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Review: Pharmacological Activity, Chemical Composition and Medical Importance of *Leonotis nepetifolia* R.Br.

Pranjal C. Tidke[1], Nikhita Chambhare[1], Milind J. Umekar[1] and R. T. Lohiya[1*]

[1]Department of Pharmaceutical Chemistry, Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, Nagpur (M.S)-441002, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

India is perhaps the most unique country in the world, with the richest tradition of indigenous and health care medical practices. Most of these practices are unique and known to very few individuals or communities. *Leonotis nepetifolia* Family (Lamiaceae) commonly known as 'Klip dagga' which has a long history of several traditional medicinal uses in many countries in the world. A huge number of phytoconstituents have been reported from the plant are allenic acid, iridoids, glycosides, terpenoids, and many more. This plant exhibited various biological activities and has been attributed to a variety of physiological effects like antifungal, antidiabetic, anxiolytic, arthritic, and many more activities. This literature review presents important species covering phytochemistry and pharmacological activities aspects systematically.

Keywords: Leonotis nepetifolia; Lamiaceae; pharmacological activity; chemical composition.

1. INTRODUCTION

Medicinal plants are known to give rich wellsprings of crude materials for self-medication in the treatment of different diseases since time in remembrance. The misuse of therapeutic plants for recuperating is quite much as old as mankind itself. The early man realized that a

**Corresponding author: E-mail: rtlohiya@gmail.com;*

couple of plant concentrates could treat different illnesses [1]. For instance, 60000 years before our human advancement, the Neanderthal man had simple information on the utilization of restorative plants developed significantly in the Greek and Roman periods, with famous figures like Hippocrates, Galen, and Dioscorides. [2] Ancient Chinese and Egyptian papyrus compositions depict therapeutic uses for plants as right on time as 3000 BC. Herbalism has a long practice of utilization outside of ordinary medication. It is turning out to be more a standard as enhancements in examination and quality control alongside signs of progress in clinical exploration show the worth of natural medication in the administration, treatment, and forestalling of illness [3].

Herbal medication is utilized to treat numerous conditions, like asthma, dermatitis, premenstrual disorder, rheumatoid joint inflammation, headache, menopausal indications, persistent weakness, and gut disorder among others. As of late, “The World Health Organization assessed that 80% of individuals overall depend on natural drugs for some piece of their essential medical care.” [4].

In many cases, researchers don't know what explicit fixing in a specific species attempts to treat a condition or disease featuring the need to embrace plant compound profiling of dynamic phytochemicals. The entire plant contains numerous fixings and they may work in a synergistic, antagonistic, or added substance way to produce an effect. Numerous components decide how successful a herb will be. For instance, the sort of climate (environment, bugs, and soil quality) in which a plant developed will influence it, as will how and when it was collected and prepared [5].

Characteristics of *Leonotis nepetifolia:* Plant contains Calyx cylindrical, blipped, tube with five annular rings inside, upper lip snared, lower lip 3-lobed. Stamens are four, didynamous hooded by the upper lip, exserted. Fibers are minutely hairy, plate copular. Ovary bicarpellary, tetralocular ovule one for every locule. Basal is style gynobasic, disgrace bifid, capitellate. Nutlets are four which are elongated, trigonous and seeds are likewise oval. It phytochemicals that are considered to add to their profile movement. Phytochemicals are mixtures or optional metabolites in plants that have valuable or deadly impacts on the body. The phytochemicals are regularly expounded for the plant guard against bugs and herbivores or to acquire a benefit over contending specialists. These phytochemicals inadvertently protect humans against disease [6]. A few phytochemicals are known to have antimicrobial properties, immune modulative properties, anticancer activity, and give nutrition to typical cell wellbeing and fixes [7] [8].

The less explored plants have been famously utilized as food added substances for quite a long time and even by nourishing industry to decrease or prevent the development of pathogenic microorganisms [9]. Anti-toxin mixes are frequently important in the treatment of some bacterial contaminations like staphylococcal diseases. These mixes are utilized, including anti-toxins like rifampicin among others, to stay away from the presence of antimicrobial resistance [10]. Plant against microbes have been discovered to be synergistic enhancers in that however they may have almost no antimicrobial properties alone, yet when they are taken simultaneously with standard medications they may improve the impact of that medication. In phytotherapy, there are outcome important benefits in associate plant separation with well-known anti-contamination agents [11],[12].

The family Lamiaceae (mint family) is generally involving around 3500 species conveyed among 200 genera, the greater part of them being herbaceous, less frequently bushes, and seldom trees [13]. The mint family is of incredible financial significance; a wellspring of fragrant cells like lavender and rosemary, flavor delivers, for example, menthe and thyme utilized for various restorative purposes including alleviation of stomach throbs, gas, and looseness of the bowels. Mint likewise has antibacterial and antiviral exercises. Lamiaceae is wealthy in flavonoids and have been accounted for to contain flavanones, flavone-C-glycosides, flavonols, and flavones [14].

The genus Leonotis has 12 species widely distributed in Pantropics which is represented by one species, *Leonotis nepetifolia* in India.[15] *Leonotis nepetifolia* is an important medicinal plant of reputed Indian traditional systems of medicine such as Ayurveda, Unani, and Siddha. This plant exhibited various biological activities and has been attributed to a variety of physiological effects. Labiatae has been used in the primitive medical treatment of cancer. Thus, every component of this plant has useful medicinal properties [16].

2. PLANT DESCRIPTION

Leonotis nepetifolia is also known as Klip dagga, Christmas candlestick, or lion's ear, is a species of plant in the genus Leonotis and the family Lamiaceae (mint) [17]. The botanical classification of the plant and its synonyms are given in Table no.1 and 2.

Table 1. Botanical classification of *Leonotis nepetifolia* [18]

Kingdom	Plantae
Division	Angiosperms
Class	Eudicots
Subclass	Asterids
Order	Lamiales
Family	Lamiaceae
Genus	*Leonotis*
Species	*nepetifolia*

Fig. 2. Whole plant of Leonotis nepetifolia

Fig. 1. Aerial Part of Leonotis nepetifolia

2.1 Geographical Indication

The plant is widely distributed in Pantropics and tropical Africa and southern India. It can likewise be discovered filling plenteously in a lot of Latin America and the West Indies. It develops to a height of 3metres and has whorls of striking lipped flowers, that are most usually orange, (Fig. 1) however, can change to red, white, and purple. It has delicate serrated leaves that can develop up to 4inches wide. It generally grows in most part fills in patches alongside the road or infertile unused agricultural land during the monsoon weather. The developed plant achieves a height of up to 2 meters. The orange-yellow coroneted verticillaster inflorescence and unmistakable scent are among the extraordinary characters of this plant [19].

Leonotis nepetifolia is an erect, loosely branched yearly that reaches around 3 meters in tallness in its single developing season(Fig. 2). The stems are strongly angled and the leaves are two by two inverse one another. The leaves are smooth with serrate edges, three-sided fit as a fiddle, and 2-5 inches in length. The inflorescence is verticillate and blossoms are borne in adjusted, cluster groups that enclose the stem. As the stems prolong, new bloom clusters keep on creating over the more seasoned ones. The cylindrical blossoms that look out of the sharp heads are orange, smooth, and long. The plant is found generally from October to February in pieces of Tamil Nadu state in India.[20].

Despite its luxurious growth in the tropical and subtropical regions of South East Asia, the plant merits consideration due to its overexploitation. The National Medicinal Plant Board has prioritized and urged this plant for cultivation. The overexploitation of the plant duly necessitates a proper investigation of the available genotypic diversity and its conservation through commercial cultivation by employing proper agro techniques. The exploration of the best varieties and improved cultivation practices would ease off the pressure on natural collection to help to achieve to urgent goal of its conservation.

2.2 Cultivation and Propagation

The assessment of literature reveals that improvement of agronomic packages which can improve and stabilize the production of the chosen plant (*Leonotis nepetifolia)* desires unique interest. The vital additives are choice of appropriate genotypes, suitable planting date(s),

premiere nutrient doses, and plant density coupled with an adequate and well-timed supply of the required amount of water.[21].

2.3 Morphology and Microscopy

Leonotis nepetifolia (Fig. 3) is deciduous, heavy, erect, woody and 2-3 m long. Leaves are 2-9 cm long with a dentate edge, trichomes on the lamina, and intense zenith. In view of its leaf shape, the plant is known as Lion's ear. Root framework is very much evolved with a various slight, bushy parallel roots emerge from fundamental essential roots (0.5-1cm in breadth). Roots are greyish-yellow in shading with not many longitudinal wrinkles. A slim segment of the leaf showed the presence of non-lignified, multicellular, trichomes on both surfaces. Single-layer of rectangular epidermal cells covered with dainty fingernail skin is noticed [22].

The mesophyll isn't separated into palisade and light parenchyma, yet, generally comprises of supple parenchyma which is slightly walled and inexactly orchestrated. In the midrib area, there are conjoint, insurance, lignified vascular packs. Firmly pressed 2-4 layers of collenchymatous cells are seen beneath the epidermis on both sides in the midrib district. Starch grains were missing.

Cortex frames a conservative zone and is made out of 3-6 or more layers of adjusted, sporadic, or digressively lengthened, flimsily walled, parenchymatous cells having earthy colored matter. Auxiliary phloem comprises slight walled cells of strainer components. Phloem strands are for the most part not noticed. Optional xylem structures significant piece of root comprising vessels, xylem filaments, and xylem parenchyma. Vessels are conveyed all through optional xylem and it contains lined pits and of different shapes and sizes, a couple having prolonged projection at one or two closures. Xylem filaments stretched, lignified with pointed closures with a decently wide lumen.

Xylem parenchyma is rectangular or square fit as a fiddle and pitted. Medullary beams are uni to triserrate, and biseriate beams[23][24]. The microscopic sections of the stem, petiole, and stomata are indicated in Figs 4,5, and 6.

Table 2. Various Synonyms of *Leonotis nepetifolia* [25]

Sanskrit	**Granthi,Granthika,Granthiparna, Granthiparni**
English	Lion’s Ear, Annual lion’s ear, Christmas candlestick
Gujarati	Matijer
Hindi	Bara guma, Lal guma
Marathi	Deepmal
Telugu	Hanumantabira, mulagolimedi
Tamil	Then thumbai
Kanada	Goa gadde, Kaaduthumbe, Ranabheri, Deepa Shoole
Oriya	Barcha
Vietnamese	“Su nhi” or “Ich mau nam”
Kenya	“muti wa Mucii”
Kinyarwanda	Igicumucumu

Fig. 3. Leonotis nepetifolia plant parts

Fig 7 shows the detailed structure of roots of *L. nepetifolia* and Fig. 8 indicates the structure of crude leaf and powder under the microscope.

2.4 Phytochemical Studies

Physicochemical screening of *Leonotis nepetifolia* revealed that it possesses good physicochemical parameters such as total ash, acid insoluble ash, water-soluble ash, loss on drying, swelling index, and foaming index. The extractive values such as alcohol soluble extract, water-soluble extract, petroleum ether, benzene, chloroform, ethyl acetate, methanol, and aqueous extract are also determined. [22]The proximate composition and extractive values of *L. nepetifolia* are shown in Table 3 and 4.

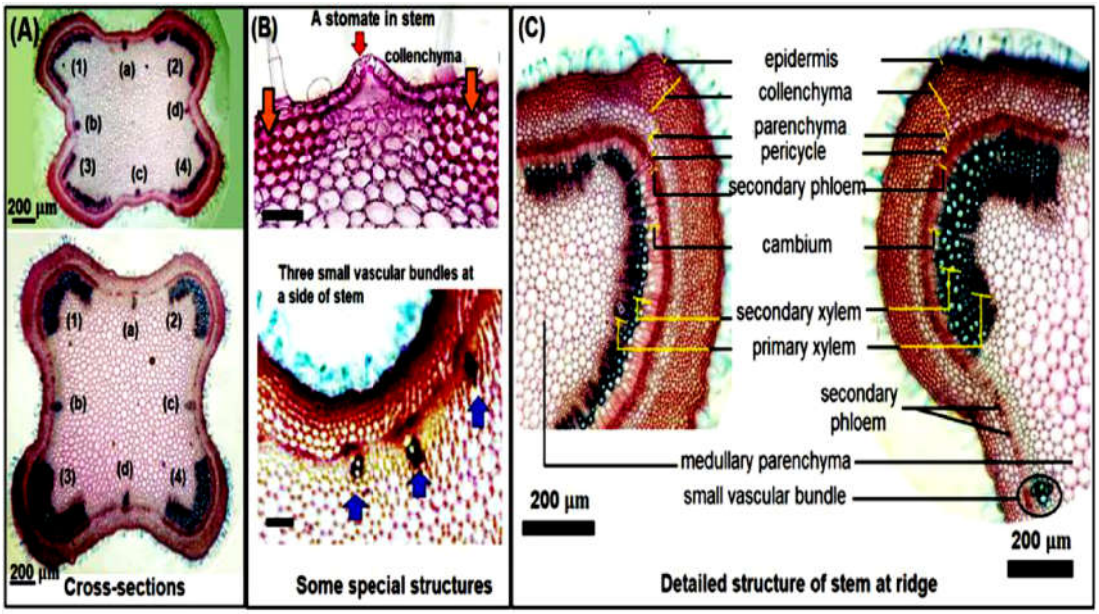

Fig. 4. Cross-section of stems (A), some special structure (B), and detailed structure at ridges (C) (1 – 4): Four ridges; (a – d): Vascular bundles at 4 midpoints of 4 edges

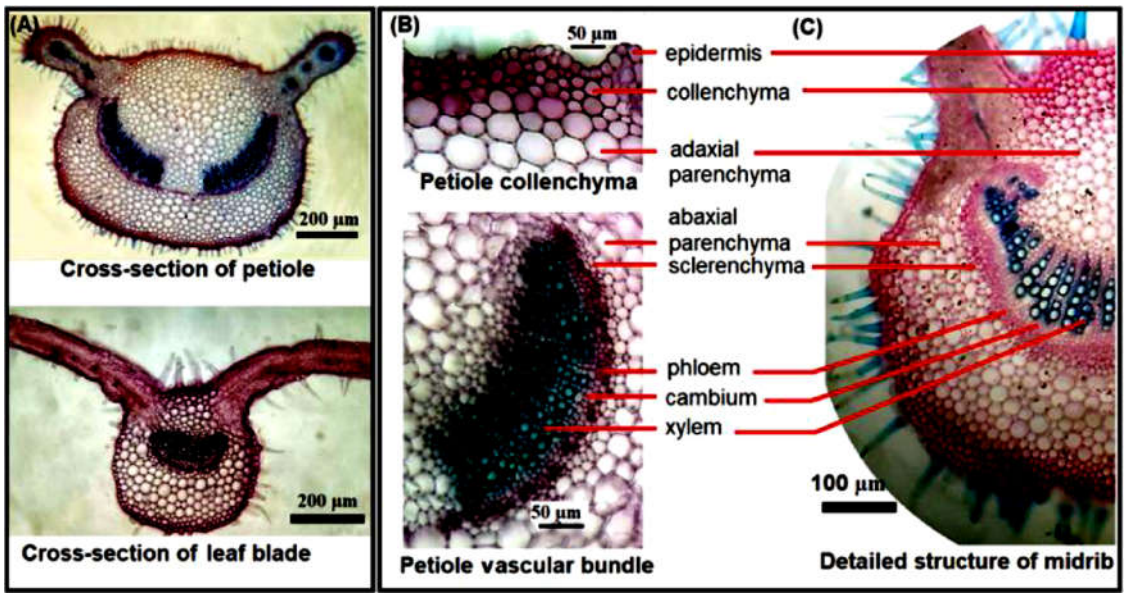

Fig. 5. Cross-section (A), and detailed structure of petiole (B) and midrib (C)

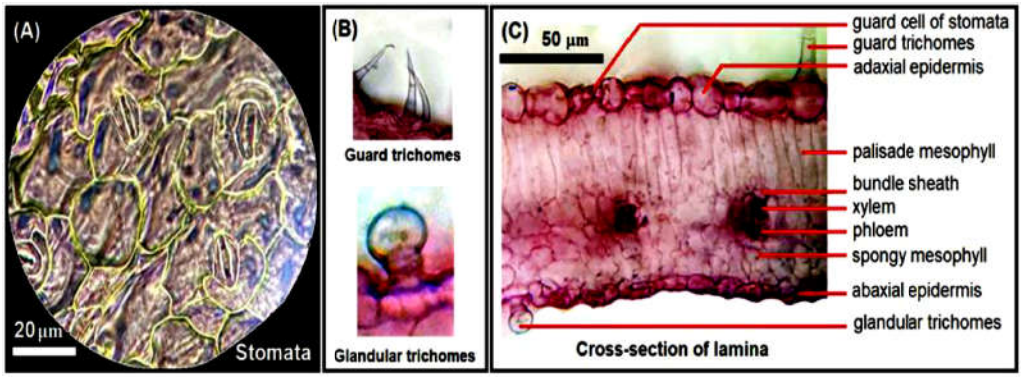

Fig. 6. Diacytic stomata (A), trichomes (B), and detailed structure of lamina (C)

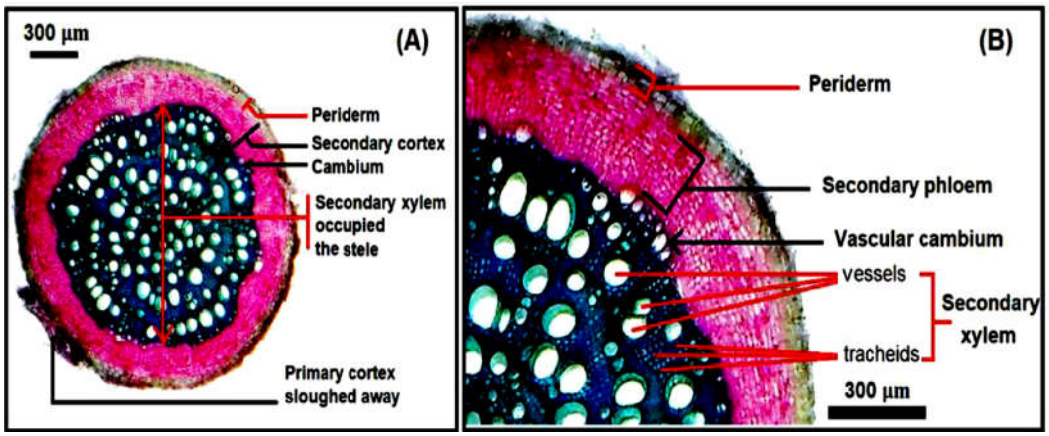

Fig. 7. Cross-section (A) and detailed structure (B) of the secondary root of Leonotis nepetifolia

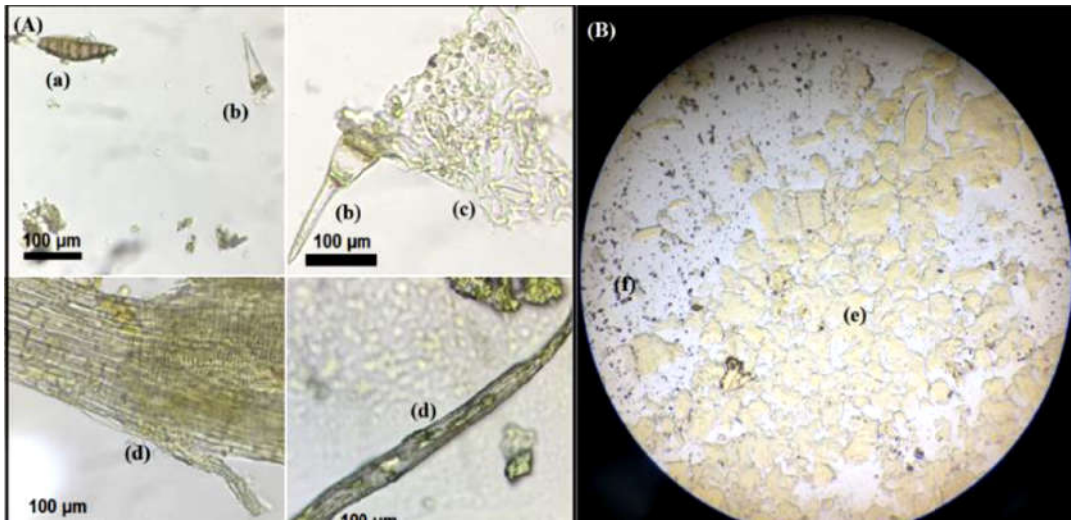

Fig. 8. Leave powder (×400) (A) and crude extract (×100) (B) observed under a microscope (a): Sclerenchyma cells; (b): Trichomes, (c): Epidermis and stomata, (d): Vascular elements; (e): Crystal of ethanol extract; (f): Unknown fragments of plants

Table 3. Proximate composition of *Leonotis nepetifolia*

Sr. No	Parameters	Observation of leaves	Observation of root
1.	Total ash	5.88 % w/w	4.083 % w/w
2.	Acid insoluble ash	1.003 % w/w	0.7067% w/w
3.	Water soluble ash	4.1 % w/w	3.15% w/w
4.	Foreign organic matter	0.88 % w/w	1.85% w/w
5.	Moisture content	7.8% w/w	5.1% w/w
6.	Foaming index	Less than 100	Less than 100

Table 4. Extractive value of *Leonotis nepetifolia* in various solvents

Sr. No	Parameters	Observation of leaves	Observation of root
1.	Alcohol soluble extractive	29.2 % w/w	21.83 % w/w
2.	Water soluble extractive	27.97 % w/w	28.39 % w/w
3.	Petroleum ether	4.48 % w/w	0.05 % w/w
4.	Benzene	4.17 % w/w	0.48 % w/w
5.	Chloroform	1.63 % w/w	2.43 % w/w
6.	Ethyl acetate	1.47 % w/w	0.16 % w/w
7.	Methanol	21.4 % w/w	22.53 % w/w
8.	Aqueous	15.04 % w/w	18.25 % w/w

2.5 Preliminary Phytochemical Screening

The petroleum ether, ethyl acetate, chloroform, methanol, and aqueous extracts were subjected to preliminary phytochemical screening for the detection of various plant constituents present. They are individually performed using different qualitative tests for alkaloids, carbohydrates, flavonoids, glycosides, protein & amino acids, saponins, fixed oils, terpenoids, phenolics, tannins, and steroids.[4][19][22][26][27][28]. Table. 5 indicates the phytoconstituents present in *L. nepetifolia*.

The availability of specific phytochemicals in plants gives it specific medicinal properties. Therefore, the presence of the above phytochemicals in *Leonotis nepetifolia* can be correlated with its medicinal properties.

2.6 Chemical Constituents

The ecological feature of secondary metabolites is commonly survival of the plant as protection as opposed to microbes, herbivores, viruses, or competing flora and signal compounds like to attract pollinating or seed-dispersing animals. Furthermore, detailed investigation and extensive research work are required to properly infer the results obtained during various studies. So there is an increase in some of the parameters of *L. nepetifolia* which has been reported in various conditions. The studies have revealed that the plant exhibits the following important constituents [29][30]. The chemical constituents present in plant *L. nepetifolia* are given in Table no. 6.

2.7 Biological Activities

This plant exhibited various biological activities such as antifungal and antibacterial, antioxidant, antimalarial, antidiabetic, antitumor, antiemetic, hepatoprotective. Details of biological activities present in various parts of plants are indicated in Table no 7.

Phytochemical examination of these plant parts indicated the presence of different bioactive compounds. Traditionally, it was used to treat kidney diseases, rheumatism, dysmenorrheal, bronchial asthma, diarrhea, fever, influenza.

2.7.1 Folklare medicinal uses

India is perhaps the most unique country in the world, with the richest tribal or folklore medicine practices. The medicinal uses of the selected plant are reported for burns, breast swelling, ringworm, scalds, skin afflictions, malaria, and rheumatic pain.

- Roots of *Leonotis nepetifolia* are considered as the botanical source of *Granthiparna* (An ayurvedic herb) which is included in the formulations such as *Brihat Guduchi taila*, *Himasagar taila*, *Nakula taila,* and *Mritasanjivani sura* [65].

Table 5. Preliminary phytochemical screening of *Leonotis nepetifolia*

Extracts Group of compounds	Petroleum ether extracts	Benzene extract	Chloroform extract	Ethyl acetate extract	Methanol extract	Water extract
Alkaloids	-	-	+	-	+	-
Terpenoids	+	+	+	-	-	-
Fixed oil and volatile oil	+	+	-	-	-	-
Saponins	-	-	-	-	+	+
Flavanoids	-	-	-	+	+	+
Proteins and amino acids	-	-	-	-	-	+
Phenolics and tannins	-	-	-	+	+	+

Table 6. Chemical Constituents in *Leonotis nepetifolia*

Sr. no.	Chemical constituents	Part used	Biological activity	References
	Labdane diterpenes	Leaf	Anti-inflammatory, Hepatoprotective	[31],
1.	Leonotinin			[32]'
				[26]
2.	Methoxy nepetaefolin	Aerial part	Antioxidant activity, Cytotoxic activity	[33]
				[34]
				[35]
3.	Nepetaefolinol	Aerial part	Antimicrobial activity	[36]
				[35]
4.	Nepetaefuran	Leaf	Antitumour ,Antioxidant,Anti inflammatory	[32]
5.	Nepetefolin	Leaf and stem	Antioxidant, Cytotoxic activity	[33],[35]
6.	Leonotin	Leaf	Antioxidant activity	[33]
7.	Bis-spirolabdane Diterpenoids			
	I. Leonepetaefolin A			
	II. Leonepetaefolin B			
	III. Leonepetaefolin C			
	IV. Leonepetaefolin D	Leaf	CNS-GPCRs activities	
	V. Leonepetaefolin E			[37]
	VI. 15-epi-leonepetaefolin A			
	VII. 15-epi-leonepetaefolin B			
	VIII. 15-epi-leonepetaefolin C			
	IX. 15-epi-leonepetaefolin D			
	X. 15-epi-leonepetaefolin E			

Sr. no.	Chemical constituents	Part used	Biological activity	References
8.	Allenic Acid			
	Laballenic Acid	Seed	Not evaluated	[38]
9.	Labdanic acid	Seed	Not evaluated	[38]
10.	Coumarin			
	4,6,7-Trimethoxy-5-methylchromen-2-one	Whole plant	Not evaluated	[39]
11.	Phenylethanoid glycosides			
	Acteoside	Stem	Antioxidant activity	[40]
12.	Martinoside	Stem	Antioxidant activity	[40]
13.	Lavanduflioside	Stem	Antioxidant activity	[40]
14.	Iridoids glycosides			
	1. 10-O-(trans-3,4-dimethoxycinnamoyl) geniposidic acid	Stem	Antioxidant activity Antioxidant activity	
	2. 10-O-(p-hydroxy benzoyl)-geniposidic acid	Stem		
	3. Loganin		α-glucosidase inhibition	
	4. Loganic acid	Stem	α-glucosidase inhibition	
	5. Shanzhiside methylester	Stem		
	6. Sweroside	Stem		
	7. Picconioside I	Stem		[40]
	8. Evofolin B			[41]
15.	Iridoids			
	Geniposidic acid	Stem	Antioxidant activity	[40]
16.	Mussaenoside	Stem	Antioxidant activity	[40]
17.	Ixoside	Stem	Antioxidant avtivity	[40]
18.	Flavonoid	Leaf and root	Antileishmanial activity, cytotoxic activity, Antimicrobial activity,	
	Cirsiliol		and Anti candida activity	[42] [43]
19.	Apigenin	Leaf and Stem, root	Antiviral activity, Antileishmanial activity, Antimicrobial activity	[44] [43]
20.	Luteolin	Leaf and Stem	Antileishmanial activity, Antimicrobial activity	[43] [44]
21.	Steroid	Leaf	Anti-inflammatory and Antitumor,	[31]
	Stigmasterol		Antifungal	[45] [44]
22.	5α-stigmast-22-ene-3-one	Aerial part	Not evaluated	[46]
23.	Triterpenoid			

Sr. no.	Chemical constituents	Part used	Biological activity	References
	Friedelin	Aerial part	Not evaluated	[46]
24.	Anthraquinones			
	I. Chrysophanol	Aerial part	Not evaluated	[46]
	II. Physcion			
25.	Isoflavone			
	4'-O-methylalpinumisoflavone	Aerial part	Not evaluated	[46]
26.	Aliphatic carboxylic acid			
	Tetracosanoic acid	Aerial part	Not evaluated	[46]

Table 7. Biological activities present in *Leonotis nepetifolia*

Sr. No.	Activities	Part used	Reference
1.	Antibacterial Activity	Leaf, Stem, Root	[4][24][20][27][28] [47] [42]
2.	Antifungal activity	Leaf,flower	[48],[49],[50]
3.	Antioxidant Activity	Leaf, Stem, Root	[20],[51],[33],[52]
4.	Larvicidal Activity	Leaf, Stem, Root	[20]
5.	Pesticidal Activity	Leaf, Stem, Root	[20]
6.	Anxiolytic Activity	Stem	[53]
7.	Antidiarrheal Activity	Leaf	[54]
8.	Anti Diabetic Activity	Whole plant	[55]
9.	Antitumor activity	Arial Part	[51]
10.	Anti Emetic activity	Leaf	[56]
11.	Cytotoxicity activity	Whole plant	[33],[42]
12.	Wound healing	Leaf,flower	[57]
13.	Hepatoprotective	Whole plant	[58]
14.	Anti-inflammatory	Flower,leaf,stem	[31]
15.	Anti Cancer activity	Leaf	[52]
16.	Antimalarial activity	Whole plant	[59],[60],[61]
17.	Antihypertensive agent	Leaf	[62]
18.	Antiproliferative activity	Leaf	[52]
19.	Spasmolytic activity	Leaf and stem	[63]
20.	Anti convulsant activity	Whole plant	[64]

- Implantation and a decoction of the leaf and stem have been utilized inside for hack, cold, flu, hypertension, looseness of the bowels, the runs, and as an emetic for snakebites. [66]
- It also reported the possible treatment of Eczema by leaf paste of *L. nepetifolia* [67]. The possible role of plant flowers and seed paste with Ghee for controlling cough and curing cuts, wounds, and burns has also been reported [68]

It is also reported that *Leonotis nepetifolia* is stronger in active constituent than cousin Leonotis leonorus especially when smoked. In Namibia, the leaves of this plant are used by women for menstrual problems as they are antispasmodic and stop bleeding. They are also purgative and have been used to promote menstruation in amenorrhea.[69] In Madagascar, the plant is used to treat rheumatism and dermatophyte diseases.[70] In the Guiana, people use this plant to deal with cramps and diarrhea and as diuretic, for skin stones, skin diseases, swelling, thrush, uterine contractions, wounds, and yaws. According to various authors, the ash and aqueous extract of the leaves of this plant are used to treat different diseases.

Silver nanoparticles were also synthesized from *Leonotis nepetifolia*. Leaf extract by one-step green synthesis method. The nanoparticles demonstrated antimicrobial, larvicidal, antifeedant, and cytotoxic activity.

The UV-Vis spectrum of colloidal solution of Silver nanoparticles from *Leonotis nepetifolia* has a maximum absorbance peak at 420 nm, which is proved the synthesis of silver nanoparticles in the colloidal solution. The XRD peaks are ascribed with the FCC structure of silver. The FT-IR spectrum ascribed the biological molecules which perform dual functions of formation and stabilization of silver nanoparticles in the aqueous medium. These results show that the inclusion of *Leonotis nepetifolia* extracts improves the solubility of silver nanoparticles, which led to a significant enhancement in the toxicity of the nanoparticles against the assessed microorganisms. It possessed biological activities like cytotoxicity, larvicidal activity, and antimicrobial activity to some extend. [71][72]

3. CONCLUSION

The present review describes the significance of *Leonotis nepetifolia* as an important medicinal plant exhibiting diverse biological activities. Since the number of phytochemical constituents identified from the *Leonotis nepetifolia* is limited it would be a rich opportunity to isolate more bioactive chemical constituents. For this plant, furthermore, it would also be valuable to determine the structure-activity relationship of the identified compounds.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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