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A COMPREHENSIVE REVIEW ON THE GENUS *LEEA* (FAMILY LEEACEAE) WITH SPECIAL EMPHASIS ON THE INDIAN SPECIES

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ABSTRACT: The genus *Leea* distributed majorly in tropical and subtropical regions of Asia, Africa, and Madagascar, belongs to the family Leeaceae. It comprises 36 species that are used worldwide for different medicinal purposes. In this decade, research interests in the genus *Leea* have grown in the fields of systematics, phylogenetic studies, analytical chemistry, identification and isolation of active metabolites, pharmacology, and phytochemistry. A wide range of phytochemicals with a variety of pharmacological activities were found to be possessed by different species of the *Leea* family, flavonoids, phenolics, triterpenoids, and tannins being the major ones. Different plant parts are claimed to be used for the treatment of human and animal ailments. Unlike members of Vitaceae, Leeaceae members (*Leea* species) do not form tendrils and include erect herbs, shrubs and trees but have shared features such as raphides, minute droplets of plant sap called pearl glands, phloem plastids, common corolla-stamen primordia, as well as similar wood and testa anatomy similar to Vitaceae family. This review reveals new insights on the genus *Leea* and the potential use of species in the genus as medicinal plants, with *Leea indica* and *Leea macrophylla* being the most important species, whose roots, leaves, and whole plants possess various pharmacological actions as they are rich in flavonoids, triterpenoids, and tannins.

INTRODUCTION: It is evident from human history that plants are of great importance in traditional as well as modern medicines. Plants naturally produce secondary metabolites, also called phytochemicals or biologically active compounds, which are involved in plant physiology, its protection mechanism, or just act as waste products for the plants, but might be of great importance to human beings. These bioactive compounds can be used as precursors for the development of natural, environment friendly, and low toxicity pharmaceuticals, nutraceuticals, flavours, fragrances, cosmetics, and pesticides due to their therapeutic and aromatic properties [1]. *Leea* is a genus of plants that are distributed throughout Northern and Eastern Australia, New Guinea, South, and South-east Asia, and parts of Africa.

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Leea contains approximately 36 species and is placed in its monogeneric family Leeaceae [1]. Out of the 36 species, India has 11 species distributed in different states, as mentioned in the database of the Botanical Survey of India [2, 3]. Various studies of different species of this genus recorded varied pharmacological actions like antimicrobial, anti-

oxidant, anticancer and nephroprotective effects. Root and leaf of *Leea macrophylla* contain vitamins like thiamine, riboflavin and ascorbic acid along with vitamin B_{12} [4]. The main active constituents found in different species are flavonoids, triterpenoids, tannins, phenolic acids, and phthalate esters [3, 4]. This review presents comprehensive information on *Leea* genus, including habit, distribution, pharmacognosy, phytochemistry, traditional uses, and pharmacological properties of plants of different species under the genus. In the review, an attempt has also been made to ponder over the significance of controversy revolving around the preferred family for the genus *Leea*.

MATERIALS AND METHODS: A thorough literature survey of the genus *Leea* with focus on Indian species was carried out, and information was gathered using scientific publications and conference proceedings from Science Direct, PubMed, Google Scholar, Web of Science, Scopus, Springer Links, and ACS Publications, Scifinder, Books, Journals, *etc*. Besides, bibliographies of referred articles on the pharmacognostic, phytochemical, pharmacological and medicinal aspects of various species of *Leea* were also referred.

Taxonomic Ambiguity: Leeaceae, earlier excluded from the family Vitaceae, is monogeneric with about 36 species, of which 11 occur in India [5]. Members of this family are primarily confined to Malaysia, Indo-china extending to Micronesia and Melanesia, tropical and subtropical Asia, Australia, and tropical Africa. The tropical plant genus *Leea*, named after the 18th-century English nurseryman James Lee, is the closest relative to the botanical family of the grapes, Vitaceae.

It was originally described by Van Royen, but was formally published by Linnaeus in 1767, with *Leea aequata* designated as the type species. *Leea* genus was formerly placed in Sapotaceae and was thought to be related to either Meliaceae or Sterculiaceae. It was also more recently associated with Rhamnales until this was refuted by molecular evidence [6-8]. In contrast, according to some taxonomists, *Leea* was originally assigned to the family Ampelideae but was transferred to the Leeaceae and then again to Vitaceae [9-14]. The Angiosperm Phylogeny Group (APG) considers *Leea* as a member of Vitaceae, under the subfamily Leeioideae Burmeister, with the rest of the 14 genera in subfamily Viticoideae Eaton. of the order Vitales, due to shared features such as raphides, pearl glands, phloem plastids, common corolla-stamen primordia as well as similar wood and testa anatomy [12, 13, 15, 16]. However, unlike members of Vitaceae, plants-species under *Leea* genus do not form tendrils and include erect herbs, shrubs, and trees (not climbing vines) with terminal inflorescence and characteristically large stipules that protect the developing leaves. *Leea* flowers also possess ovaries with secondary septa and a distinct elaborate floral tube capped by stamens fused at the center [11, 15, 16].

The stamens detach as a coherent unit sometimes during anthesis to reveal the receptive stigma [8, 17]. The APG IV system places *Leea* in the subfamily Leeoideae (Vitaceae) [18]. It is occasionally tagged in its own monogeneric family, Leeaceae based on morphological differences between it and Vitaceae [10, 11, 15, 16]. These differences include ovule number per locule (two in Vitaceae and one in Leeaceae), carpel number (two in Vitaceae and three in Leeaceae), and the absence or presence of a staminoidal tube (present in Leeaceae) and floral disc (present in Vitaceae).

Pollen structure has also been examined for taxonomic demarcation, though studies have concluded that the pollen of Leeaceae is unique compared to Vitaceae, suggesting the families should remain separate [11, 17]. Researchers noted the presence of trihydroxy compounds in *Leea*, a phytochemical trait lacking in the grapes. On the basis of these morphological differences and phytochemical differences, it has been preferred by the researchers to continue segregation of *Leea* into its own family, Leeaceae, as originally described earlier [19].

Habit and Distribution: *Leea* species grow in dry deciduous forests, open grasslands, and montane or lowland rainforests throughout the Old World tropics from Africa to Asia, North-east Australia, New Guinea, and Islands of the Pacific, but are most diverse in Indo-malaya, including India, Indo-china (including Cambodia, Laos, Myanmar, Thailand, and Vietnam), tropical China and Malaysia (including Brunei, Indonesia, East Timor, New Guinea, Philippines, and Singapore) [20]. In

India, it has a brief distribution of various species found in the Indian subcontinent:

- *Leea aequata* L. in Uttar Pradesh, Bihar, West Bengal, Sikkim, Assam, Arunachal Pradesh, Odisha, Madhya Pradesh, Maharashtra, Karnataka, Tamil Nadu and Andaman islands [3, 9].
- *Leea alata* Edgew in Gangetic plains, Eastern and Central India, ascending up to 1500 m in the Himalaya, Himachal Pradesh, Uttar Pradesh, Bihar, West Bengal, Sikkim, Assam, Arunachal Pradesh, Meghalaya, Odisha, and Madhya Pradesh [3, 9].
- *Leea angulata* Korth. Ex Miq. in the coastal belts and Nicobar islands [9].
- *Leea asiatica* (L.) in Ridsdale in evergreen, deciduous and lower mountain forests, up to 2250 m in the Himalaya, Uttar Pradesh, in grasslands and the plains of Jammu and Kashmir, Himachal Pradesh, Madhya Pradesh, Bihar, West Bengal, Sikkim, Tamil Nadu, Kerala, Arunachal Pradesh, Assam, Odisha, Nagaland, Manipur, Mizoram, Andhra Pradesh, Meghalaya, Rajasthan, Bihar, Deccan (Sandur hills), Maharashtra, Karnataka and Andaman islands [3, 9, 20].
- *Leea compactiflora* Kurz. in evergreen forests up to 2000 m in Uttar Pradesh (Terai), West Bengal, Sikkim, Arunachal Pradesh, Nagaland, Assam, Manipur, Mizoram and Meghalaya [9, 21].
- *Leea grandifolia* Kurz. in the coastal areas, Andaman and Nicobar islands [9].
- *Leea guineensis* G. Don in Uttar Pradesh, Sikkim, Assam, Manipur, Tamil Nadu, Meghalaya, Maharashtra, and the Andaman islands [22-23].
- *Leea indica* (Burm. f.) Merr. in Punjab, Uttar Pradesh, Bihar, West Bengal, Sikkim, Arunachal Pradesh, Assam, Goa, Nagaland, Mizoram, Tripura, Madhya Pradesh, Meghalaya, Odisha, Maharashtra, Andhra Pradesh, Tamil Nadu, Kerala, and Andaman and Nicobar islands [20-23].
- *Leea macrophylla* Roxb. ex Hornem. in Sub-Himalayan tract up to 2250 m and the Western Ghats, Uttar Pradesh, Bihar, West Bengal, Sikkim, Assam, Meghalaya, Odisha, Madhya Pradesh, Maharashtra, Andhra Pradesh, Karnataka, Tamil Nadu, Kerala, and Andaman island [20-23].
- *Leea rubra* Blume ex Spreng. in West Bengal, Assam and Meghalaya [21, 22].
- *Leea setuligera* Clarke in Assam, Maharashtra (Khandala) and Karnataka (Konkan) [9, 22].

Pharmacognostical Features: The distinguishing morphological features of some commonly occurring Indian species of genus *Leea* are mentioned in **Table 1.**

Phytochemistry: The major classes that have been studied in different species of *Leea* are flavonoids, triterpenoids, and phenolic acids. *Leea indica* [Local names- Bandicoot berry (English), Kurkurjihwa (Hindi)] [24]. It is one of the most important species of genus *Leea* in India, and different parts are reported to show the presence of 23 known chemical compounds, including 11 hydrocarbons, phthalic acid, palmitic acid, 1-eicosanol, solanesol, farnesol, three phthalic acid esters, gallic acid, quercetin, lupeol, *β*-sitosterol and ursolic acid [26-29]. *L. macrophylla* [Local names- Hastikarnapalasha, Hathikana (Hindi), Dholsa-mudrika, Samudraka (Sanskrit)] [30]. The leaf is documented to contain abundant phenolic constituents such as flavonoids, leucoantho-cyanidins, p-hydroxybenzoic acid, syringic acid and gallic acid [25].

Oleanolic acid, oleanolic acid derivative 7α, 28-olean diol and stigmasterol have been isolated by chromatograpy from the ethanolic extract of the root [31]. Root and leaf are reported to contain appreciable amounts of vitamin B_1 (thiamine), vitamin B_2 (riboflavin), vitamin C (ascorbic acid) and vitamin B_{12} [4]. Chlorogenic acid, a phenolic acid, is noted to be present in root [32]. Compounds identified in the ethanol extract of root by GC-MS are 2,2-Bis (chloromethyl)-1-propanol; 2H – Pyran – 2 - one; tetrahydro-4-hydroxy-6-pentyl; butylated hydroxytoluene; benzaldehyde; 3-ethoxy-tetradecanoic acid; pentadecanoic acid; n-hexadecanoic acid; l-(+)-ascorbic acid; 2,6-dihexadecanoate; 9-octadecenoic acid; 1,2,3-propanetriyl ester; octadecanoic acid; 12,13-epoxy-octadec-9-enoic acid; eicosanoic acid; docosanal;

(2,3-diphenylcyclopropyl)methylphenyl sulfoxide; 2 – Hydroxy – 4 – methoxy - 7 - methyl 7, 8, 9, 10, 11, 12, 13, 14 – octahydro – 6 –oxabenzo-cyclododecen – 5 - one; bis (2-ethylhexyl) phthalate; (2,3-diphenylcyclopropyl)methylphenyl sulfoxide, (2,3-diphenylcyclopropyl)methylphenyl sulfoxide; 7-methoxy-3-(3,4-dimethoxyphenyl)-4H – chromen – 4 - one; tetrapentacontane; 1,54-dibromo - 2, 2 – dimethyl – 6 - methylene-1-(3,5-dihydroxy – 1 - pentenyl) cyclohexan - 1-perhydrol; stigmasta-4,7,22-trien-3β-ol; cholesta-4,6-dien-3-ol; (3β) - stigmasterol; γ - sitosterol; ergosta-4,6,8, 22-tetraen-3-one; 4,22-cholestadien-3-one; cyclopropa-33-norgorgostan-3-ol, 3',6-dihydro-(3β,5β,6α,22.xi.,23.xi.); γ-sitostenone and cholesterol epoxide. The major components noted amongst these are n-hexadecanoic acid (37.15%), 9-octadecenoic acid, 1, 2, 3-propanetriyl ester (18.87%), octadecanoic acid (12.56%), γ-sitostenone(5.88%) and γ-sitosterol (4.13%) [33].

TABLE 1: DISTINGUISHING MORPHOLOGICAL FEATURES OF COMMON INDIAN SPECIES OF GENUS LEEA

L. aequata [10, 11, 21]	***L. compactiflora*** [22]	***L. guineensis*** [23]	***L. indica*** [24, 25]	***L. macrophylla*** [25]	***L. rubra*** [23]
Large shrubs, young branches villous	Undershrubs, up to 3 m tall, branches often ribbed	Very variable, erect or suberect, evergreen shrub or small tree growing 5-10 m tall rarely densely hairy, villose or papillose	Erect shrub or small tree, 2-10 m tall, with aerial roots	Herbaceous shrub or small tree, 2m tall	semi-woody shrub up to 3 m tall
Leaves: **Type**: Compound, Alternate, Pinnate, stipulate **Shape**: Oblong-obovate, leaflets oblong-lanceolate, cuneate to truncate **Apex:** Acuminate to caudate **Base**: Subcordate or rounded, petiolate **Margin**: Sharply serrate **Surface**: Pubescent to densely hairy, caduceus, membranous, hispid with scattered grey hairs above, hirsute on nerves, rough with scattered rounded brown peltate glands beneath **Venation**: Lateral nerves 8-12 pairs, slender, arched	**Leaves:** **Type**: Compound, unipinnate, rarely trifoliate **Shape**: Narrowly winged **Apex:** Acute **Base:** Sessile, unequal **Margin:** Dentate-serrate **Surface**: Glabrous on both sides, minutely pubescent on nerves beneath, chartaceous to subcoriaceous, reddish, sparsely distributed stellate pearl glands **Venation**: Secondary nerves 8-12 pairs, curved near the margins	**Leaves:** **Type:** 2-3 odd pinnate compound **Shape:** Elliptic to lanceolate leaflets **Apex:** Acuminate **Base:** Cuneate to rounded, less frequently truncate or unequal **Margin:** Undulate **Surface**: Light green, sometimes with slight red tinges, but mature to a glossy green, mature, tiny translucent, globoidpearl glands **Venation**: Nerves 8-10 pairs, often with hairy domatia, glabrous or pubescent	**Leaves:** **Type**: Compound, bipinnate to tripinnate, alternate, spiral, stipules purple, sheathing **Shape**: Obovate-oblong leaflets ovate to lanceolate **Apex**: Acuminate to caudate **Base:** Acute to rounded **Margin**: Serrate to dentate **Surface**: Glabrous, drying brown **Venation**: Midrib raised above; secondary nerves 7-12 pairs; tertiary nerves reticulo-percurrent	**Leaves:** **Type:** Simple **Shape**: Broadly ovate, nearly as broad as long, lower leaves 60 cm long, upper leaves 15-23 cm long **Apex:** Acute or acuminate **Base:** Petioles 5-12 cm long, deeply striated **Margin**: Coarsely serrate or sub-lobed **Surface**: Pubescent beneath, main nerves opposite, very prominent and 8-10 pairs, pearl glands absent, upper leaves light yellowish-green, lower leaves dark green **Venation**: Lateral nerves to 14 pairs, pubescent to hairy	**Leaves:** **Type:** Compound**,** 2-4 pinnate, alternate, petiolate stipules as a narrow wing, similarly long **Shape**: Leaflets numerous, ovate to ovate-oblong A**pex:** Acute to shortly acuminate **Base:** Rounded to acute **Margin:** Crenate to shallowly serrate **Surface**: Glabrous or less frequently with small hairs along the nerves, chartaceous, pearl glands apparently absent from the leaflets **Venation:**Nerves 5-10 pairs, sometimes with minute hairs, often winged
Inflorescence: Corymbs, 5-**Merous Flowers:** Greenish white, calyx lobed halfway down, glabrous to densely pubescent, covered with pearl glands outside, lobes deeply cleft, ovary 4-7 loculed	**Inflorescence:** Reddish, glabrous or minutely pubescent, peduncle, 4-20 cm long bracts and bracteoles inconspicuous **Flowers:** Red, calyx glabrous, corolla tube with staminodial lobes, ovary 6-locular	**Inflorescence:** Terminal clusters (cymes to 3-5" wide) **Flowers:** Reddish-orange outside and a paler yellowish-orange inside, Lobes tiny each 1/2" wide	**Inflorescence:** Corymbose cymes **Flowers:** Calyx green, petals cream forked near the margin, and spreading	**Inflorescence:** Terminal, much-branched, puberculous, corymbose cymes, up to 30 cm long **Flowers:** Greenish white, calyx 5-lobed, pubescent, lobes 3-angled, linear-ovate, greyish-pubescent to papillose	**Inflorescence:** Rusty pubescent, generally compact, bracts deltoid-triangular **Flowers:** Pentamerous, bright red with a yellow central disc, glabrous, shallowly retuse or cleft

Fruit: Globose-depressed, 6-7 mm, orange-red, black when ripe, seeds 3-6 **Flowering and fruiting**: July-December	**Fruit:** Berry, 0.5-1 cm across, red, bluish purple when ripe, seeds 4-6 **Flowering:** May-June **Fruiting:** August-January	**Fruit:** 5-15 mm, rounded purple fruits which ripen to scarlet, seeds 5 by 4 mm usually 6, rumination outline simple and endosperm simply ruminate **Flowers** may bloom throughout the year in ideal growing conditions	**Fruit:** Berry, depressed, globose, 0.7-1 cm across, purple black, seeds 4-6 Flowering and fruiting: July-December	**Fruit:** Berry globose, 6-8 cm in diameter, black, 3-6 celled, depressed globose, usually 3-6 lobed **Flowering and fruiting:** November-December	**Fruit:** Sub-globose berries, 8-10 mm, dark red or purple when ripe; Seeds 6, 7-10 mm wide, rumination outline simple and endosperm simply ruminate **Flowering and fruiting:** November-December

L. guineensis: Quercetin - 3' - sulphate – 3 - O - α-L-rhamnopyranoside, quercetin-3,3'-disulfate and quercetin-3,3',4'-trisulfate, along with kaempferol, quercetin, quercitrin, mearnsitrin, gallic acid, and ethyl gallate have been isolated and identified from the leaf [34].

L. asiatica: About 24 compounds have been identified during the phytochemical analysis of *L. asiatica,* including a phenolic glucoside, seven triterpenoids, eight flavonoids, two phenolic glycosides, four diglycosidic compounds, and two miscellaneous compounds [35].

Traditional Uses: The whole plant of *Leea indica* is used traditionally for the treatment of headaches, body pains, and skin complaints. The root is valued in diarrhoea, colic, dysentery, and as a sudorific. Leaves are consumed for the treatment of cancer, diabetes, and injuries [36]. A leaf is roasted and applied to the head in vertigo. The juice of young leaves is useful as a digestive. Inflorescence extract is used to cure chest pain in children [28, 36].

Leea species including *L. asiatica, L. guineensis, L. indica* and *L. macrophylla* are used to treat skin lesion and wounds. The leaf of *L. macrophylla* possesses anodyne property and is applied to wounds and sores. It is also used for guinea worm and ringworm [37]. It is also noted to be traditionally used for tonsillitis, tetanus, nephrolithiasis, rheumatism, arthritis, snake bites, sore, pain and blood effusion [38, 39]. The plants of *L. macrophylla* possess tikta, katu rasa, sangrahi, vikashiguna, ushnaveerya, madhuravipaka properties and have Rasayana karma. *L. macrophylla* bearing either unifoliate, trifoliate or 1 to 3 pinnate leaves should be considered as botanical equivalents of classical Ayurvedic plant Hastikarna or Hastikarnapalasha [40]. In Ayurveda, it is indicated in worm infestation, dermatopathies, wounds, inflammation and in symptoms of diabetes [41]. Dried powder of its root with clarified butter is prescribed in the morning as age sustainer [4]. The leaves are also used in making small flute [42]. They are also used as platters [25]. The root is said to yield a dye [43]. *L. macrophylla* contains vitamin C that maintains collagen protein necessary for the formation of connective tissue in the skin, ligaments, and bones. It protects thiamine and riboflavin from oxidation. Thus it plays a vital role in nutrition point of view [4].*L. aequeta* finds its use in itching and dyspraxia [24]. Its leaves and twigs have been used as antiseptic to treat wounds [25].

Ethnic Uses: Ethnopharmacological use of *L. macrophylla* is documented for the urinary problem by local tribes of Bihar. The leaves have been used in goitre, gastric tumor, lipoma, and tetanus. Some other tribes use the leaf as vegetables [4]. Crude leaves and powder are traditionally used in cancer, urolithiasis, wounds, sores, goitre, gastric tumor, tetanus, and urinary disturbances.

Leaf juice is also used as an anti-inflammatory agent in boils, arthritis, gout, and rheumatism. It is also applied externally to allay pain and to stop the effusion of blood. A leaf is extensively used by the Ayurvedic physicians in the preparation of seasonal tonic modaka [44]. Also, the dried root powder mixed with clarified butter is prescribed in the morning as age sustainer [4, 44]. An ethnobotanical survey of this plant shows some important therapeutic uses in cancer, dysentery, body ache, and sexual disability [45]. Besides, *L. macrophylla* is a non-woody forest product used as ethnic food in India [46].

Its leaves are eaten as vegetables, and the roots of the plant are cooked as vegetables [25, 47, 48]. The fruits are consumed orally in the form of juice and considered very nutritive [47, 49].

Pharmacological Properties: Several investigations carried out by researchers show that many species of *Leea* genus possess remarkable pharmacological activities, including anticancer, anti-bacterial, thrombolytic, anti-inflammatory, anti-urolithiatic, antioxidant, anti-hyperglycaemic and many more as described below [24, 25].

Anticancer Activity: Mollic acid arabinoside isolated from *L. indica* is found to trigger induction of mitochondria-mediated apoptosis in Ca-Ski human cervical cancer cells [28]. *L. macrophylla* also showed cytotoxic effects in a study using brine shrimp lethality bioassay. The lethal concentration (LC_{50} values) of the ethanolic extract, as well as carbon tetrachloride, chloroform and ethyl acetate soluble fractions of roots, were found to be 2.39, 0.049, 4.53, and 0.09 µg/ml, respectively, which were comparable to the standard vincristine sulphate who's LC_{50} was 0.34 µg/ml [50].

Anti-diarrheal Activity: The methanolic extract of leaf of *L. indica* is shown to possess anti-diarrhoeal activity in castor oil-induced diarrhoea in mice [51].

Anti-hyperglycaemic Activity: The alcoholic and hydroalcoholic extracts of *L. indica* leaf revealed hypoglycemic activity by significantly reducing blood glucose level in a study using glucose tolerance test and alloxan-induced diabetes model in rats [52].

The methanolic extract of *L. macrophylla* leaf also exhibits significant effects in ameliorating the diabetic markers such as insulin and other diabetic-related markers, especially LDL, HDL, LDH, creatinine, uric acid and CK-MB, in fructose-fed streptozotocin (STZ)-induced type 2 diabetes [44].

In another study, *L. macrophylla* root extract is reported to upregulate the mRNA expression for antioxidative enzymes and to repair the necrosis of pancreatic β-cell and kidney tissues in fructose-fed STZ-induced type 2 diabetic rats at the doses of 50, 100, and 200 mg/kg. Conversely, the glucose tolerance ability, liver glycogen level, serum insulin, organ weight, and pancreatic morphology are shown to be improved significantly along with the diameter of the islet of Langerhans (µm), area occupied by β-cell/islet of Langerhans (μm^2) and a number of β-cells/islet of Langerhans [33].

Anti-inflammatory Activity: Leaves of *L. macrophylla* and *L. guineensis* have been used to treat inflammatory diseases. The methanolic extract of *L. macrophylla* leaf is noted to inhibit prostaglandin PGE2, Interleukin IL-6, and cause reduction of tumor necrosis factor TNF-α. Furthermore, oral administration of methanol extract of leaf of *L. macrophylla* at the doses of 100 and 200 mg/kg is reported to exhibit significant dose-dependent inhibition of carrageenan-induced inflammation and reduction of the granuloma tissue formation [53]. *L. guineensis* leaf is reported to possess anti-oedematogenic activity in carrageenan-induced rat paw oedema assay [54].

The methanolic extract of *L. indica* roots (at 200 and 400 mg/kg doses) is shown to exert significant anti-inflammatory activity in dinitrobenzene sulfonic acid (DNBS)-induced Intestinal Bowel Disease (IBD) in animal experimental models when compared with standard sulfasalazine (360 mg/kg) [55].

Antimicrobial Activity: The essential oil obtained from flowers and the ethanolic extract obtained from leaf of *L. indica* showed significant activity against Gram-positive and Gram-negative bacteria. It was observed that the extract inhibits Gram-positive bacteria more as compared to Gram-negative bacteria as indicated by the lowest Minimum Inhibitory Concentration (MIC value). Essential oil of *L. indica* is also reported to be effective in inhibiting moulds like *Aspergillus niger* and *Penicillium* spp [27]. The ethanolic extract of *L. indica* leaf also inhibits the growth of *Aspergillus flavus* and *Candida albicans* [51, 56].

L. macrophylla extract, and its successive fraction from root tubers have also been shown to have more pronounced effect in the case of Gram-positive bacteria as compared with Gram-negative strains. Crude extract of *L. macrophylla* leaf has displayed mild to moderate antimicrobial activity against *Bacillus cereus, Bacillus subtilis,* and other test organisms, including *Escherichia coli, Pseudomonas aeruginosa, Salmonella paratyphi, Shigella dysenteriae,* and *Shigella sonnei,* along with strong antifungal activity against *Pityrosporum ovale, Trichophyton* spp., *Candida albicans, Cryptococcus neoformans,* and *Microsporum s*pp. The ethyl acetate extract of seed

is noted to be strongly effective against *S. aureus* as compared to n-hexane, chloroform, and methanol extracts [41]. The ethanolic extract of the root is demonstrated to be highly effective against *S. aureus*, *S. flexneri,* and *S. boydii*, whereas less effective against *S. typhi* and *Klebsiella pneumonia*. The depicted MIC values ranged from 0.195 to 3.125 mg/ml [57].

Antinociceptive Activity: *L. indica* and *L. macrophylla* leaves have been assessed for their analgesic effect. Both plants are reported to exhibit central and peripheral analgesic effects in mice. The ethanolic extract of *L. indica* has been shown to exert analgesic activity in acetic acid-induced writhing test and formalin-induced licking test [58]. In acetic acid-induced writhing test, the ethanolic root extract at the dose of 200 mg/kg reduced the number of writhes significantly with 62.37% of inhibition. It has been noted that the methanol extract of leaf *L. macrophylla* in the oral dose of 100 and 200 mg/kg exhibits significant central and peripheral analgesic activity in hot-plate test and acetic acid-induced writhing test in experimental mice [50].

Antioxidant Activity: The leaf extracts of *Leea* species are reported to possess antioxidant potential using different assays that measure free radical scavenging activity, such as 2,2-diphenyl-2-picrylhydrazyl hydrate (DPPH) radical scavenging activity, ferric thiocyanate (FTC), superoxide dismutase (SOD), and lipid peroxidation assay, the activity is attributed to the presence of secondary metabolites like gallic acid and quercetin [59]. The methanolic extract of *L. indica* is shown to exhibit scavenging activity against DPPH radicals. The crude ethanol extract, along with hexane, ethyl acetate, and aqueous fractions of ethanol extract obtained from the leaf of *L. indica* have been demonstrated to display antioxidant activity through DPPH radical scavenging, superoxide radical scavenging, and reducing power assays [60]. *In-vitro* studies of different fractions *L. macrophylla* leaf have also shown strong free radical scavenging ability due to the presence of phenolics [34, 61, 62]. In an experimental study, administration of the *L. macrophylla* root to the STZ-induced diabetes animals has been shown to upregulate the expression profile of genes responsible for antioxidant enzymes suggesting the pancreas protecting effect of the plant that is mediated through an antioxidant dependent event [44]. Quercetin - 3'- sulphate – 3 – O – α – L – rhamno-pyranoside, quercetin-3,3'-disulphate, and a new flavonoid sulphate, quercetin-3,3',4'-trisulphate, together with kaempferol, quercetin, quercitrin, mearnsitrin, gallic acid, and ethyl gallate isolated from the leaf of *L. guineensis* are recorded to show antioxidant effect on DPPH free radical scavenging assay [34].

Antiurolithiatic Activity: Administration of the ethanolic extract of the whole plant of *L. macrophylla* (500 mg/kg orally) to rats for 14 days is reported to significantly reduce as well as prevent the growth of kidney stones and improve the renal impairment in the ethylene glycol-induced urolithiasis model in rats [37, 57].

Antiviral Activity: The essential oil of *L .indica* is shown to exhibit antiviral activity against *Herpes simplex* virus. The extract is also reported to be ineffective against vesicular stomatitis virus [63].

Cardiotonic Activity: It is reported that with the increasing dose of *L. macrophylla* aqueous and alcoholic extracts from 0.1 ml to 0.4 ml, a significant increase in the force of contraction (positive inotropic effect) and the heart rate (positive chronotropic effect) is observed [64].

Enzyme Inhibitory Activity: The plant of *L. indica* is shown to possess inhibitory activity against enzymes such as phosphodiesterase, pancreatic lipase, and glucosidase. The methanolic extract of *L. indica* leaf is also observed to be effective in inhibiting the activity of lipase by 48.5% against porcine pancreatic lipase [65].

Hepatoprotective Activity: Different extracts of *L. macrophylla* are also reported to possess significant hepatoprotective effect in a study, which demonstrated that most of the extracts except methanol extract (200 mg/kg) helps in normalizing the serum creatine kinase (CK-MB) level in hepatic damage, but the ethyl acetate extract (200 mg/kg) and chloroform extract (100 mg/kg) restore the serum CK-MB level [62]. Aqueous extract of *L. guineensis* seed is found to protect the liver against dichlorovos-induced toxicity in rats. The ethanolic extract of *L. indica* stem bark has been shown to

have a protective effect against paracetamol-induced hepatotoxicity in rats [66].

Hypolipidemic Activity: In an experimental study, the administration of alcoholic and hydro-alcoholic extracts of *L. indica* leaf is shown to significantly decrease the levels of triglycerides, total cholesterol, LDL and VLDL and increase HDL in rats, indicating hypolipidemic activity of the leaf extract [52].

Nephroprotective Activity: The leaf of *L. asiatica* has been proven to afford protection in cisplatin-induced nephrotoxicity in mice. Among the methanol, ethyl acetate and petroleum ether extracts of the *L. asiatica* leaf that were evaluated for *in vitro* and *ex vivo* antioxidant activities, the methanol extract is shown to exhibit better antioxidant effects. The effect is attributed to higher amounts of phenolics (77.75 ± 0.87 mg Gallic acid equivalent/g of dry material) and flavanoids (60.98 ± 0.58 mg Quercetin Equivalent/g of dry material).

The extended study with fractions of the methanolic extract obtained using methanol, ethyl acetate, petroleum ether against cisplatin (20 mg/kg, i.p.)-induced nephrotoxicity has revealed that pretreatment with methanol extract (150 and 300 mg/kg) and its fractions especially methanol and ethyl acetate fraction (at 75 and 150 mg/kg, respectively) significantly reduces blood urea nitrogen, serum creatinine, uric acid and malondialdehyde levels along with increased total protein and albumin levels. Ethyl acetate fraction is indicated to produce highest nephroprotective activity, possibly by inhibiting lipid peroxidation process [67].

Neuroprotective Activity: The methanol extract of the root of *L. macrophylla* (100 and 200 mg/kg) is reported to reduce locomotor activity and increase the duration of sleeping of animals.

The extract is also shown to reduce the content of malondialdehyde, nitric oxide, and advanced oxidation protein product and increase the activities of superoxide dismutase, catalase, and glutathione peroxidase in hippo-campus [68].

Thrombolytic Activity: The ethanol extract of *L. indica* leaf has been reported to have thrombolytic activity in an *in vitro* clot lysis assay, where it produced 39.3% of clot lysis activity [69]. According to another study, the crude extract of *L. macrophylla* is observed to exhibit 20.61% clot lysis compared to the standard streptokinase (81.53%) in the anti-atherothrombosis assay [57]. The whole plant extract of *L. macrophylla* is also shown to have the highest clot lysis activity (47.47%) as compared to the extracts of other plants like *Ocimum tenuiflorum*, *Andrographis paniculata*, *Adhatoda vasica* and *Litsea glutinosa* [70].

Wound-healing Activity: In an experimental study using the incision model, *L. macrophylla* has shown complete wound contraction in 20 days with topical application, whereas 22 days by oral treatment. This effect has been attributed to increased collagen synthesis and reduced inflammation through effects on proinflammatory cytokines and vascular endothelial growth factor (VEGF), enhanced cellular proliferation as well as potential antioxidant and free radical scavenging effects, probably mediated due to the presence of polyphenols, mainly chlorogenic acid in the extract [32].

CONCLUSION: The genus *Leea* consists of many medicinally important species found to be growing throughout the world. There is a lack of knowledge on some species within the genus that provides a huge opportunity for future research. However, the scientific exploration of various plant species among this genus has proven the therapeutic importance of this genus with a variety of pharmacological actions that are attributed to a wide range of phytochemicals occurring in the species. This review acknowledges a few species out of the 36 species of *Leea* genus that are found around the world with keen stress on important species found in India.

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