal control rats (Fig. 1), and this action may be due to degradation of structural protein, and fats. A significant ($p<0.001$) increased body weight in diabetic rats was observed after administration of both doses of ethanol extract (200 and 400mg/kg) and in glibenclamide when compared to diabetic control rats[22,23,24,25].

Table 3: Effect of ethanol extract on glucose level in streptozotocin induced diabetic in rats

Groups	Blood glucose level in mg/dl			
	0 day	7th day	14th day	21st day
I	76.5±1.72	77.8±1.70	81.6±1.62	82.3±2.02
II	[a]299.3± 3.46*	[a]305.0± 2.98*	[a]307.5± 2.78*	[a]313.0± 1.65*
III	[b]301.5± 1.92[ns]	[b]269.8± 2.84*	[b]239.1± 3.04*	[b]196.6± 2.98*
IV	[b]306.0± 2.29[ns]	[b]257.3± 2.30*	[b]213.5± 2.32*	[b]162.0± 1.75*
V	[b]301.8± 2.70[ns]	[b]244.5± 3.62*	[b]183.8± 3.62*	[b]114.1± 1.99*

All values are expressed as mean ± SEM for six animals; [a]$p<0.001$ compared to normal control; [b]$p<0.001$ compared to diabetic control; *statistically significant; and ns-non significant

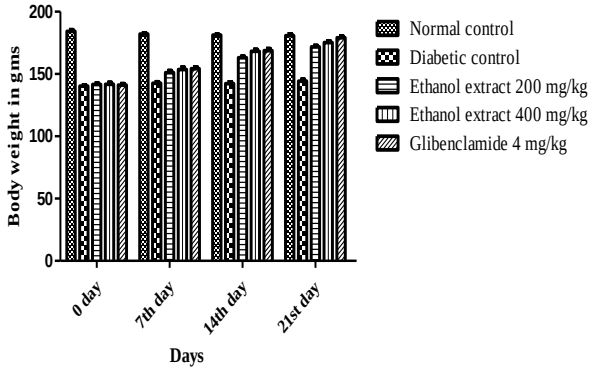

Fig.1: Effect of ethanol extract of leaves of *A.madraspatana* on body weight of streptozotocin induced diabetes in rats.

This action may due to the preventive effect of ethanol extract on structural protein degradation. There are many reports available to support the multiple mechanisms of anti-diabetic plants exerting their blood glucose lowering effects, such as regeneration of damaged pancreatic islet β-cells, inhibition of carbohydrate metabolizing enzymes, enhancement of insulin secretion, release, and sensitivity. The ethanol extract of leaves of *A.madraspatana* may exert the lowering blood glucose level, possibly by above mechanism (s) and the anti-diabetic activity of both doses of the extract was comparable to that of standard drug glibenclamide. The similar anti-diabetic activity produced by some other plants like *Merremia emarginata*[26], *Ipomoea mauritiana*[27], *Chloroxylon swietenia*[28], Phytosaponin[29], *Praecitrullus fistulosus*[30] in streptozotocin induced diabetic model.

Histopathological study:

The anti-diabetic activity of ethanol extract was further confirmed by a histopathological study of the pancreas (Figure 2A-2D). Histology of the pancreas sections of the control rats showed the normal pancreatic β-cell. The pancreas sections of carbon streptozotocin treated rats showed the complete destruction of pancreatic β-cell due to the induction of streptozotocin when compared to normal control rats. The pancreatic sections of ethanol extract treated rats showed an increase in pancreatic β-cell count and remodeling of the structure of the pancreas when compared to the glibenclamide treated and control group's rats.

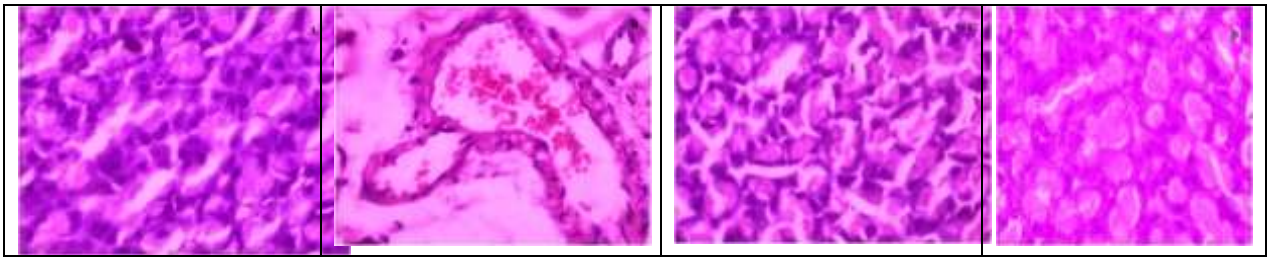

Fig.2: Histopathological slides of pancreas of different animal groups, Normal control (A); Diabetic control (B); Test group (C); Standard control (D)

CONCLUSION:

The results of the present study indicate that the ethanol extract of leaves of *A.madraspatana* possess the anti-inflammatory, and antidiabetic activities and further studies are required to isolate and characterize the active phytoconstituents, which are responsible for the anti-inflammatory and antidiabetic efficacy. This investigation will be a valuable platform for identifying the lead molecules for anti-inflammatory and anti-diabetic activities in future.

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