Review Article

Prosopis cineraria and Its Various Therapeutic Effects with Special Reference to Diabetes: a Novel Approach

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ABSTRACT

Prosopis cineraria (L.) Druce, commonly called ''khejri'' (synonyms: jambi, jambu, shumi, jandi) is a leguminous, multipurpose tree species distributed in the arid and semi-arid regions of India, Afghanistan, Pakistan, Iran and Arabia. Since all parts of the tree are useful, it is called 'Kalptaru'. Prosopis cineraria (L.) Druce is an important herbal plant as mentioned in ancient literature. It is used traditionally for treatment of various ailments like leprosy, dysentery, asthma, leucoderma, dyspepsia and earache etc. Pharmacological activities like analgesic, antipyretic, antihyperglycemic, antioxidant, antihypercholesterolemic, antitumor, nootropic have been reported from different plant extracts. Numerous bioactive compounds such as flavonoids, alkaloids, diketones, phenolic contents, free amino acids, patulitrin, spicigerin, prosogerin A,B,C,D, lipids, b-sitosterol, sugars and vitamins have been isolated from various parts of the plant. The present study deals with various pharmacological effects of plant *P. cineraria*.

Keywords: *Prosopis cineraria,* khejri, diabetes.

INTRODUCTION

Plants have been an exemplary source of medicine. Ayurveda and other traditional medicinal systems mention the use of plants in treatment of various human ailments. India has about 45,000 plant species and among them, several thousands have been claimed to possess medicinal properties. The *Prosopis cineraria (*L) Druce is an important tree (Khejri- a local name in Rajasthan)for the Thar Desert with hard climatic adaptation and one of the lifeline in desert habitat as mentioned in ancient literature. This is a species representing all five F viz., Forest, Fiber, Fuel, Fodder and Food. *Prosopis cineraria* (L.) Druce (Syn. *Prosopis spicigera* L.) (Family Fabaceae (Leguminosae), sub. family Mimosaceae) is a small to moderate sized tree found in the regions of Arabia and various parts of India such as Rajasthan, Gujarat, Haryana, Uttar Pradesh and Tamilnadu. Prosopis spices have also been used in indigenous system of medicine as a folk medicine for various ailments. Reported to be astringent, demulcent, and pectoral, *ghaf* is a folk remedy for various ailments. In India, the flowers are mixed with sugar and administered to prevent miscarriage[1].

In Las Bela, India, the ashes are rubbed over the skin to remove hair (perhaps *Leucaena* ashes should be tried as well). The bark, considered anthelmintic, refrigerant, and tonic, is used for asthma, bronchitis, dysentery, leucoderma, leprosy, muscle tremors, piles, and wandering of the mind. Smoke from the leaves is suggested for treatment of eye troubles, but the fruit is said to be indigestible, inducing biliousness, and destroying nails and hair. A northern Indian community - Punjabis consider the pod as an astringent [2].

CHEMICAL COMPOSITION

Prosopis has been found to contain 5-hydroxytryptamine, apigenin, isorhamnetin-3-diglucoside, l- arabinose, quercetin, tannin and tryptamine. The isolation of a flavone glycoside Patulitrin 3, 5, 6, 3, 4- pentamethoxy-7-hydroxy flavone from flowers of Prosopis cineraria has been reported. The fruits of *Prosopis juliflora* D.C. (leguminosae) were found to contain the same compound. Many researchers found that patulitrin showed significant activity against the Lewis lung carcinoma *in vivo*.

Patulitrin Prosogerin-E Seeds contain non-glycosidic polyphenolics, gallic acid, patuletin, luteolin, and a new compound named prosogerin –E (6, 7-dihydroxy-3', 4', 5'-trimethoxyflavone). Other compounds are glycosidic polyphenolics, patulitrin, and rutin. Seeds also contain fixed oils (4.5%), fatty acid such as palmitic acid, stearic acid, oleic acid & linoleic acid, Sterols like Campstool, Stigmasterol, β- Sitosterol,Stimasta– 5, 24(28)-dien-3 β-ol, Stimasta-1,3,5-triene, Stimasta-4,6-dien-3-one etc. 11 Amino acids isolated from leaves and pods are Aspartic acid, Glutamic acid, Serine, Glycine, Histidine, Threonine, Arginine, Alanine, Proline, Tyrosine, Valine, Methionine, Cysteine, Isoleucine, Leucine, Phenylalanine and Lysine.

Fresh, ripe pods contain 7-10% preformed water, and on a dry matter basis contain 9-17% crude protein, 1.2-4.3% ether extractives, 16-34% crude fibre, 47-61% nitrogen free extracts, 28% acid detergent fibre, 8% acid detergent lignin, 4-5% ash, 0.14-0.29% silica, 0.3-0.5% calcium and 0.40-0.44% phosphorus[3].

THERAPEUTIC PROPERTIES

Antidiabetic effect

Diabetes, often referred to as diabetes mellitus, describes a group of metabolic diseases in which the person has high blood glucose (blood sugar), either because insulin production is inadequate (Type 1) or because the body's cells do not respond properly to insulin (Type 2), or both. Patients with high blood sugar will typically experience polyuria (frequent urination), they will become increasingly thirsty (polydipsia) and hungry (polyphagia). Several drugs such as biguanides and sulfonylureas are presently available to reduce hyperglycemia in Diabetes Mellitus. These drugs have side effects and thus search for a new class of compounds is essential to overcome these problems. Management of diabetes without any side effect is still a challenge to the medical community. There is continuous search for alternative drugs; therefore it is prudent to look for options in herbal medicine for diabetes as well.[4]

Antihyperglycemic, and antioxidative potential of Prosopis cineraria bark

Dried bark was size reduced to coarse powder and soxhlet extracted with 50% aqueous ethanol. Diabetes was induced in Swiss Albino mice by single intraperitoneal injection of alloxan monohydrate, 150 mg/kg body wt, freshly dissolved in normal saline[5]. One week after alloxan injection the fasting blood glucose (FBG) concentration was determined by means of one touch ultra glucometer. Mice showing fasting blood level greater than 140 mg/dl were considered diabetic [6,7] and selected for treatment with glibenclamide (10 mg/kg body wt.) or bark extract (300 mg/kg body wt.). The drug and the bark extract were administered orally, once in a day for 45 days. Body weight loss of mice was controlled as compared to control group. Treatment with bark extract significantly reduced the glucose level by 27.3% which was comparable to a certain extent with that of glibenclamide, which produced 49.3% reduction. It was observed that after inducing diabetes, the level of hepatic, pancreatic and renal GSH content decreased significantly in diabetic control group (DC) as compared to normal control group (NC). Declined activity of antioxidant enzymes and concentration of non-enzymatic antioxidants were also normalized by drug treatment, thereby reducing the oxidative damage in the tissues of diabetic animals and hence indicating anti-diabetic and antioxidant efficacy of the extract[8]

Antihyperglycemic and antihyperlipidaemic activity of Prosopis cineraria leaves

Leaves were homogenized to fine powder and soxhlet extracted with 500 ml distilled ethanol. 40 rats were injected intraperitonally with a single dose of 50 mg/kg streptozotocin in freshly prepared cold citrate buffer. Diabetes was confirmed after 48 hrs of streptozotocin injection[9]. The animals having fasting blood glucose more than 200 mg/dl were selected for experiment. Animals were divided in 4 group out of which group 1 was normal group, group 2 includes disease control group, group 3a, 3b, and 3c were diabetic rats treated with aqueous extract of *Prosopis cineraria* leaves at dose 250 mg/kg/d, 500 mg/kg/d, 750 mg/kg/d[10] and group 4 was diabetic rats treated with metformin 100 mg/kg/day, p.o for 12 weeks. Body weight and blood glucose was measured at 5 days interval. Blood samples were collected. Blood glucose levels cholesterol, trglycerides HDL and LDL levels were measured. Blood glucose levels were significantly decreased in leaf extract and metformin treated groups. There was significant increase in lipids level except HDL level which decreased in diabetic control rats on the other hand a significant decrease in lipids level except HDL level was observed in leaf extract and metformin treated groups.[11]

Antibacterial effect

Dried pods were powdered and 25 gms of powder was used for extraction using soxhlet apparatus. The antibacterial activity was tested against four clinical isolate which include gram negative bacteria *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhi.* Identified isolates were stored in 20% glycerol at -20° and subculture on the nutrient agar at 37°C for 24 hours before use. Bacterial strains were inoculated into 10 ml of sterile nutrient broth, and incubated at 37°C for 24 hours. The antimicrobial susceptibility was determined by using Agar Well Diffusion Method[12]. The entire nutrient agar surface was seeded with the inoculums suspension and allowed to dry for 5 minutes. The wells of 6mm were created and 70µl of the each extract was poured into it. The plates were kept in refrigerator for about 15 minutes for proper diffusion of the extract and then were incubated at 37°C for 24 hours. At the end of incubation zone of inhibition was measured in millimeters. This exercise was done in triplicates to ensure reliability. Later dried pods were tested for antimicrobial phytoconstituents.

For alkaloids, 200 mg of plant material was boiled with 2% HCL 1 ml portion of filtrate was measured in four test tubes. Each test tube was treated with 2 drops of mayer's reagent, dragendroff's reagent, wagner's reagent and hager's reagent. For tannins, about 200 mg of plant material was boiled in 10 ml of distilled water and was filtered. To the 2 ml of filtrate add 2 ml of $FeCl_3$ solution. Greenish to black colour was observed. For saponins, to 100 mg of powdered plant material was boiled with 5 ml of distilled water. The mixture was filtered and 1 ml of filtrate was shaken vigorously and observed for froth formation. For flavonoids, about 200 mg of plant material was dissolved in diluted NaOH and then HCL was added to it. Yellow solution turns to colourless shows the presence of flavonoids. For glycosides, to 2ml of the filtrate, 1ml of Glacial acetic acid, $FeCl_3$ and conc. H_2SO_4 was added. A green Blue color indicates the presence of glycosides. Among the tested four gram negative bacteria, K.pneumoniae was more susceptible to methanol,

chloroform and aqueous extracts. The minimum zone of inhibition was observed in *P. aeruginosa.* It was observed that methanol extract showed better results against all pathogens in comparison to standard antibiotic.[13]

Analgesic and anti-pyretic effect

About 250 gm of coarsely powdered plant material was subjected to soxhlet extraction. Albino *Wistar* rats weighing 150 ± 25 gms in a group of 6 were taken. Analgesic activity was performed using Eddy's hot plate maintained at a temperature of 55 ± 1°C .[14] The basal reaction time of all animals towards thermal heat was recorded. The animal which showed fore paw licking or jumping response in 6-8 sec were taken for study. Male albino rats were divided into 5 groups of 6 animals. Group 1 received 1% CMC (3 mg/kg p.o.), group 2, 3 and 4 received petroleum ether, ethyl acetate and ethanol extracts of *Prosopis cineraria* stem bark of dose 300 mg/kg, orally as suspension in 1% CMC solution respectively respectively. Group five received Pentazocine (5mg/kg, p.o) as reference drug. 60 min after the administration of test and reference compounds, the animals in all the six groups were individually exposed to the hot plate maintained at 55°C and observations were recorded for 3 hours. The time taken in seconds for fore paw licking or jumping was taken as reaction time [15].

For anti-pyretic Male Albino rats were taken grouped into 5 groups each having 6 animals. Fever was induced by injecting 2 ml/kg (s.c) of 20 % aqueous suspension of Brewer's yeast in normal saline solution below the nape of the neck. After 18 hours of yeast injection, the rectal temperature, animals that showed an increase of 0.3–0.5ºC in rectal temperature was selected [16]. Group first received 1 % CMC (3 ml/kg, p.o). Group second, third, and fourth received petroleum ether, ethyl acetate and ethanol extracts of *Prosopis cineraria* stem bark of dose 300 mg/kg, orally as a suspension in 1 % CMC solution respectively. Group five received Paracetamol (100 mg/kg, p.o) as standard drug. Rectal temperature was observed using tele-thermometer at 30 minutes intervals up to 180 minutes. In Eddy's hot plate method, Ethanol extract (300 mg/kg, p.o) exhibited significant analgesic activity, when compared with other extracts while In the screening of anti-pyretic activity, Petroleum ether extract (300 mg/kg, p.o) exhibited significant anti-pyretic activity, when compared with other extracts.[17]

Antidepressant and skeletal muscle relaxant effect

Dried coarse powder of *Prosopis cineraria* leaves were extracted with soxhlet extractor with water and concentrated to dryness. Swiss Albino mice (6-8 weeks) of either sex weighing 25-30 gms were used. For antidepressant activity, forced swim test was performed. In this test, mice were divided into 3 groups containing 5 animals each. Group 1 was control group treated with distilled water, group 2 with imipramine (15 mg/kg) and group 3 were given *Prosopis cineraria* leaves extract (200 mg/kg), each group of animals were individually forced to swim in open glass chamber (25×15×25) of height 15 cms and maintained at temperature 26±1 ºC .[18] In starting 2 mins animals showed vigorous movement, period of immobility was recorded during next 4 mins to 6 mins testing period. Mice were considered to be immobile when it gets tired of struggling and become motionless and only make movement to keep its head above the water. After swimming test, mice were towel dried and returned to their housing condition.[19]

For skeletal muscle relaxant activity, mice were divided into 3 groups containing 5 animals each. Group 1 was control group treated with distilled water, group 2 treated with diazepam (20 mg/kg) and group 3 treated with *Prosopis cineraria* leaves extract (200 mg/kg). Animals remaining on rota-rod (20-25 rpm) for 2 mins or low successive trials were used for further experimentation. Test compounds can be administered either intraperitonally or orally. 30 mins after i.p. administration or 60 mins after oral administration of mice were placed on rotating rod and fall off time was oted at 30, 60 and 120 mins after drug administration. Difference of fall time of control group with drug treated were taken as skeletal muscle relaxant activity.[20, 21] Mice treated with *P. cineraria* and imipramine treated show significant decrease in duration of immobility as compared with control group in forced swim test. Similarly, mice treated with *P.cineraria* and diazepam show significant decrease in fall off time of rota rod after 30, 60 and 120 mins as compared to control group.[22]

Hypolipidemic and antiatherosclerotic effects of *Prosopis cineraria* bark extract

Dried coarse powder of bark was extracted in 70% ethanol by soxhlet extraction. Male New Zealand white rabbits weighing 1.25-1.50 kgs of age 10-12 months were used. Hyperlipidemia was induced in rabbits with high-fat diet and cholesterol administration for 15 days. Animals were divided into 4 groups, group 1 is taken as control group, group 2 as hyperlipidaemic control, group 3 as hyperlipidaemic animals treated with *P.cineraria* bark extract (500 mg/kg bw) for 45 days and group 4 as hyperlipidaemic animals treated with atrovastatin (.25 mg/kg bw) for 45 days. The total cholesterol (TC), triglyceride (TG), LDL-Cholesterol, HDL-Cholesterol, atherogenic index, ischemic indices and toxicity profile were estimated from serum samples. In hyperlipidaemic rats there was increase in total cholesterol and LDL-cholesterol while no change observed in HDL-cholesterol. In *P.cineraria* treated animals, total cholesterol level and LDL-cholesterol were reduced Triglycerides and VLDL levels were also reduced. There was no toxicity effects observed of *P. Cineraria*. There was reduction in atherosclerotic plaque formed in cholesterol fed rabbits while atrovastatin treated group showed no plaque formation. There was no effect on body weight and weight of organs except liver and aorta.[23]

Nootropic Activity

Methanolic extract of dried stem bark of *P.Cineraria* (200, 400 and 600 mg/kg body weight p.o.) was administered once in a day for 7 days to rats and these rats were then subjected to Morris water-maze (MWM) test for spatial reference memory (SRM) and spatial working memory (SWM) versions of memory testing. The inhibitory effect of the extract on acetylcholinesterase (AChE) in discrete rat brain regions (prefrontal cortex [PFC], hippocampus [HIP] and amygdala [AMY]) was also investigated using acetyl thiocholine iodide and dithiobisnitrobenzoic acid reagent. The extract shows improved both spatial reference and working memories in the MWM test in terms of decrease in escape latency during SRM and increase in time spent in the target quadrant during SWM probe trial. A ceiling effect was observed at 400 mg/kg. Pre-treatment for 7 days significantly inhibited the activity of AChE in the HIP, PFC and AMY.[24]

Effect on Respiratory, Gastrointestinal and Vascular Disorders

Methanolic extract of *P. cineraria* caused relaxation of the spontaneous contractions in isolated rabbit jejunum preparations at concentration range of 0.01–5.0 mg/mL, with an EC_{50} value of 0.835 mg/mL. Extract also caused relaxation of K^+ (80 mM)-induced contractions at concentration range of 0.3–5.0 mg/mL with an EC_{50} value of 2.015 mg/mL. The extract caused a complete relaxation of carbachol(1 μM)- and high K+ (80mM)-induced contractions in isolated rabbit tracheal preparation in concentration-dependent manner, with respective EC50 values of 0.568 mg/mL and 0.586 mg/mL. The extract is also used on cumulative addition to isolated tissue baths caused a concentration-dependent relaxation of phenylephrine (1 μM)- and K+ (80mM)-induced contractions in isolated rabbit aorta rings, with respective EC50 values of 0.513 mg/mL) and 0.525 mg/mL. Hence *P.Cineraria* is having effective spasmolytic bronchodilator and vasodilator activity.[25]

Anticonvulsant effect

Anticonvulsant activity of the methanolic extract of *Prosopis Cineraria* (Linn) Druce stem barks was studied against maximal electro shock (MES) and Pentylenetetrazole (PTZ) induced convulsions in mice. Swiss Albino mice weighing 18-25 gms were taken for the study. For MES method[26-29] the electrical shock applied (150 mA for 0.2 s) through corneal electrodes to albino mice produced convulsion and those showing response were divided into four groups of eight animals each. Group 1 was administered normal saline (5ml/kg) orally which served as negative control. II group of animals were treated with phenytoin sodium (25 mg/kg, i.p.) which served as positive control. III and IV groups of animals were treated with methanolic extracts at different dose level. Drug pretreatment was given 30 min prior to the electric shock and animal were observed for hind limb tonic extension (HLTE) in seconds.

For PTZ method.[30] PTZ at the dose of 80 mg/kg (minimal dose needed to induce convulsions) was injected i.p. to induce clonic-tonic convulsions in mice. The test animals (n=6) received 200mg/kg, 400 mg/kg of methanolic extract orally as a suspension prepared in normal saline and standard group received phenytoin (25 mg/kg) injected i.p. PTZ was injected i.p. 60 min after the administration of drug. Occurrence of HLTE and duration of seizures were noted. If no HLTE occurred during the time limit, the animals were considered protected. Methanolic extract of Prosopis Cineraria at doses of 200 and 400 mg/kg and Phenytoin (25 mg/kg) have shown significant reduction ($p<0.001$) in duration of convulsions. The methanolic extract has good anticonvulsant activity.[31]

Antioxidant activity

Leaf extract of *P.Cineraria* was extracted and was studied for various scavenging activity. For Diphenyl picryl Hydrazyl (DPPH) radical scavenging activity, the ability of plant extracts were seen to scavenge the stable free radical DPPH and convert it into Diphenyl picryl hydrazine. The absorbance was measured spectrophotometrically at 517 nm.[32] The scavenging ability of the plant extract was calculated.

For Azino bis ethyl bezthiozoline sulphonic acid (ABTS) scavenging activity, the percent inhibition of ABTS radical by plant extracts were determined by the ability of plant extracts to scavenge the cationic free radical ABTS. The extent of decolorization was measured at 745nm.[33] For Hydrogen peroxide scavenging activity, The ability of the plant extracts to scavenge Hydrogen peroxide radical was determined by measuring the decrease in absorbance at 230nm spectrophotometrically.[34] The absorbance of the solution was taken at 230 nm against blank solution containing the plant extract without H2O2. For Inhibition of Nitric oxide generation, the extent of nitric oxide generation was studied using Griess reagent method.[35] From the results it was evident that all the six extracts of leaves could scavenge DPPH, ABTS and hydrogen peroxide radicals.

Toxicity studies

Leaves and stem bark of *Prosopis Cineraria* were extracted in 50% ethanol and acute and sub- acute toxicity studies were done. Adult female and male wistar rats, 125-175g were used. In acute toxicity, animals were divided into nine groups, each group having 3 animals. Group 1 was treated as control receiving vehicle while other groups received *P.Cineraria* leaves and bark extract separately in a dose 50, 500, 1000 and 2000 mg/kg. The animals were observed continuously for the first four hours and then they were observed each hour during 24 h after administering leaves and bark extract to observe any changes in the behavioral responses and also for tremors, convulsion, salivation, diarrhoea, lethargy, sleep and coma and monitored for any mortality. [36]

For sub acute toxicity studies, female rats were divided into seven groups and each group consists of 6 rats. Six

groups of rats received leaves extract and bark extract separately in a dose of 200, 500 and 1000 mg/kg orally for 28 days. The group which served as control received equivalent quantity of normal saline orally. Animals were observed for signs and symptoms, behaviour alteration, food and water intake, body weight changes and other biochemical and haematological changes.

In acute toxicity studies, there was no significant changes in behaviour, breathing, cutaneous effects, sensory nervous system responses and gastrointestinal effects in rats and no mortality occurred within 24h under the tested dose of leaves extract and bark extract. Similarly, there were no significant changes in behavioural, locomoter, biochemical and haematological parameters.

CONCLUSION

Prosopis cineraria which is also known as khejri locally, has various pharmacological actions which can contribute a lot to the world's health as herbal plant. Various part of herbal plant *Prosopis cineraria* is used like leaves, bark, twigs, flowers, fruits and pods in treatment of various therapeutic effects. Leaves of these plants are used as anti hyperglycemia, anti hyperlipidemia, anti oxidant analgesic, anti pyretic, anti depressant and skeletal muscle relaxant activity. The bark of plant exhibit anti diabetic, anti atherosclerotic, nootropic activity while pods were reported to have anti bacterial effect. *Prosopis cineraria* is reported to have many phytoconstituents and various pharmacological activity for which there is still further extensive research has to be done.

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