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An Update of *Leucas aspera*– A Medicinal Plant

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ABSTRACT

Medicinal plants have been used for prevention and treatment of diseases and they find application in food, agriculture, cosmetic and pharmaceutical industry. A diverse range of phytochemicals and their promising biological activities raise the significance of medicinal plants and promoted for further research. Likewise, *Leucas aspera* has been investigated for its phytochemicals such as terpenes, sterols, glycosides, alkaloids, flavonoids, lignans, long-chain fatty compounds and therapeutic actions like antimicrobial, antioxidant, anti-inflammatory, anticancer, antidiabetic activities. It also has applications in green synthesis of Nanoparticles and it is being suggested to use as larvicidal, antivenom and phytotoxic agent. Further research will expand the scope for new drug design and discovery against specific targets of chronic diseases. This review organizes the current literature on *L. aspera* and explains its taxonomical classification, botanical and microscopic description, phytochemistry, pharmacological outcomes and also emphasizes the current applications and future directions of *L. aspera*.

INTRODUCTION

Medicinal plants are the only source for the treatment of diseases in ancient days and since then numerous herbs and plants have been recognized as medicinal plants because of their potency to cure various ailments [1]. Medicinal plants are the rich source of lead molecules for new drug discovery and hence the biological importance of medicinal plants is increasing rapidly nowadays [2-4]. The newly discovered and the existing medicinal plants are being screened for many diseases to identify the significant therapeutic importance. Several medicinal plants have been investigated against mitigation and cure of a variety of devastating diseases such as cancer [5]. *Leucas aspera* is one of the herbs found momentous due to its overriding medicinal outcomes. *L. aspera*,a species within the *Leucas* genus and the Lamiaceae family, is an aromatic herb widely distributed in tropical Asia, Africa and grows as a competitive weed in highland crop fields, homesteads, fallow lands and roadsides [6]. Many phytochemicals belong to the classes of terpenes, terpenoids, sterols and fatty compounds, glycosides, long-chain compounds, flavonoids, lignans, alkaloids and others were identified and isolated by different extraction methods [7-9].These extracts were being investigated for their biological activities such as antimicrobial, antioxidant, anticancer, phytotoxic, antivenom, thrombolysis, hepatoprotective, anti-inflammatory, analgesic, antinociceptive, antiulcer, antimalarial, antipyretic and antidiabetic activity. But all this literature is scattered and one cannot get the whole data of plant at a single destination. This context provoked us to review and organize the literature and, in this review we explained the taxonomical classification, macroscopic and microscopic description, phytochemistry and phytochemical classification along with pharmacological investigations and also emphasized the current applications and future scope of *L. aspera* medicinal plant.

TAXONOMICAL CLASSIFICATION: [8]

Table 1: Taxonomical Classification of *Leucas aspera*

Kingdom	**:** Plantae, Plant
Subkingdom	**:** Tracheobionta, Vascular plant
Super division	**:** Spermatophyta, Seed plant
Division	**:** Angiosperma
Class	**:** Dicotyledonae
Subclass	**:** Gamopetalae
Series	**:** Bicarpellatae
Order	**:** Tubiflorae
Family	**:** Labiatae
Genus	***:*** *Leucas*
Species	***:*** *aspera*

Fig 1: Arial parts of the *Leucas aspera* plant

BOTANICAL AND MICROSCOPIC DESCRIPTION: [7, 10-11]

Leucas aspera is an annual, branched, herb erecting to a height of 15 to 60 cm with stout and hispid acutely quadrangular stem and branches.

Microscopic:

Root: Cylindrical, zig-zag, smooth, long with numerous wiry, fine rootlets, size variable, fracture, fibrous; taste, characteristic.

Stem: Light greenish-yellow, surface rough, hairy, quadrangular with four prominent furrows, up to 4 mm thick, nodes and internodes distinct; taste, slightly bitter.

Leaf: Yellowish-green, 3-9 cm long, 1-2.5 cm wide, ovate or ovate- lanceolate, subacute, more or less pubescent, crenate, serrate; taste, pungent.

Inflorescence: Sessile, white, crowded in dense, globose, about 2-3.5 cm across, surrounded by numerous foliaceous bracts, thin, lanceolate, acute, ciliate, 1.2-1.5 cm long and 0.3-0.35 cm wide; calyx, tubular, slightly curved, 1-2.25 cm long, glabrous in lower part, hairy on upper part, 10 dentate with a villous throat; corolla, white, 1.7-2 cm long, bilipped, upper lip about 4 mm long, wooly, lower lip nearly twice as long as upper one; lateral lobes small.

Fruit: Schizocarpic carcerule, nutlets 3 mm smooth, brown.

Seed: 0.3 cm long and 0.1 cm wide, oblong, trigonous, smooth, dark brown.

Microscopic:

Root: Shows a single layered epidermis composed of rectangular, thin-walled cells; secondary cortex consists of thin-walled, tangentially elongated, parenchymatous cells; secondary phloem consists of sieve elements and phloem parenchyma; secondary xylem consists of vessels, tracheids, fibres and xylem parenchyma; vessels long with spurs, vessels and tracheids have simple pits, xylem fibres much elongated with pointed ends and have moderately thick walls, some having simple pits; medullary rays 1-2 seriate, up to 8 cells high.

Fig 2: Transverse section of root side and front view

Stem: Shows squarish outline with four ridges and furrows, consists of a single layered epidermis, composed of oval to rectangular, thin-walled cells having a number of uni to tricellular trichomes; secondary cortex 5-9 layered, consisting of 3-5 layers of circular, oval or irregular collenchymatous cells at the ridge and 2-4 layers of thin-walled, tangentially elongated, parenchymatous cells; endoderm is single layered, consisting of barrel shaped, thin-walled cells; pericycle single layered of thin-walled cells comparatively smaller than the cells of endodermis, a few pericyclic cells converted into pericyclic fibres; phloem very narrow consisting of usual elements; xylem consists of vessels, tracheids, fibres and large amount of xylem parenchyma; vessels mostly cylindrical with simple pits and spiral thickening; tracheids and xylem parenchyma have simple pits on their walls; pith wide consisting of circular to oval, thin-walled, parenchymatous cells.

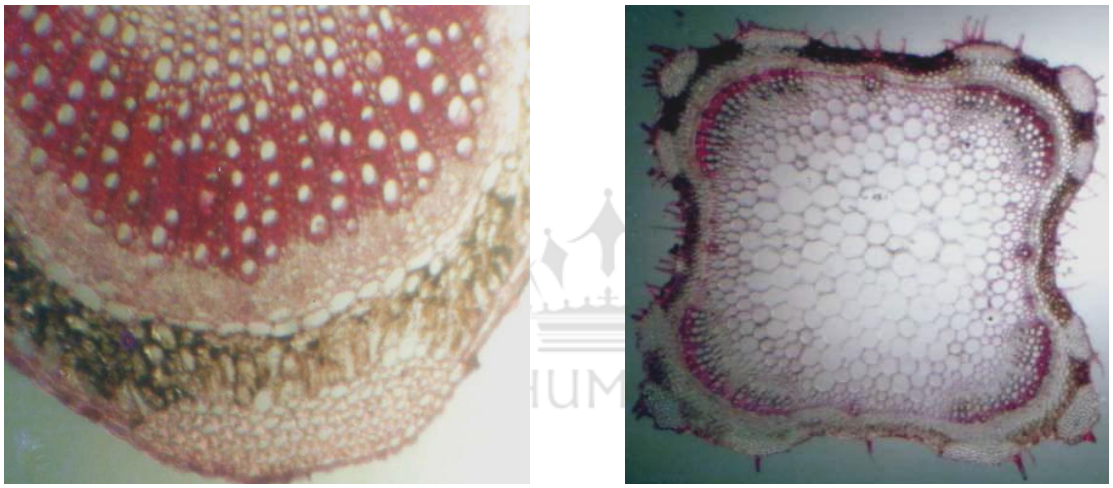

Fig 3: Transverse section of stem side view and front view

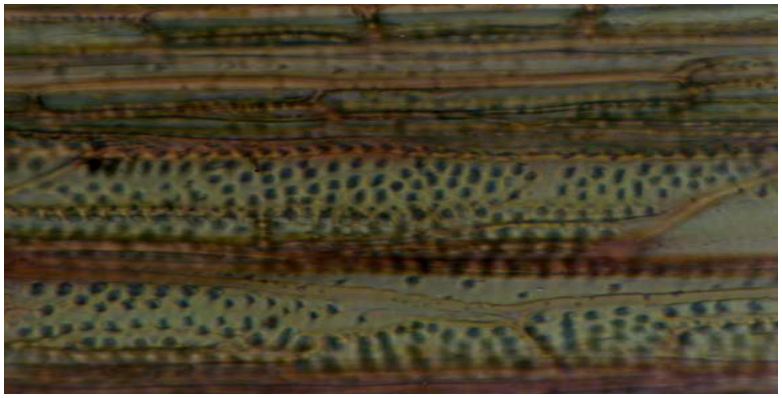

Fig 4: Transverse section of stem showing xylem and phloem

Leaf:

Petiole - shows a single layered epidermis, uni-to tricellular trichomes with pointed ends, cortex consisting of single layered, round to angular collenchyma; parenchyma consists of thin-walled cells containing prismatic crystals of calcium oxalate, vascular bundles 4, 2 smaller located towards each comer and 2 larger in center.

Midrib - shows epidermis on either side with uni to tricellular trichomes, followed by 1-2 layers collenchyma towards lower surface, 3-4 layers towards upper surface, followed by round to oval parenchyma, 4 - 7 layered; vascular bundle arc-shaped, present in center.

Lamina - shows epidermis on either side with uni to tricellular trichomes rarely on upper surface; palisade single layered; spongy parenchyma 3-5 layered, irregular, thin-walled stomatal index 16.6-40.5 on lower surface, 16.6-30.7 on upper surface; palisade ratio7-9.

Fig 5: Transverse section of Trichome of leaf

PHYTOCHEMISTRY:

Notwithstanding their role as primary source for food and fodder, plants are considered to be a rich source of chemical components of medicinal importance. Diverse organic and aqueous extraction methods were employed to extract these components. The preliminary investigation for phytochemicals of *L. aspera*, revealed the presence of a broad range of phytochemicals including alkaloids, glycosides, steroids, lignans, flavonoids and terpenoids [12-13] oleanolic acid, ursolic acid, 3-sitosterol [14-15], nicotine [16], sterols [17], galactose, glucoside [15].

However, the qualitative and quantitative analysis of various extracts gave an important data regarding existence and distribution of different phytochemicals in and among the plant parts. The total phenolic and flavonoid contents were determined using specified standard protocols as 417 mg Gallic Acid Equivalents/gm, 610 mg Quercetin Equivalents/gm of dry weight [18], and 28.33 mg GAE/gm, 3.96 mg Rutin equivalents/gm of extract [19], in organic and aqueous extractions respectively. Two types of alkaloids, six types of flavonoids and two types of steroids were found in the fingerprinting analysis of methanolic extract of whole plant *L. aspera* using HPTLC [20]. Twenty three compounds were identified by Gas Chromatography coupled with Mass Spectrometry (GC-MS) analysis of methanolic extracts of leaves. These belong to the chemical classes of fatty acid esters, fatty acid amide, triterpene, diterpene alcohols and phytol. Among those, Phytol, 9,12,15-Octadecatrienoic acid methyl ester (z,z,z), n-Hexadecanoic acid, Squalene, 1, 2 Benzenedicarboxylic acid bis(2-methylpropyl) ester were present in the concentrations of 24.55%, 22.97%, 17.17%, 5.28%, 4.44% respectively as major components [21]. Similarly, hydro-distillation of areal parts yielded essential oil in which forty three compounds represent 98.1% of the total essential oil. In this oil β-caryophyllene (34.2%), 1-octen-3-ol (14.8%), α-humulene (6.3%), α-pinene (5.8%), epi-α-bisabolol (4.6%) and limonene (4.5%) were considered as main constituents. The oil was found to be rich in sesquiterpene hydrocarbons (47.7%), followed by others (long chain hydrocarbons (LCH), oxygenated LCH and phenyl derivative constituents) (20.2%), monoterpene hydrocarbons (14.8%), oxygenated sesquiterpenes (14.8%) and oxygenated monoterpenes (0.6%) in the GC-MS analysis [22].u-farnesene (26.4%), x-thujene (12.6%) and menthol (11.3%) among 25 compounds, and amyl propionate (15.2%) and isoamyl propionate (14.4%) among 10 compounds identified as major constituents in leaf and flower extracts respectively [23]. Linoleic acid (48.11%), oleic acid (42.07%), palmitic acid (6.25%), stearic acid (2.84%) and linolenic acid (0.65%) represented the chemical constituents of seed. The unsaponifiable fraction contains 3-sitosterol and ceryl alcohol [24]. Catechin [25] and phytol [26] were found in whole plant extracts. Shoot contained novel phenolic compounds (4-(24-hydroxy-1-oxo-5-n-propyltetracosanyl)-phenol) [27], aliphatic ketones (28-hydroxypentatriacontan-7-one, 7-hydroxydotriacontan-2-one) [28], long-chain compounds (1-hydroxytetratriacontan-4-one, 32-methyltetratriacontan-8-ol) [29], nonatriacontane [27], 5-acetoxytriacontane, β-sitosterol [28] and dotriacontanol [29] and Leucolactone (I) [30].

For the first time, four flavonoids and eight lignans were isolated from *L. aspera*. Flavonoids include Acacetin (LA4), Apigenin 7-*O*-[60-*O*-(*p*-coumaroyl)-b -D-glucoside (LA5), Chrysoeriol (LA6), Apigenin (LA7), while lignanes include nectandrin B (LA1), *meso*-dihydroguaiaretic acid (LA2), macelignan(LA3), (-)-chicanine(LA8), Licarin A(LA9), *erythro*-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl)propan-1-ol (LA10), myristargenol B(LA11), machilin C (LA12). Among which LA8 was identified as new antipode of (+)-chicanine and LA9 was found to be a mixture of two enantiomers of (7*R*, 8R) - and (7*S*,8*S*)-licarin-A [31]. Along with the known structures like asperphenamate, maslinic acid, (-)-isololiolide, and linifolioside, four new diterpenes (Leucasperones A,B and leucasperols A,B) [32], two new labdane type diterpenes (rel 5S,6R,8R,9R,10S,13S,15S,16R)-6-acetoxy-9,13;15,16-diepoxy-15-hydroxy-16-methoxylabdane and rel 5S,6R,8R,9R,10S,13S,15R,16R)-6-acetoxy-9,13;15,16-diepoxy-15-hydroxy-16-methoxylabdane) [6], and three new isopimarane glycosides (Leucasperosides A, B, C) [32] structures were determined by detailed spectroscopic analysis.

PHYTOCHEMICAL CLASSIFICATION:

1. Terpenes and Terpenoid compounds:

Oleanolic acid; Ursolic acid; Phytol; Squalene; β-caryophyllene; α-humulene; α-pinene; epi-α-bisabolol; Limonene; u-farnesene; x-thujene; Menthol; Leucolactone (I); Maslinic acid; (-)-Isololiolide; Leucasperone A; Leucasperone B; Leucasperone C; rel 5S,6R,8R,9R,10S,13S,15S,16R)-6-acetoxy-9,13;15,16-diepoxy-15-hydroxy-16-methoxylabdane; rel 5S,6R,8R,9R,10S,13S,15R,16R)-6-acetoxy-9,13;15,16-diepoxy-15-hydroxy-16-methoxylabdane

2. Sterols and Fatty compounds:

3-Sitosterol; 9,12,15-Octadecatrienoic acid methyl ester; n-Hexadecanoic acid; Linoleic acid; oleic acid; Stearic acid; Linolenic acid; Ceryl alcohol; Dotriacontanol

3. Glycoside compounds:

Glucoside; linifolioside; Leucasperosides A; Leucasperosides B; Leucasperosides C

4. Long-Chain compounds:

(4-(24-Hydroxy-1-oxo-5-n-propyltetracosanyl)-phenol); 28-Hydroxypentatriacontan-7-one; 7-Hydroxydotriacontan-2-one; 1-Hydroxytetratriacontan-4-one; 32-Methyltetratriacontan-8-ol; Nonatriacontane; 5-Acetoxytriacontane

5. Flavonoid compounds:

Catechin; Acacetin; Apigenin 7-*O*-[60-*O*-(*p*-coumaroyl)-b -D-Glucoside; Chrysoeriol; Apigenin

6. Lignane compounds:

Nectandrin B; *meso*-Dihydroguaiaretic acid; Macelignan; (-)-Chicanine; Licarin A; *erythro*-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl)propan-1-ol; Myristargenol B; Machilin C

7. Miscellaneous compounds:

Nicotine alkaloid; Galactose sugar; 1, 2 Benzenedicarboxylic acid bis(2-methylpropyl) ester; 1-Octen-3-ol; Amyl propionate; Isoamyl propionate; Asperphenamate.

PHARMACOLOGICAL INVESTIGATIONS:

From the above data, *L. aspera* contains around 60 chemical compounds belonging to different phytochemical classes. It is a known fact that phytochemicals contribute to vast varieties of pharmacological activities. *Dronapushpi*, as titled in Ayurveda, has many therapeutic uses against Sotha (swelling, tumor, arthritis), Kasa (cough), Kamala (jaundice), Tamaka Svasa (bronchial asthma), Agnimandya (digestive impairment), Visamajvara (Intermittent fever) [10]. Apart from these, literature survey revealed that *L. aspera* exhibited different types of pharmacological activities as mentioned below.

Antimicrobial activity:

L. aspera root, flower, leaf and stem showed good antibacterial activity against *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Salmonella typhimurium, Salmonella choleraesuis, Shigella flexneri* [33]. Methanolic and ethanolic extracts showed good antibacterial activity against *E. coli* and, *Staphylococcus epidermidis* and *Klebsiella pneumonia* respectively [34]. Methanolic extracts of leaves showed high

antibacterial activity than ethanolic and petroleum ether extracts. Ethanolic extract of whole plant exhibited potent bactericidal activity at higher concentrations in a time and dose-dependent manner against *E.coli* in colony forming unit method [18]. Gram-positive bacteria *(B. cereus, B. subtilis, B. megaterium, S. aureus)* found to be more sensitive than gram-negative bacteria *(S. typhi, S. paratyphi, S. dysenteriae, E. coli, V. cholera, P. aeroginosa)* to the ethanolic extract [35]. Ethanolic extract of matured areal parts inhibited the growth of *E.coli, K. Pneumoniae, S.typhi* [36]. 80% ethanolic extract showed good antibacterial activity against *S. aureus* and *Bacillus subtilis* [37-38]. Ethanolic extracts showed high activity against *Shigella dysenteriae* [39].

The methanolic extract of flowers, its fractions, the alkaloidal residue and the expressed flower juice showed good antimicrobial activity against bacteria *(S. aureus, Bacillus subtilis, Streptococcus pyogenes, E. coli, Klebsiella pneumonia, P. aeruginosa)* and fungi *(Candida albicans ' Cryptococcus neoformans ' Aspergillus niger ' Trichophyton mentagrophytes*) in zone of inhibition method [40]. Methanolic extracts showed high activity against *P. aeruginosa* [39]. The dichloromethane fraction of the methanolic extract of leaves had strong antibacterial activity [41]. Ethyl Acetate extract of flowers revealed its potential antimalarial activity against *Plasmodium falciparum* [42] and, ethyl acetate fraction of leaves exhibited significant bactericidal activity against gram-positive bacterial strains in disc diffusion method [41]. Chloroform and ethanolic extracts showed antifungal activity against *Trichophyton* and *Microsporum gypseum*. *L. aspera* reported to have both fungicidal and fungistatic action [43].

Volatile oil from *L. aspera* plant showed good antibacterial activity against *P. aeruginosa, Haemophilus influenza, S. aureus*, and *Candida albicans* but didn't show antibacterial activity against *Bacillus subtilis, Proteus vulgaris, Neisseria gonorrhea, Tricoderma vibriae* [44]. The essential oils possessed bacteriostatic activity against *S. aureus, Vibrio cholerae, S. typhi, Klebsiella aerogenes, E. coli, Proteus vulgaris, Pseudomonas pyocyanea* and *Dys. Flexneri* [45].

Antioxidant activity:

Reduction of liver antioxidant molecules such as glutathione-S-transferase, superoxide dismutase, catalase, glutathione peroxidase and elevation of Malondialdehyde (MDA) was observed in Dalton's ascitic lymphoma bearing Swiss mice. Upon treatment with ethyl

acetate extract restored the antioxidant enzymes and reduced MDA as well, which was further confirmed by histological examination of hepatoprotective effect by free radical scavenging antioxidant capacity of certain molecules in the extract [46]. Ethanolic extract of whole plant showed IC50 of 99.58±1.22µg/ml with reference to standard ascorbic acid 1.25±0.95 µg/ml in DPPH assay [35]. Methanolic extract of the root possessed good antioxidant activity with IC50 value of 6.552µg/ml in DPPH assay [47].

Aqueous extract of whole plant significantly elevated antioxidant enzymes like superoxide dismutase, catalase, glutathione peroxidase and decreased lipid peroxidation levels in liver and showed hepatoprotective action in D-GalN induced hepatotoxic rats [19]. Ethanolic extract of root showed a significant free radical scavenging activity with an IC50 of 8µg/ml by DPPH assay [48]. Methanolic extract of whole plant exhibited DPPH free radical scavenging activity with an IC50 value of 100µg/ml [31]. 95% ethanolic extract of leaves showed nitric oxide and superoxide anion (NBT method) scavenging activity and protected cadmium chloride induced DNA damage (comet assay) in hepG2 human lung cancer cells [49]. n-hexane, chloroform, ethyl acetate and ethanolic extract of areal parts showed DPPH free radical scavenging activity with IC50 values of 929, 1114, 77.29 and 71.4µg/ml respectively [50]. Methanolic extract of leaves showed promising DPPH free radical activity in dose-dependent manner and the IC50 was found to be 150µg/ml [51].

The extracts of roots exhibited high free radical scavenging activity with the mean percentage of 32.36±1.19%. Scavenging activity of flower, leaf and stem extracts were 26.39±0.07%, 17.04±0.82% and 13.42±0.56% respectively. The scavenging activity of these extracts was lower compared with both antioxidants, BHT (65.67±0.58%) and vitamin E (41.67±0.58%) [33]. Naja naja venom induced a significant decrease in antioxidant superoxide dismutase, glutathione (GSH) peroxidase, catalase, reduced GSH and glutathione-S-transferase activities and increased lipid peroxidase (LPO) activity in different organs such as heart, liver, kidney and lungs [52]. Triterpenoid, from methanolic extract at a dose of 75 mg per mouse significantly attenuated (neutralized) the venom-induced antioxidant status and also the LPO activity in different organs [53].

Anticancer activity:

Ethyl acetate extract of areal parts showed cytotoxic effects in Dalton's Ascitic Lymphoma (DAL) bearing Swiss albino mice in *In vitro* MTT and Trypan blue assay [46]. Ethanolic

extract of whole plant exhibited cytotoxic activity in brine shrimp lethality bioassay and the LC50 values were found to be 181.68±2.15 [35] and 181.67±1.65 [54] µg/ml respectively, with reference to standard vincristine sulfate (0.76±0.04 µg/ml). 80% ethanolic extract of root was found to show significant and dose-dependent cytotoxic activity in brine shrimp nauplii bioassay method and LC50 was found to be 52.8µg/ml [48]. Brine shrimp lethality bioassay of crude methanolic extract of leaves determined the LC50 values of the sample and vincristine sulfate 30.00µg/ml and 10.44µg/ml respectively [51]. Ethyl acetate extract of flowers exhibited good cytotoxic activity in MTT assay and the TC50 was found to be 63±1.6 µg/mL in HeLa cells [42]. Ethanolic extract of areal parts was evaluated for its anti-psoriatic activity in HaCaT cells by MTT assay in which the extract showed promising skin keratinocyte antiproliferative activity and it was reported that anti-psoriatic activity was mediated by inhibition of nitric oxide production and lipid peroxidation [55].

Anti-inflammatory and analgesic activity:

It is evident that ethanolic and aqueous extracts showed anti-inflammatory effect whereas petroleum ether and ethanolic extract showed significant analgesic effect with reference to the standard diclofenac sodium and analgin respectively [56]. Methanolic extract of whole plant was tested for its anti-inflammatory activity by prostaglandin inhibitory effect on prostaglandin-induced contraction in guinea pig ileum and was found to be efficient in Magnus assay method [31, 32]. Aqueous and alcoholic extracts showed significant anti-inflammatory effect in both acute and chronic inflammatory models, and also reduced the degranulation of mast cells dose dependently [57]. Ethanolic extract of areal parts showed marked decline in CRP, TNF-_ and IL-2 levels in Arthritic rats caused by PMNL accumulation and its effect of reducing paw edema is related to inhibition of cyclooxygenases and lipoxygenases, the predominant enzymes of prostaglandin biosynthesis [50]. Different doses (100mg/kg, 200mg/kg,and 400mg/kg)of ethanolic extract of leaves showed significant anti-inflammatory activity in both acute as well as chronic inflammation studies. The dose of 400mg/kg produced a percentage inhibition of 60.64% which was comparable to standard drug Diclofenac (60.70%) in carrageenan model, whereas in cotton pellet method for Diclofenac was 60.27% and for three different doses of test(100,200,400mg/kg) was 50.85%,57.63%, and 58.42% respectively [58].

Anti-diabetic activity:

Methanolic extract of leaves and stem of showed antihyperglycemic activity in glucose challenged Swiss albino mice in a dose-dependent manner and reduced 34.01% and 28.39% serum glucose levels at 400mg/kg body weight respectively in glucose oral tolerance test [59]. Similarly, the methanolic extract of whole plant at a dose of 400mg/kg body weight reduced blood glucose levels to 34.45% in streptozotocin induced diabetic rats [60]. Ethanolic extract of whole plant showed good anti-diabetic activity in glucose oral tolerance test, alloxan induced and streptozotocin induced diabetic rats [61-62]. Ethanolic extract of leaves lowered blood glucose levels in dose-dependent manner and mitigated the patho-biochemical changes induced by experimental diabetic mellitus (type1) in rats [63].

Larvicidal activity:

Methanolic extract of whole plant was evaluated for larvicidal activity against fourth-instar, the larvae of *Aedes aegypti, Anopheles stephensi*, and *Culex quinquefasciatus*. The isolated compound catechin showed pronounced larvicidal activity at very low concentrations. The LC50 and LC90 values of catechin were 3.05and 8.25 ppm against *A. aegypti*, 3.44 and 8.89 ppm against *A. stephensi*, and 3.76 and 9.79 ppm against *C. quinquefasciatus*, respectively [25]. Methanolic extract of flower has larvicidal effect against fourth-instar larvae of *Anopheles subpictus* and *Culex tritaeniorhynchus* with the LC50 and LC90 values of 53.16±3.64, 233.18±25.68 and 81.24±5.16, 300.45±31.60 in ppm respectively [64]. Hexane, chloroform, ethyl acetate and methanolic extracts of leaf and flower has LC50 and LC90 values of 152.18, 692.71; 118.29, 638.92; 111.43, 635.02; 107.73, 411.13 respectively against third instar larvae of *C. quinquefasciatus* [65]. Ethanolic extract of whole plant showed larvicidal and pupicidal activity against I, II, III, IV instar larvae of Anopheles stephensi with LC50 values of 9.695%, 10.272%, 10.823%, 11.303% and against pupae was 12.732% [66].

Miscellaneous:

Ethanolic extract of root prolonged the pentobarbitone induced sleeping time in open field test and the hole cross test in Swiss albino mice. These results suggested the presence of some CNS active constituents in roots [67]. In contrast, aqueous extract treatment with CCl_4 decreased the hexobarbitone induced sleeping time in mice [19]. Aqueous suspension of leaves did not alter the behavior of Wister albino rats in Rotarod, Actophotometer and

William's maze tests, despite it promoted the intake of water, food and gain of body weight indicating that *L. aspera* can be used as an anabolic and nutraceutical aid [68].A mixture of two labdane type diterpenes obtained from 70% methanol extract of whole plant inhibited the germination and seedling growth of garden cress and barnyard grass with IC50 values of 31-80µM and thus these compounds were reported as phytotoxic in nature [6]. Ethanolic extract of whole plant reported to have blood clot lytic or thrombolytic activity [15]. Histopathological results of d-GalN treated rats liver showed the evidence of bridging necrosis and periportal inflammation. A dose of aqueous extract 200 mg/kg showed low periportal infiltration by eosinophils and at 400 mg/kg showed no marked hepatocellular necrosis [19].

A cold methanolic extract of whole plant was reported to have the similar hepatoprotective activity confirmed by carbon tetrachloride method [69]. Fresh leaf extract showed protective activity against liver disorders evidenced by the restoration of biological markers such as GOT, GPT, Alkaline phosphate, glucose, bilirubin, cholesterol and total protein, which were altered upon treatment with carbon tetrachloride [70]. Hydro-alcoholic leaf extract was investigated on male Wister albino rats for its hepatoprotective activity and the results obtained were positive [71]. The juice obtained by grinding leaves with common salt which is filtered through fine cotton or cloth can be dropped into the ears to alleviate toothache [72]. Alcoholic extract of spreng demonstrated antiulcer activity by reducing acid secretion and ulcer score [73]. The crude ethanolic extract of areal parts reported to have acaricidal property against Rhipicephalus (Boophilus) annulatus by blocking eclosion of eggs from treated ticks [74]. Aqueous extract of whole plant showed antivenom activity against venoms of *Daboia russelli russelli* (Russell's viper) and *Naja naja* (Indian cobra) and it was confirmed by neutralization of typeI phospholipase A2 (PLA2) enzyme by active principle Leucasin [75].1-Hydroxytetratriacontane-4-one (C34H68O2) is a diterpene, obtained from methanolic extract of leaf, antagonized the cobra venom induced lethal effects in a mouse model [53]. It was reported that the whole plant extract possesses antidiuretic and laxative activity in animal model [76].

CURRENT APPLICATIONS AND FUTURE DIRECTIONS:

Nanoparticles have numerous applications in different fields like medicine, manufacturing, energy, electronics and environment. Leaf extract of *L. aspera* can be used in the green synthesis of silver [77, 78] and cerium dioxide Nanoparticles [79]. It is an inexpensive,

nontoxic and eco-friendly bio-mediated combustion route of nanoparticles synthesis. Malaria, dengue, Chikungunya, Zika fever and yellow fever are the mosquito vector-borne diseases. Mosquito repellents and larvicidal compounds can control the spread of these diseases. Natural mosquito repellents are better than chemical origin. It would be a better approach to use locally available *L. aspera* extracts as larvicide in stagnant water bodies. *L. aspera* extract has significant antivenom activity [53,75] and, identification and isolation of those antidote constituents can majorly replace the commercial antivenoms. World health organization reports that agriculture workers are the major victims of snake bites. Since *L. aspera* grows abundantly as a weed in fields, it can be used as an instant antidote for venom. Two novel compounds obtained from *L. aspera* extract have phytotoxic activity [6] and hence they can be used as natural weedicides. Medicinal plant drug discovery continues to provide new and important lead molecules against various pharmacological targets including cancer [2-4]. These phytochemicals can be employed in computational and molecular modeling studies to design and discover new drugs against specified targets.

CONCLUSION

Literature survey suggests the medicinal importance of *L. aspera.* Phytochemical and pharmacological investigations revealed the presence of various chemical constituents like terpenes, sterols, glycosides, lignans, flavonoids and long-chain fatty compounds which are responsible for biological activities such as antimicrobial, antioxidant, anti-inflammatory, anticancer, antidiabetic, larvicidal, antivenom, phytotoxic activity. Despite its application in green synthesis of Nanoparticles, majority of research work done is limited to its preliminary evaluation. It is imperative to identify and isolate the promising active constituents and to study them in mechanistic levels against specific targets of deadly diseases. Extensive research has to be done in this direction to transform *L. aspera*, the roadside weed into an important medicinal plant.

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