

Review Article Therapeutic Efficacy of *Leonotis nepetifolia*- A Review

R. Sonia Palaramb¹, M. Thenmozhi²

¹Research Scholar, Department of Biotechnology, Vels Institute of Science, Technology and Advanced Studies, Pallavaram, Chennai – 600 117, India

Assistant Professor, Department of Biotechnology, SRM Arts and Science College, Kattankulathar, Kanchipuram, Tamil Nadu -603203, India

²Associate Professor, Department of Biotechnology, Vels Institute of Science, Technology and Advanced Studies, Pallavaram, Chennai – 600 117, India

ABSTRACT

Leonotis nepetifolia belonging to the family *Lamiaceae* consists of potent medicinal properties and is widely used in many countries to cure human ailments. A good number of bioactive compounds has been reported in this plant and is commonly found in southern parts of India. Studies were investigated on antidiabetic activity of alloxan induced diabetic rats which provided significant results. Various bioactive compound present in the methanolic extract of this plant showed anticonvulsant activity. Cytotoxic tests were also found to be positive when treated on vero (African green monkey kidney) and human epidermoid carcinoma cells. Antiinflammatory activity of stigmasterol is also well documented for this plant. Hepatotoxic tests were also carried out on swiss albino rats for aqueous and methanolic extract which proved that the compounds in the extracts were hepatoprotective. To prove the efficacy of ethanolic extract of *Leonotis nepetifolia* for antifertility activity, research was carried out in male Albino rats and it showed good results. This plant also possesses significant antibacterial, antifungal, antipesticidal, spasmolytic activity, and can also be used as an effective tranquilizer. Research works can be extended on this versatile plant to formulate a novel drug in future as *Leonotis nepetifolia* possess various medicinal properties.

Key words: *Leonotis nepetifolia*, hepatoprotective, tranquilizer, novel drug.

INTRODUCTION

Leonotis nepetifolia commonly known as lion's ear is an erect herb commonly found in Africa, Southern India and tropical Asia. Barchibuti is the trade name of the plant and its ayurvedic name is Granthiparni. The plant is called in different common names namely Knod grass (English), Ranabheri (Telugu), Dipmal (Marathi), Gathivan (Hindi), Matijer (Gujarati). Countries like Kenya, Canada, Brazil, Madagascar and many African countries reported the medicinal properties of this plant and is used to treat diseases like fever, diarrhoea, rheumatism, bronchial asthma, dysmenorrhoea¹. *Leonotis nepetifolia* can be found in waste areas, flood plains, roadsides, disturbed sites and overgrazed pastures. It also grows in savannah vegetation in Western Australia. *Leonotis nepetifolia* reproduction takes place by seeds. Seeds spread through water and there is no special adaptations to aid dispersal. Honey bees account for visiting the flower and it could be the major pollinator². The plant is tall, erect and grows to a height of 1-2 meters. The aromatic stem is stout, deeply sulcate, grows upto 8 feet tall and is a straight, pubescent, obtusely tetragonous. Petioles are winged in the upper part and are 2.5-10cm long. This plant prefers to grow to temperature of more than 300° C and rainfall of 1600-2000mm. It also prefers to grow in soil with humus content having Ph of 4.6 to 6.5. Leaves deeply crenate to serrate, base truncate to cuneate, ovate and acute (fig.1). Flowers are in axillary, orange- scarlet, globose spinous whorls of verticils. Calyx mouth obliques, tubular, valuate, spinescent, coriaceous, 8- 10 toothed. Stamen are didynamous hooded by the upper lip, four, protruding. This plant possess nutlets which are four in number and they are trigonous and oblong. They have seeds which are also oblong in shape. Ovary is tetralocular possessing one ovule per locule, and they also contain filaments which are disc copular and minutely bearded³⁻⁵. *Leonotis nepetifolia* basal is capitellate, stigma is bifid and the style is gynobasic.

Alkaloids (stachydrine and leonurine), diterpenoids (leocardin), iridoid glycosides (leonurin, leonuridine, leonuride), flavanoids (apigenin, rutin, quercetin, hyperoxide) tannin, oil, vitamins are the various phytochemical compounds present in this plant. Beta-sitosterol and campesterol n- octacosanoic acid, n- octacosanol, quercetin, coumarin like 4, 6, 7- trimethoxy -5- methylchromene- 2-one are the compounds present in the parts of the root. Palmitic acid, linoleic acid, oleic acid and stearic acid are the acids present in seed oil. Neptaefuranol, neptaefolin, neptaefuran, neptaefolinol and 6- octadecadienoic acid are compounds of leaves. Diseases like hernia, diabetes, hepatitis and rheumatism can be

cured by the leaves extract. For skeletal muscle stimulant and for treating jaundice the stem of this plant is used. For diuretic and antimalarial activity the seeds play a significant role. Jaundice, burns and cut wounds can be cured using the flower extracts⁶⁻⁹.

Scientific classification

Domain	:	Eukaryota
Kingdom	:	Plantae
Phylum	:	Spermatophyta
Subphylum	:	Angiospermae
Class	:	Dicotyledonae
Order	:	Lamiales
Family	:	Lamiaceae
Genus	:	Leonotis
Species	:	Leonotis nepetifolia



Fig.1: Leonotis nepetifolia

For burns, seed flower and inflorescence (ash and paste) of the plants are used. To treat paralysis, the whole plant of Leonotis nepetifolia is applied externally. For wounds the inflorescence paste is mixed with the oil of groundnut for healing. To treat the disease eczema, the ground paste of the leaf is applied on the surface of the skin. The whole plant's ash can be mixed with mustard oil and applied externally to relieve breast pain during the period of post natal. To alleviate burning sensation caused due to scorpion sting, the crushed leaves can be applied on the affected area. Decoction from leaf, flowers and stem can be administered to treat jaundice. The roots of L.nepetifolia is considered as an ayurvedic herb and it is added in formulations such as Himasagamtaila, Nakulataila, Mritasanjeevanisura ,Brihatguduchi taila¹.

Anti-oxidant activity

In order to determine the antioxidant activity of ethanolic extract of Leonotis nepetifolia various assays were carried out namely hydroxyl radicals, DPPH and nitric oxide radical scavenging methods. Using the different concentrations like 1.25, 2.5, 5.0, 10.0, 20.0 µg/ml an important factor IC₅₀ values were calculated by using the extracts and in terms of percentage inhibition, the botanical extracts radical scavenging activities were determined. The results of DPPH assay proved that with inhibition percentage of 60.57%, extract of Leonotis nepetifolia was effective in scavenging free radicals. With the standard, the methanolic extract was well comparable and it was more effective in all antioxidant assay. The quantified values of phenol and flavonoid was found to be 0.107% and 0.089%. It was due to the flavonoids the strongest antioxidant activity was reported in ethanolic extract¹⁰.

Anti-inflammatory activity

On TPA- induced edema model, aerial parts of the versatile plant *Leonotis nepetifolia* possess anti-inflammatory activity. All the extracts were chromatographed to isolate the possible involved components. Flowers, leaves and stems of *Leonotis nepetifolia* were studied separately. Only stigmasterol and leonotinin were isolated although several coumarins, iridoids and diterpenoids have been isolated from this species. The anti-inflammatory activity of stigmasterol is well documented. It is well known that with an infiltration of neutrophils the hyperproliferative response was initiated and phorbol esters like TPA induce skin inflammation^{10,16}. It was also known that release of arachidonic acid and prostaglandins occurs when Phospholipase A₂ (P2A) is stimulated by TPA. It has been reported that the ethanolic extract of *Leonotis nepetifolia* showed very high inhibitory activity for the synthesis of prostaglandins¹¹⁻¹⁶.

A potent tranquilizer

Leonotis nepetifolia's stem methanolic extract with concentration of (37.5, 75 and 150 mg/kg) in mice was carried out to determine the tranquilizing effect. Acute toxicity tests were carried out to determine the LD₅₀ values, using the methanolic stem extract of *Leonotis nepetifolia*. Exploratory activity was determined using the Hole board assay and to detect the anxiolytic compounds, staircase test was carried out. For determining the motor coordination, diazepam-induced sleep onset and mouse beam walk assay were employed. Intraperitoneal LD₅₀ value of 3.8 g/kg was showed in the result. Sleep for prolonged duration was induced when diazepam at the highest dose (150 mg/kg) was administered. The doses tested for (37.5, 7.5 and 150 mg/kg) showed no observable motor coordination effects. When a group of mice was injected with anxiolytic dose of diazepam it showed significant effects and at 150 mg/kg the number of rearings decreased in the staircase test. Thus the crude methanolic extract of *Leonotis nepetifolia* has potential anxiolytic activity and thus can be used as a tranquilizer¹⁷.

Spasmolytic activity

Agonistic- induced and electrically cooled contractions were carried out in-vitro in rat uterus and left atrium and in guinea-pig ileum and trachea to determine the action of hydro alcoholic and tea extracts of stems of *Leonotis nepetifolia*. The tea extract (500-2000 µg mL⁻¹) antagonized responses to prostaglandin F_{2a} in a typically non-competitive manner and also caused parallel and graded rightward shifts of concentration-response curves to bradykinin. Hydro alcoholic extract reduced their maximal contractile effects and also caused rightward displacements of the curves to bradykinin-acetylcholine (ACh), angiotensin II, oxytocin and BaCl₂. It was also observed that both the extracts (30-3000 µg mL⁻¹) relaxed uterine preparation pre contracted with KCl (80 mM), and more than tea extract, hydroalcoholic extract was found to be more potent. The relaxant response to the former was potentiated-2 fold by 3-isobutyl -1-methyl xanthine (10 µM) and was unaffected by propranolol (1 µM) or forskolin (10 µM). In the guinea-pig ileum the tea extract caused non-competitive antagonism of ACh -induced contractile responses and hydro alcoholic extract shifted the ACh- and bradykinin -induced contractile curves to the right and markedly inhibited their maximal effects. Both extracts (3-3000 µg mL⁻¹) caused contractions and inhibited ileal strips. The hydro alcoholic extract (0.1-1000 µg mL⁻¹) caused a graded long-lasting inotropic effect in the rat electrically-stimulated left atrium. Thus the findings provide experimental support that this plant possess inherited anti-asthmatic and anti-diarrhoeal properties and showed that the pharmacological effects of the extracts of *Leonotis nepetifolia* may result from the potentiation of the CAMP system¹⁸.

Wound healing activity

The studies were conducted using the ethanolic extract of *Leonotis nepetifolia* to determine its healing effect on burned wounds. After heating to 80-85°C for 20 seconds a rod of 2.5cm diameter were used to create wound. Experimental rats were treated with plant extract ointment, control rats were not treated with any drugs and Standard drug treated rats were dressed with soframycin for carrying out the wound healing activity. Decreased period of epithelialisation and increased rate of contraction were observed in the rats treated with plant extracts and it healed the wounds fast.

In the granulation tissues of plant extract treated wounds, there was reduction in the lipid peroxide when treated with standard and control drugs and biochemical studies also indicated that there was significant increase in hexosamine, super oxide dismutase and hydroxyl proline. From the results obtained it has been reported that the ethanolic extracts of *Leonotis nepetifolia* possess wound healing activity¹⁹.

Anticonvulsant activity

On crude methanolic extracts of *Leonotis nepetifolia* at 150,300 and 600 mg/kg, anticonvulsant activities were carried out using maximal electroshock test (MEST) in chicks, and seizure tests were also carried out in mice by inducing the alkaloid strychnine (STN) and the drugs pentylentetrazole (PTZ) and 4- aminopyridine (4- AP). 66.66% of protection were caused against PTZ induced seizure leading to the significant (P < 0.05) increase in the mean onset of seizure in the extract concentration of 150 mg/kg. Anticonvulsant activity were also observed against STN induced seizures as 66.67% of mice were secured against convulsion and thereby had significantly decreased the activity of seizure onset. No activity were reported by the extract against MEST and 4- AP induced seizures. It was hence proved *Leonotis nepetifolia* possess many bioactive compounds in the methanolic crude extract that showed anticonvulsant activity and thus proving that this plant can be used in the treatment of epilepsy²⁰.

Anti-bacterial and Anti-fungal activity

Antimicrobial assays were carried out against five disease causing bacterial strains to determine the *in vitro* activity of the crude extracts of *Leonotis nepetifolia*. The assays reported the very highest activity was exhibited by *Streptococcus pneumonia* with inhibition zone of 20mm, 6mm for *E.coli*, 23mm for *Staphylococcus aureus* with no inhibition for *Klebsiella pneumonia* and *Pseudomonas aeruginosa*. In the study conducted it was observed that the gram+ve bacteria were more affected to the plant extract than gram negative bacteria. As the gram negative bacterial cell wall outer membrane acts as a barrier to environmental substance including antibiotics they were considered to be more resistant. The results indicated that due to the various phytochemical compounds present in the plant extracts it possess significant antibacterial activity.

Antifungal activity were also studied using the methanolic extract of *Leonotis nepetifolia* against *Ascochyta blight* (*Phoma exigua*) pathogen *in vitro*. To obtain final concentration values of 40.0, 20.0, 10.0, 5.0, 2.5, 1.25, 0.63, 0.31 and 0.16mg/mL⁻¹ (w/v) respectively, the various laboratory assays were performed against the disease causing pathogen by carrying out two fold serial dilution. As per disc diffusion method by Kiaby- Bauerin a Completely Randomised Design (CRD), the experiments were repeated in triplicates. It was observed that with Minimum Inhibitory concentration of 1.25mg/mL⁻¹, antifungal activities were observed to all the concentration for *Leonotis nepetifolia*. The average diameter of zone of inhibition at 40.0mg/ mL⁻¹ were compared to Carbendazin a synthetic fungicide used as a positive control. The results obtained indicated that the methanolic extracts of *Leonotis nepetifolia* possess antifungal activity and can be used as a alternative to synthetic fungicide²¹.

Cytotoxic activities

The studies were carried out using the three solvents namely water, ethanol and DCM and the cytotoxicity tests were carried out on vero (African green monkey kidney) and also on KB (Human epidermoid carcinoma) cell lines with positive control as taxotere. In order to determine the major chemical class present in the plants, the TLC chemical screening were carried out. The medium used for studying the cytotoxic effect was Dulbeccos modified eagles medium supplemented with 25mM glucose 10% (v/v) fetal calf serum, 100µg/ml streptomycin, 100 UI penicillin and 1.5µg/ml fungizone. The tests were performed in triplicates. In the first analysis, no cytotoxic activity were observed on verocells but the extract possess (87%) cytotoxic effect on Human epidermoid carcinoma cell lines. Components which presented best selectivity indexes can serve as chemical tracers for the manufacturing of new drugs²².

Hepatotoxicity

It is known that administration of high dose of analgesic drug acetaminophen (APAP) increases the risk of liver injury. The remedy to treat APAP- induced liver failure is the standard antidote N-acetyl cysteine. By modulating the activities of antioxidant enzymes, research were carried out to exhibit protection against APAP induced hepatic injury with the known antioxidant phytochemical compounds in *Leonotis nepetifolia* extracts. To Swiss albino mice, orally *Leonotis nepetifolia*'s aqueous and methanolic extracts ranging from 250mg/kg to 1000mg/kg along with high dose of APAP (550mg/kg), were administered as pre and post treatment. The animals were euthanized and blood and liver were collected after 24 hours of administering the final dose to collect the enzymes of the liver (ALT and AST) for the purpose of histological assessment and antioxidant enzyme assays. On pre-treatment and post treatment with methanol and aqueous botanical extracts, the extracts protected against hepatic injury. It was observed that the extracts invalidated the APAP-induced increase in ALT and AST respectively by 14-fold and 4-fold, including tissue damage (P<0.05). There was also an increase in GPx activity which would ultimately scavenge the peroxide reactive species and hyperperoxide generated by high dose APAP. From the findings it has been proved that significant reduction in Superoxide (SOD) activity can be brought about by the antioxidant phytochemical in *Leonotis nepetifolia* acting as free radical scavengers²³.

Anticancer activity

Experimental animals after 24th day of tumour inoculation was administered with ethanolic extract of *Leonotis nepetifolia* for 14 days at the dose level of 100, 200 and 300mg/kg.bw./day. By studying the parameters such as lifespan, haematological, tumour volume, PCV, viable and non viable cell counts the antitumour effects of EELN was assessed. It was observed that there was decrease in the ascites fluid volume, PCV, body weight, viable cell counts and increase in the mean survival time of animals having cancer after the administration of ethanolic extracts. It was also noted that in dose dependent manner the antioxidant enzymes were brought back by the ethanolic extracts of *Leonotis nepetifolia* and there were also alterations in the levels of haematological parameters in mice. With that of the standard drug 5-fluorouracil the results obtained were comparable²⁴.

Anti-diabetic activity

The studies were investigated on alloxan induced diabetic rats to determine the antidiabetic activity of ethanolic extracts of *Leonotis nepetifolia*. To alloxan induced diabetic rats, EELN was administered at a dose of 250 and 500mg/kg. The procedure involved the use of 0.5ml of 25% dextrose after 2 hours of alloxan and 5% dextrose solution and libitum for next 24 hours. As a reference standard, glibenclamide was used. The results and glibenclamide showed

the dose dependent effect. Than in the untreated group, the reduction of blood glucose in the treated group appeared to be higher. The antidiabetic effect given by the ethanolic extract may be due to the inhibition of intestinal absorption of glucose or by an increase in pancreatic beta cell function or due to increased uptake of glucose at the tissue level. Significant results ($p \leq 0.05$) were observed in ethanolic extracts on alloxan model and this supports that the idea of using *Leonotis nepetifolia* as herbal drug for diabetes²⁵.

Effect as nanoparticle

Studies were carried out to determine the activity of *Leonotis nepetifolia* mediated silver nanoparticle (AgNPs) against *Culex quinquefasciatus*, *Aedes aegypti*, *Helicoverpa armigera* and *Spodoptera litura*. The biosynthesis of AgNPs were characterised using the various techniques such as fourier transform infrared spectroscopy, SEM, TEM, dynamic light scattering, UV- visual spectroscopy, energy dispersive x-ray spectroscopy and zeta potential analysis. Antifeedant activity against larva of *S. litura* and *H. armigera* respectively at 78.77% and 82.16% were showed by AgNPs. LC_{50} values of 47.44ppm and 35.48ppm were recorded when larvae treated with biosynthesised AgNPs. For controlling the pests it was reported that the production of silver nanoparticle used *Leonotis nepetifolia* as a eco-friendly approach²⁶.

Antifertility

Research were carried out to determine the antifertility activity of ethanolic extracts of *Leonotis nepetifolia* in male Albino rats. Growing of Male wistar rats weighing 160-250g is essential for carrying the antifertility activity and the parameters that has to be checked under regular intervals are temperature, humidity and 12 hour light-dark cycles, . With five rats each the animals were grouped into four. Normal saline was administered to control group (group I). Specified doses like 100mg/kg for group II , 150mg/kg for group III and 200mg/kg for group IV of *Leonotis nepetifolia* ethanolic extract was administered to other three groups of rats for a period of 55 days. In the treated groups, the weight of accessory sex organs/testis, sperm count and motility decreased significantly. When compared to control group, levels of serum hormones and certain biochemical variables also showed variation. The reports revealed decreased counts of females impregnation in treated adult male rats. Hence the research concluded that the *Leonotis nepetifolia* extract possess antiinfertility effect as it repressed the sperm motility, concentration and testosterone levels²⁷.

CONCLUSION

Leonotis nepetifolia has been used in various traditional systems of medicine. This plant possess large scale of pharmacological activities and considering the potentiality of *Leonotis nepetifolia* against various human diseases , further studies are called for the development of its agrotechniques to cater the demand for the plant in various traditional systems of medicine. However continued experimentation and clinical trials on human population has to be performed to verify the efficiency of *Leonotis nepetifolia*. Various tissue culture methods for mass production and improved agro techniques can be carried out to save this wild population from extinction. Hence this versatile plant *Leonotis nepetifolia* along with its potent bioactive compounds and wide range of benefits can be utilized in research work and also to formulate a novel drug that could cure human ailments..

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