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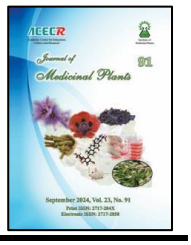

Review Article

A review on ethnopharmacology and phytochemistry of *Premna mollissima* Roth.

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ABSTRACT

Background: *Premna mollissima* Roth. belong to family Lamiaceae is a small deciduous tree commonly called as dusky fire brand bark. It is distributed in tropical or subtropical climate, often in hilly or forested areas of India, Sri Lanka, Bangladesh and Myanmar. **Objective:** To summarize a systemic review of the ethno-pharmacology and phytochemical study of *P. mollissima* Roth. It also includes the therapeutic importance as stated in literature and the pharmacological aspects which have been already explored in the present-day scientific parameters. **Methods:** An ethno-pharmacological review of *P. mollissima* was done through the texts, as well as searching research articles related to its pharmacognosy, traditional uses, phytochemistry, and therapeutic activities available on Pubmed, Science Direct, Google Scholars, Scopus, and Web of Science from their dates of inception till present. The following keywords were applied to the literature search *"Premna mollissima"*, "Agnimantha", "phytochemistry" to find the description of the plant. **Results:** Various chemical constituents can be obtained from the plant such as premnine, 7-deacetylpremnine, premnalatifolin, quercetin, etc. The root, leaf and bark is used in Ayurveda and folk medicine for the treatment of different ailments such as dropsy, treatment of edema, boils, fevers, rheumatism, neuralgia, etc. Various studies have indicated its astringent, anti-inflammatory, anti feedant, diuretic, digestive, and antibacterial properties. **Conclusion:** This study is an attempt to compile an up-to-date and comprehensive review on *P. mollissima* Roth. covering its traditional and folk medicinal uses, phytochemistry and pharmacology. It will help future researchers to explore more about its active phytoconstituents and pharmacological activities.

1. Introduction

Premna mollissima Roth. (Earlier *Premna latifolia* Roxb.) syn. *Gumira mollissima* (Roth) Kuntze, *P. mucronata* Roxb.(family Lamiaceae), commonly known by various names such as: jhatela, bakarcha, basota, agnimantha, nelli, gonderi, gunara, munja, nappa and dusky fire brand bark in different parts of the world and is distributed in southern Asia including Cambodia, China, India, Indonesia, Laos, Malaysia, Myanmar, Nepal, Philippines, Sri Lanka, Thailand and Vietnam [1]. It is a deciduous tree about 20-25 ft tall with a spreading crown and a natural inhabitant of lower and outer sub-tropical, Himalayan tracts extending from Chenab in north-west India to Bhutan in the east

Abbreviations: DPPH, 2,2-diphenyl-1-picrylhydrazyl; ABTS, 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid)

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and extending to an elevation of 1500 meter [2]. In the western Sub-Himalayan tract it is often found in the mixed forest which marks the transition stage between the riverine forest of *Acacia catechu* and *Dalbergia sissoo*, and the final stage of sal forest on the more elevated lands [3]. Various studies on phytochemical composition of *P. latifolia* have reported the presence of active ingredients such as glycosides, steroids, saponins, phenols, flavonoids, terpenoids, and tannins [4]. The Ayurvedic Formulary of India (2000) [5] describes *P. latifolia* Roxb. as a substitute of *P. integrifolia* Linn. which is one of the ingredients in dashmula (an ancient ayurvedic formulation made up of ten herbs which is used in various ayurvedic medicines). Different parts of the plant can be used medicinally like root, leaf and bark. The leaves of are reported to have diuretic properties, useful in agalactia, dropsy, dyspepsia, flatulence, neuralgia, piles, rheumatalgia and tumours [1]. The root is effective as appetizer, astringent, useful in abscess, asthma, bronchitis, cardiac disorders, diabetes, diarrhoea, inflammations, rheumatoid arthritis, rhinitis, etc. [6] and also applied after parturition in Burma [7]. The stem bark is applied to heal various skin diseases, wounds and to reduce fever [8].

Taxonomical classification of *Premna mollissima* Roth.-

Kingdom	Plantae
Phylum	Angiosperms
Class	Eudicots
Order	Lamiales
Family	Lamiaceae
Genus	*Premna*
Species	*mollissima*

2. Material and Method

A literature-based search was performed covering research articles that have been published online, to retrieve information on Ethno-pharmacology, phytochemistry, active constituents, molecular pharmacology, Ethnobotany from accessible online databases, such as Pubmed, Science Direct, Google Scholar, Scopus and Web of Science from their dates of inception till present using the key search terms of "*Premna mollissima*, "dashmoola", "Premnine". This review also includes literature collected via traditional texts and modern pharmacological books.

3. Ethno-botany

The family of genus *Premna* L. was transferred from Verbenaceae to Lamiaceae [9], subfamily Viticodeae [10]. There are 46 species recognized in the Flora of China [11] and 14 species occurring in the Flora Malesiana area [12]. The generic name is derived from the Greek "premnon" meaning tree stump, referring to the often short and twisted tree trunks of *P. serratifolia*. Most of the *Premna* species are widespread but a series of morphologically closely related and generally geographically restricted species occur from India to New Guinea [13]. The genus *Premna* contains about 200 species worldwide which are mainly distributed in the Old World tropics from Africa to China, throughout Indochina and Malaysia, to Australia and the Pacific [9]. Most species of *Premna* are small trees or shrubs, rarely lianas. However, some of the rare and geographically restricted species are exclusively lianas (*P. trichostoma*), about 35 species of *Premna* are reported from India [14]. It is a large shrub or small tree having smooth bark, grayish white in colour, leaves are cordate or ovate, cuneate, rounded, flowers are greenish yellow, small, in paniculate corymbs, borne in flat-topped 60–80 mm long compact corymbose inflorescences that are produced at branch-ends. Individual

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inflorescences produce 101±56 flowers over a period of one week. drupe 4-celled. Trunk is 1.2 m in girth, leaves 5-17 cm long and are aromatic when crushed. The fruit is nearly a globose indehiscent drupe, 6×4 mm across, green initially, bluish-black or black upon ripening, and shiny, seated on saucer shaped sub entire calyx. [3, 15, 13].



Fig. 1. *Premna mollissima* Roth.

4. Climate and soil

The plant is well adapted to the sub-tropical hilly tracts in outer Himalayas with average annual rainfall around 100 cm, and the tropical regions of eastern and Peninsular India. In north India, it is often found on dry slopes and large, natural, degraded soil bunds. The plant grows on average clayey or pebbled shallow soils. Plantation on deep loamy soil with good drainage and a pH range of 7.3 to 8.0 have shown good results [16].

5. Propagation technique

Seeds are used as propagation material which, have a short viability of about three months. Seeds are sown in June, preferably in poly bags, immediately after collection and drying for a few days. The pulp of the fruit withers off after drying. As the seed is hard and stony, seed pre-treatment such as soaking the seeds in water for a minimum of 72 hours is necessary. Seed germination is around 70 %. Mechanical or acid scarification improves seed germination to 85%. About 100 gm seed is sufficient to raise plants for one hectare of land. Vegetative propagation is done through air layering and root coppices during the rainy season [16].

6. Traditional uses of *P. mollissima*

P. mollissima is of great value in ethnobotany. Almost all parts, i.e. root, leaf and bark have numerous medicinal uses. The root is used in many Ayurvedic preparations such as amrtarista, dantyadyarista, dasamularista, cyavanaprasa, brahma rasayana, dashamoola kwath, maharasnadi kwath, saptasara kvatha churna, narayana taila, brhatmasa taila and rasnadi churna [17]. Root is reported to be an appetizer, astringent and bitter, useful in abscess, asthma, bronchitis, cardiac disorders, cough, diabetes, diarrhoea, inflammations, neuralgia, obesity, rheumatoid arthritis, rhinitis, stomach disorders and as a post-delivery tonic for women [6, 18]. The roots are applied after parturition in Burma

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[7]. The leaves reported as diuretic, useful in agalactia, allergy, colic, cough, dropsy, dyspepsia, flatulence, neuralgia, piles, rheumatalgia and tumours [1]. The stem bark is applied to heal wounds, eczema, ring-worms, boils, skin diseases, itches and to reduce fever [8]. *P. latifolia* Roxb. is the most exploited wild food plant used during famine among the Karbi tribe. Nutritional analysis reported that bark of the plant is rich source of protein and carbohydrate. It also contains a good amount of amino acid and reducing sugar. Fresh moist bark is popularly used as medicine for relieving from stomach disorder including blood dysentery, painful micturition and also from bruises, burn and minor cuts among the Karbis [19].

7. Chemical constituents of *P. mollissima*

Diterpene: The genus *Premna* is mainly characterized by its diterpenoid constituents [9]. Various studies have identified 91 skeletons of diterpenes within Lamiaceae, of which 13 skeletons were frequently identified [20], and abietane diterpenes were highlighted as the most abundant and widespread within Lamiaceae. Eighteen abietanes, a nor-abietane, two secoabietanes and a abietane have successfully been identified in the plant [21], Some of them are -5,6-Double bond of 6a,11,14,16(or 17)-tetrahydroxy-abieta-8,11,13-triene,5,6-Double bond and enolic 6-OH of 6a,11,14,16(or 17)-tetrahydroxy-abieta-8,11,13-triene [21], 6a,11,14,16-tetra-O-acetylabieta-8, 1, 13 – trien – 7 - one [23], 13 –Formyl -11, 14 dihydroxypodocarpa -8,11,13-triene (Premnolal) [23, 25], 6,7-Dihydropremnolal [23], Sandaracopimar-15-en-8b-ol [25], Sandaracopimar-15-en-1b,8b-diol [21, 24].

Essential oil: Constituents obtained by hydrodistillation and ethanolic extraction method were 3-Hexanol, alpha-Pinene, Pinane, 1-Octen-3-ol, beta-Pinene, 3-Octanol, alpha-Phellandrene, 2(10)-Pinene-3-one, -Phellandrene, 2(3H)-Furanone, 5-ethenyl dihydro-5-methyl, cis-Linalool oxide, Linalool oxide-trans, Nonanal, Linalool [2].

Fatty acid: Hydrocarbons and lipid-related constituents have been identified. Compounds isolated are Decanoic acid, Pentadecane, 1-Dodecene, 1-Dotriacontanol, Decane, 2-methyl, Octdecane, Heptadecane, 2, 6, 10, 15 tetramethyl, Tetradecanoic acid, Eicosane, Heptadecanoic acid. [2].

Sterol: Three skeleton type of pentacyclic triterpenes have been reported from the genus *Premna*, i.e. lupane, oleanane and ursane. Common plant sterols, such as stigmasterol, and their glycosides, are widely distributed among *P. latifolia* such as Stigmasterol β -Sitosterol [26, 27].

Sterol glycoside: β -Sitosterol-3-O-b-D-glucoside [23, 27, 28, 29]

Iridoid glycoside*:* The name ‘iridoid’ itself comes from iridodial and related compounds isolated from the defense secretion of Iridomyrmex species [30]. Classification of naturally occurring iridoids involves large groups, yet there are four distinguish classes i.e. the non-glycosidic iridoids, iridoid glycosides, iridoid acetal esters, and secoiridoid glycosides. Iridoid obtained from *P. latifolia* are Bisdesoxydihyromonotropein 7-deoxyloganic acid, Geniposidic acid [27, 29].

Lignan: Premnalatin have been isolated from the plant [27].

Favonoid glycoside: Apigenin 7-O-b-D-glucopyranoside-4'-acetate, Apigenin 7-O-b-D-apiofuranosyl (1!2)-a-L-rhamnopyranoside [28].

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7.1. Phyto-components identified in the plant

66 different compounds with 10 major components have been identified in methanolic extract by GC-MS analysis, which ensure the pharmacological potency of the plant [30] (Table 1) (Fig. 2).

Table 1. Components identified in the GC-MS analysis of the plant extracts

No.	Name of the compound	Nature of compound	Peak area (%)	Biological activity
1	Squalene	Triterpene	13.57	Skin emollient, antioxidant Antitumor
2	Ergosta-5,7,9(11), 22-tetraen-3-ol, (3.beta.,22E)-	Phytosterol	0.15	Antitumor
3	Stigmasterol	Steroid	3.73	Anti-osteoarthritic
4	γ-Sitosterol	Phytosterol	10.13	Antidiabetic
5	Lupeol	Triterpenoid	0.33	Prostate and Skin cancers, Anti-inflammatory
6	*β*-Amyrin	Triterpene	2.27	Analgesic, Anti inflammatory, Anticonvulsant, Antidepressive, Hepatoprotective, Antihyperglycemic Hypolipidemic
7	*α*-Amyrin	Triterpenoid	2.05	Anti-inflammatory, Antinociceptive, Antioxidant, Antipruritic, Gastroprotective
8	γ - Sitostenone	Phytosterol	0.35	
9	Ursolic aldehyde	Triterpenoid	1.01	Anti-glycative
10	Betulin	Triterpene	0.72	Antimalarial, Anti-inflammatory, Antifungal

7.2. Active chemicals isolated from various parts of Premna mollissima Roth.

Leaves: Iridoid glycoside (7- deoxyloganic acid, Geniposidic acid) [27, 39], diterpenes (Nellionol, Premnolal, Latifolionol, Latiferanol) and saponins [21], essential oil (terpendiol, *α*-pinene), Premnine, Latanoprost Acid, *β*-Sitosterol, Lupeol, 1-octen-3-ol (35.69 %), terpendiols I and II, *δ*-guaiene, 2-undecanone, *α*-pinene, palmitic, 8,11,14- docosatrienoic acid, stearic, linoleic, arachidic, behenic and lignoceric acids, eicosane, 3-octanone, ethyl hexanol, linalool, methyl salicylate and (E)-caryophyllene, furanoid premnalatin [31], premnoside A, apigenin-4'- methoxy-7-O-arabino-rhamnoside and 5-hydroxy-4'-methoxyflavone-7-O-trioside, hexadecanoic acid (25.04 %), octadecanoic acid (6.82 %), 9, 12-octadecadienoic acid (4.19 %) [2, 32].

Stem bark: Premnalatifolin, (dimeric diterpene), hexadecanoic acid and 1-octen-3-ol icetexane diterpenes latifolionol, dihydrolatifolionol, latiferanol [31], Dihydrolatifolionol, iridoids, 7- deoxyloganic acid and geniposidic acid [2].

Root: Iridoid Glycosides (premnine, 7-deacetylpremnine, luteolin and premnalatifolin), Triterpene (Betulinic acid), Alkaloids

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(premnamine, vallesiachotamine), fatty acids, stigmanstane esters and n tetracosanol [31]

Root Bark: Hydroxysandaracopimar-15-enes, bisnorditerpene (premnolal) and diterpenes (nellionol, dehydronellionol and anhydronellionol) [24], 5 dehydronellionol, sandaracopimar-15-en-8 *β*-ol and *β*-sitosterol, 14*α*- hydroxyisopimar-7,15-diene, 7*α* hydroxysandaracopimar (8, 14), 15-diene, 7*α* hydroxyisopimar-8,15-diene and 1α, 8*β*,11*α*-triol - sandaracopimar-15-ene [21], myristyl lignocerate (tetradecyl tetracosanoate, *β*-sitosteryl oleate, 1-hexacosanol and new monoterpenic esters 1-benzoyloxy-10 plamityloxy geranilane, 1- benzoyloxy-10-(octadec-9''-enoyl) geranilane and 1- benzoyloxy-10-octadecanyl geranilane (33) (Fig. 3).

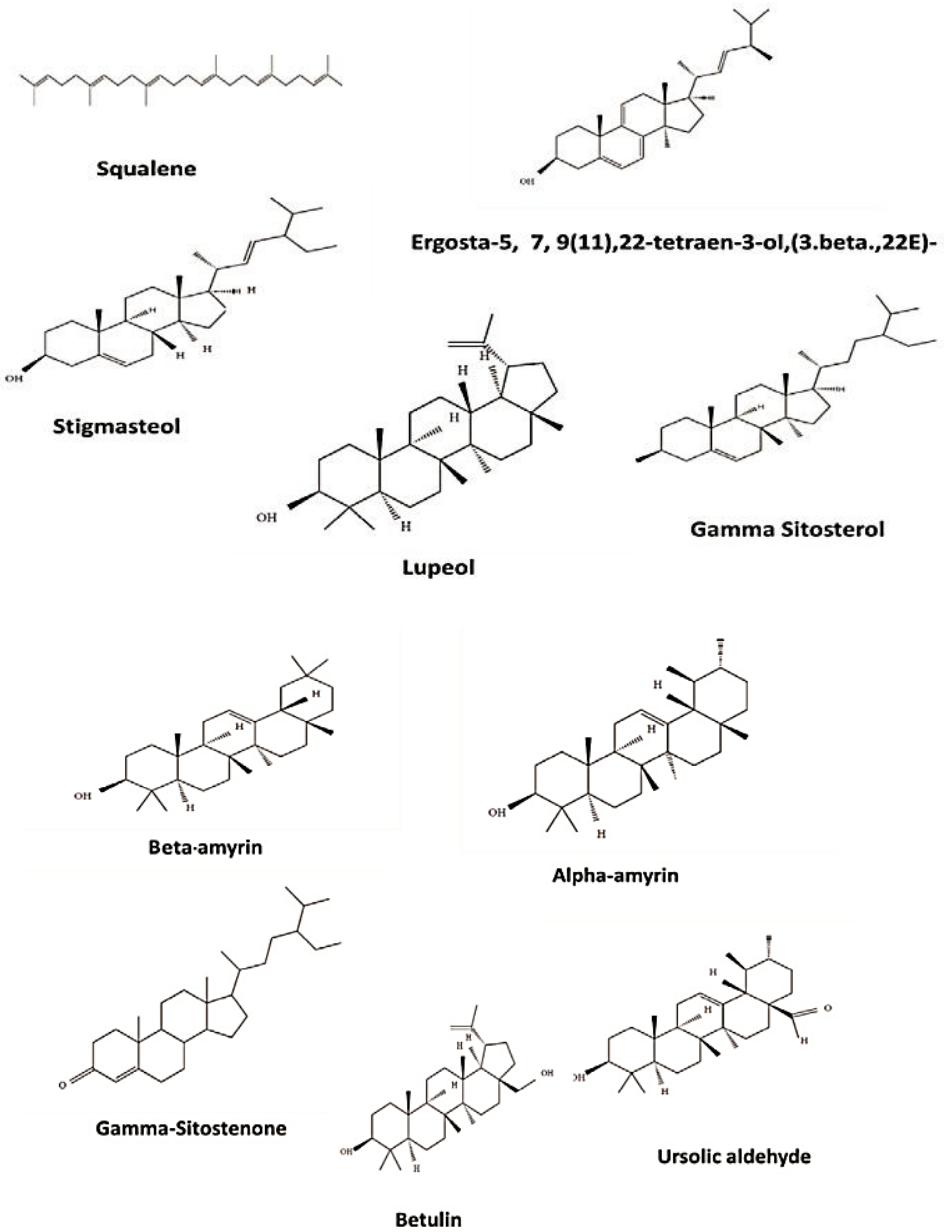

Fig. 2. Structure of phytoconstituents obtained from phytoscreening of *P. latifolia* Roxb. [30]

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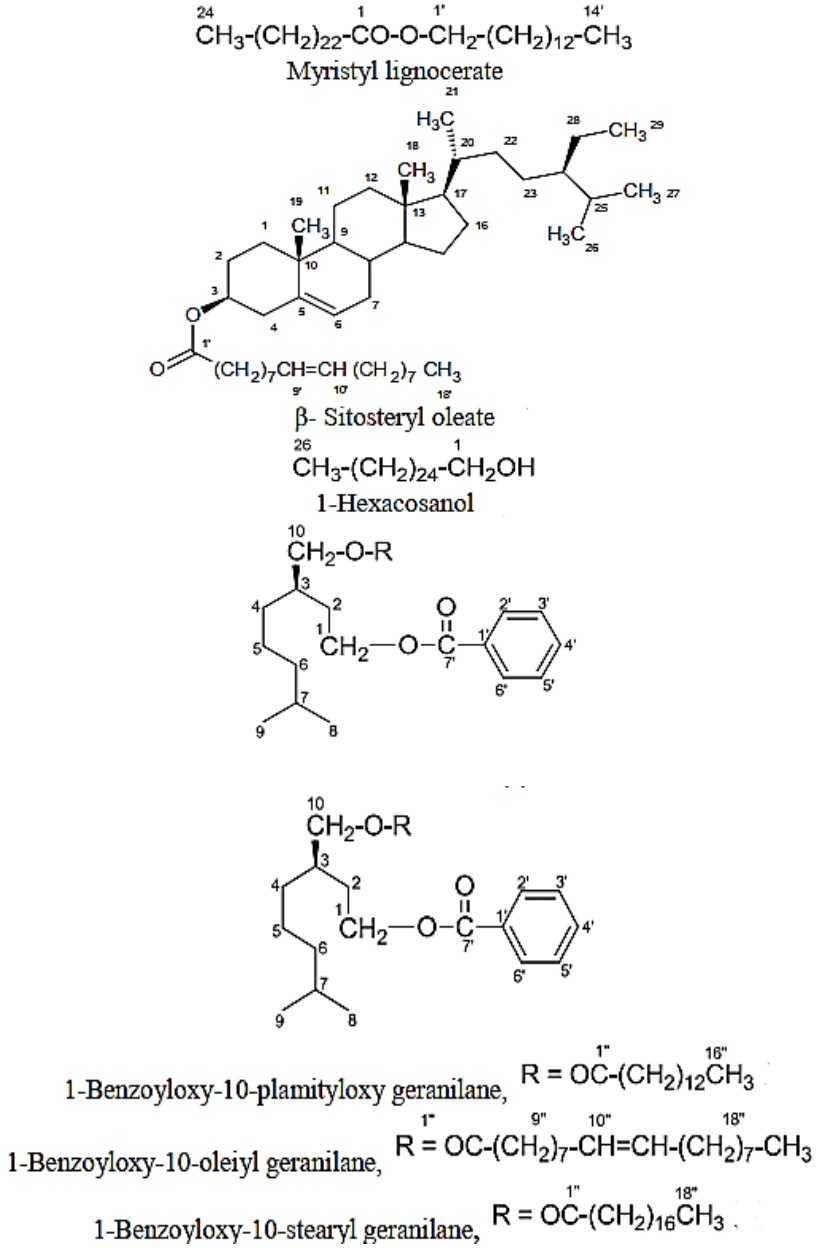

Fig. 3. Compound isolated from root bark of *P. mollissima* [33]

8. Pharmacological activities of various extracts of *P. latifolia* Roxb.

Antimicrobial activity: The leaves of *P. latifolia* Roxb. EtOH extract exhibits zone inhibition (8-10 mm) against the growth of *Pseudomonas aeruginosa, Staphylococcus aureus, Micrococcus. luteus, M. roseus* and *Candida albicans* [34]. Studies validates the antifungal properties of *P. latifolia* when tested against *Fusarium* and *Rhizopus* which shows moderate rate of inhibition. The fungal activity of the *P. latifolia* might be due to the presence of various secondary metabolites [36]. The bark of the plant is reported to treat ringworm in skin [36].

Antibacterial activity*:* Ethanol leaf extracts of *Premna latifolia* possess showed antibacterial activity against against four pathogenic bacteria with maximum zone of inhibition [37].

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Anti-inflammatory effect: The leaf decoction of *P. latifolia* against carrageenan induced rat hind paw edema. The result signified that the leaves shows good anti-inflammatory effects [38]. Also, MeOH ext. of leaves exhibited significant anti-inflammatory activity on the three animal models, dose dependently using carrageenan-induced paw edema, cotton pellet-induced granuloma, and acetic acid-induced vascular permeability models [39]. .

Anti-oxidative effect*:* Bark and leaf extracts were evaluated for antioxidant activities by DPPH radical and ABTS scavenging assay. The methanolic extract of bark and leaves of *P. latifolia* showed the presence of maximum phytochemicals (12&11) when compared to other solvent extracts viz. hexane (PLHEX) (10&9), ethanol (PLETH) (9&8), and chloroform (PLCHLO) (8&7) respectively. The amount of phenolics and flavonoids present in solvents were in the order of Methanol > Hexane > Ethanol > Chloroform. The study indicates that the bark possess greater antioxidant potential in comparison to leaves and the extract could be used as a probable antioxidative agent [4]. The isolated flavones from *P. latifolia* leaves showed significant DPPH radical scavenging potential which indicates the potential antioxidant properties of the plant [28]. Other studies related to radical scavenging activity and antioxidant properties of *P. latifolia* are also reported [40]

Antifeedant activity: Evaluation of phytochemicals and antifeedant properties of oil isolation using fresh leaves of *P. latifolia* reveals presence of hexadecanoic acids namely, 9,12-octadecadienoic acid, 8,11,14-docosatrienoic acid and octadecanoic acid. Oil showed antifeedant activity against polyphagous crop pest *Spodoptera litura* [2].

Wound healing*:* Wound healing activity of the plant was studied using excision wound model. Animals were divided into three groups of six male rats each as control group (GI) dressed with compound free simple ointment. Test group (GII) treated with 50 % aqueous ethanolic extract of *P. latifolia* stem (10 % w/w) in ointment vehicle and standard group (GIII) group treated Nitrofurazone ointment, Himedia (0.2 % w/w). The wound healing potential was further supported by the DPPH free radical scavenging and antibacterial activity of the plant. The phytochemical estimations were done using standard methods. The 50 % aqueous ethanolic extract of *P. latifolia* showed significant wound healing activity [41].

Anticalculogenic effect: Stem and leaves of *P. latifolia* assessed by scanning electron microscope analysis, which revealed the anticalculogenic effect of the plant [42].

Larvicidal effect: Evaluation of *P. latifolia* extracts using crude aqueous, chloroform, methanol and essential oil was done to see larvicidal effect using fourth instar larvae of *Aedes albopictus* Skuse. Authors reported essential oil constituents namely, *β*-cadinene (33.62 %), phytol (27.28 %) and a-selinene (9.42 %). The study reported that essential oil showed good amount of larvicidal action [43].

Antidiabetic effect: Ethanolic root extracts of *P. latifolia* was tested for glucose lowering action in STZ-nicotinamide induced diabetic rat model. *In vitro* inhibitory activities of enzymes, alpha-amylase and alpha-glucosidase were also assessed. Authors measured blood levels of creatinine, glucose, urea and nitrogen. Enzyme levels in liver and pancreas were also studied. As per their report, two fractions showed good antidiabetic activity. [44].

Conclusion

In the present review the importance of *P. latifolia* in various aspects have been explored.

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The plant have been used to treat various ailments since ancient time. Investigating the chemical components is necessary to determine the mechanisms of action of potential markers and the structure-activity relationship between the constituents found in the root, stem, bark, and leaves. These findings give foundation for using the plant medicinally, as well as for the synthesis of active compounds and the use of clinical trials as a tool for creating Ayurvedic formulations. Due to the presence of several chemical constituents, *P. latifolia* can be used as a good source of active therapeutics. In Indian market, there are many Ayurvedic preparations containing parts of *P. latifolia* as important ingredient and are widely utilized. Depending on the primary information available on this plant, the isolation and identification of active constituents, modern pharmacological evaluations on isolated compounds and their toxicity testing is to be explored which can help in future research work.

Author contributions

SR: Methodology, Investigation, Writing Original draft preparation, MT: Reviewing.

Conflicts of interest

We declare no conflict of interest.

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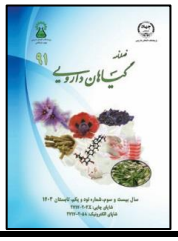

مقاله مروری

مروری بر اتنوفارماکولوژی و فیتوشیمی *Premna mollissima* Roth.

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اطلاعات مقاله

گل واژگان:

Premna mollissima Roth.

نعناعیان

ضد التهاب

آگنیمانتا

آیورودا

چکیده

مقدمه: گیاه دارویی *Premna mollissima* Roth. متعلق به تیره نعنائیان و درختی کوچک و خزان کننده است که معمولاً به نام dusky fire brand bark نامیده می‌شود. این گیاه اغلب در اقلیم‌های گرمسیری یا نیمه گرمسیری مناطق تپه‌ای یا جنگلی هند، سریلانکا، بنگلادش و میانمار پراکنده است. **هدف:** یک مرور سیستماتیک از مطالعه اتنوفارماکولوژی و فیتوشیمیایی گیاه *P. mollissima* است که شامل اهمیت درمانی (همانطور که در متون علمی ذکر شده) و جنبه‌های دارویی آن (که قبلاً در پارامترهای علمی امروزی مورد بررسی قرار گرفته‌اند) می‌شود. **روش بررسی:** مرور علمی قوم-داروشناسی گیاه *P. mollissima* از طریق متون علمی و همچنین جستجوی مقالات تحقیقاتی مرتبط با فارماکولوژی، کاربردهای سنتی، فیتوشیمی و فعالیت‌های درمانی گیاه در پایگاه‌های علمی Pubmed، Science Direct، Google Scholars، Scopus و Web of Science از تاریخ پیدایش تاکنون صورت پذیرفت. برای جستجوی ادبیات کلمات کلیدی ""*Premna mollissima*"، "Agnimantha" و ""Phytochemistry"" برای یافتن توضیحات گیاه استفاده شد. **نتایج:** از گیاه می‌توان ترکیبات شیمیایی مختلفی مانند پرمنین، ۷-داستیل پرمنین، پرمنلاتیفولین، کوئرستین و غیره به دست آورد. ریشه، برگ و پوست این درخت در طب آیورودا (طب سنتی هندوستان) برای درمان بسیاری از بیماری‌ها مانند آبریزش بینی، خیز، کورک، تب، روماتیسم، بیماری‌های عصبی و غیره استفاده می‌شود. مطالعات مختلف نشان‌دهنده خاصیت قابض، ضد التهاب، مدر، مغذی، هضم کننده و ضد باکتریایی آن است. **نتیجه‌گیری:** این مطالعه تلاشی برای گردآوری یک مرور جامع و به‌روز در مورد گیاه *P. mollissima* است که مشتمل بر مصارف طب سنتی و عامیانه، فیتوشیمی و داروشناسی گیاه است. این تحقیق به محققان آینده کمک می‌کند تا بیشتر در مورد ترکیبات فعال گیاهی و اثرات دارویی آن تحقیق کنند.

مخففها: DPPH، 2,2-diphenyl-1-picrylhydrazyl؛ ABTS، 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid)

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