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Critical review on *Agnimantha* (*Premna integrifolia* Linn and *Clerodendrum phlomodis* Linn)

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Abstract
The *Agnimantha* i.e *Premna serratifolia* Linn. Synonym *Premna integrifolia* Linn is a large, thorny deciduous shrub or a tree, up to 9 meters in height, commonly seen at Indian and the Andamans coasts. The Agni means fire and *Mantha* means churning. When the plant woods rubbed each other, generate fire, so named as *Agnimantha*. In *Ayurveda* the roots and leaves are most used parts for various medicinal preparations. The roots are considered as astringent, stimulant, liver tonic, laxative, carminative and antibacterial. Leaves infusion with pepper is useful in cold and fever, leaf sap is useful to alleviate headache. It can be used as hypoglycemic, anthelmintic, aphrodisiac, anti-inflammatory, analgesic and antimicrobial agent. It cure diseases like urticaria, asthma, haemorrhoids, erysipelas, fever, worms, allergic conditions. It is described in one of the ingredient in Dashamoola. The Agnimatha is of two types *Viz*; *Laghu Agnimatha* (*Premna integrifolia* Linn), and *Brihat agnimantha* (*Clerodendrum phlomidis* Linn). The present review dealt with the brief introduction and pharmacological actions, its traditional uses, modern research activities and also discussed the botanical description, chemical composition, biological activities on the basis of digital scientific database

Keywords: *Agnimantha*, *Premna integrifolia* Linn, *Premna mucranata*, *Clerodendrum phlomidis* linn, pharmacological actions

Introduction
The *Premna serratifolia* Linn. (Syn. *Premna integrifolia* Linn), is a large, thorny deciduous shrub or a tree, up to 9 meters in height, commonly seen at Indian and the Andaman coasts. In *Ayurveda* the roots and leaves are most used parts for various medicinal preparations. The roots are considered as astringent, stimulant, liver tonic, laxative, carminative and antibacterial. Leaves infusion with pepper is useful in cold and fever, leaf sap is useful to alleviate headache [1, 2]. The roots are useful in vitiated conditions of *Vata*, *Kapha*, neuralgia, inflammations, cardiac disorders, cough, asthma, bronchitis, leprosy, skin disorders, dyspepsia, flatulence, constipation, fever, diabetes and anorexia [3]. In Vietnamese traditional medicine, the leaves of *Schisandra*. *Chinensis* (Turcz) Ball belongs to Schisandraceae family, are used to treat indigestion, dysuria and dysentery; roots against indigestion, stomach ache and fever [4]. The root of methanolic extract showed better immunomodulatory activity in experimental mice. A paste of its roots with water and butter fat is given in urticaria.

Discussion
Various pharmacological actions along with its formulations discussed systematically;

Rasa Panchaka [5]
Rasa**:** *Tikta* (Bitter), *Katu* (Pungent), *Kashaya* (Astringent)
Guna**:** *Ruksha* (Dryness), *Laghu* (Light for digestion)
Virya**:** *Ushna* (Hot in potency)
Vipaka**:** *Katu* (Pungent)

Karma*: *Shothahara (Anti-inflammatory), ***Vedanasthapana*** (Which relieves pain)
Doshaghnata*: *Kapha-Vatahara (Subside *Kapha* and *Vata Doshas*)

Vishistha Yogas
Amritarishta, Dantyadyarishta, Dasamularishta, Agastya Haritaki Rasayana, Chyavanaprasha, Brahma Rasayana, Dashamula Katutraya Kwatha Churna, Rasnadi Kwatha Churna, Saptasara Kwatha Churna, Indukanta Ghrita, Dashamulaghrita, Dhanvantara Ghrita, Mahapancagavya Ghrita, Lasunadi Ghrita, Sukumara Ghrita, Dhanvantara Taila, Narayana Taila, Mahanarayana Taila, Mahavishagarbha Taila, Sahacharadi Taila [6]**.** *Guduchyadi Taila, Dashamula Taila, Vajrakapata Rasa, Shirahsuladivajra Rasa* [7]**,** *Dashamularka, Tagaradi Kwatha Churna, Bhunimbadi Astadashanga Kwatha Churna, Viratarvadigana Kwatha Churna* [8].

Botanical Description [9]
It is small tree, branches are spiny, bark is thin pale and exfoliating wood is light brown and scented. The leaves are ovate or ovate oblong, long acuminate base rounded cordate or tapering, entire or irregularly dentate blade 7-15 cms long petiole is 2.5 cms long.
The flowers are arranged in terminal, corymbose, trichotomous panicles ane are greenish in colour, calyx comprised of 4-5 sepals, with rounded and nearly equal teeth. Corolla lobes are equal or bilabiate, upper lip retuse or emargiate, lower lip of 3 equal lobes and throat closed with white hair. Fruit is globose drupe, green when young, dark at maturity, 3-5mm in diameter. The mature trees start flowering in April and fruiting in May and June.

Chemical Composition
Premnacorymboside A, scutellarioside II, quercetin - 3-rutinoside, leonuriside A were isolated from the stem bark [10]. Alkaloid contents like premnine, ganikarine, premnazole are reported in root from different researchers [11]. 1β, 3α, 8β-trihydroxy-pimara-15-ene; 6α, 11, 12, 16- tetrahy-dxy-7-oxo-abieta-8, 1, 13-triene; 2α, 19- dihydroxypri -mara-7,15-diene were identified in root bark [12].

Synonyms [13]
Arani, Ketu, Tarkari, Vaijayantika, Mathana, Vanhimathana, Ganika, Ganikarika, Pavana, Jayanti, Vijaya, Jaya.

Gana
According to *Acharya Charaka* [14] *Shothahara, Sheetaprashamana, Anulomana.*
According to *Acharya Sushruta* [15] *Brihatpanchamula, Vatasanshamana, Viratarvadi, Varunadi*
According to *Acharya Vagbhata* [16]- *Brihat Panchamula,*
Acoording to *Dhanwantari Nighantu* [17] *Guduchyadi Varga*
According to *Raja Nighantu* [18] *Prabhadradi Varga*
According to *Madanapala Nighantu* [19] *Abhayadi Varga*
According to *Kayadeva Nighatu* [20] *Oshadhi Varga*
According to *Priya Nighantu* [21] *Haritakyadi Varga, Brihat Panchamula*
According to *Bhavaprakasha Nighantu* [22] *Guduchyadi Varga*
According to *Chandra Nighntu* [23] *Niruha Gana*

Pharmacological actions as per *Ayurvedic* science [24]
Dosha Karma. Due to *Ushna Virya* it subsides *Kapha* and *Vata Doshas*. Therefore it is recommended in *Kapha Vatajanya* diseases
Sansthanika Karma (**Systemic actions**)-***Bahya*:** External Application- As it is *Ushna* it alleviates *Shotha* (Edema), and *Vedana*(Pain). Therefore it is used in edema and pain.
***Pachana Sansthana*:** Due to *Ushna Virya* it acts as *Dipana* (Appetizer), *Pachana* (Digestive), and *Anulomana*. Therefore it is indicated in *Agnimandya* (Loss of appetite), *Amadosha*, *Vibandha* (Constipation).
***Raktavaha Sansthana*:** The *Agnimatha* is *Raktashodhaka* (Purifies the blood), *Hridayottejaka* (Cardiac stimulant), and *Shothahara* (Subsides edema). Therefore it is advised in *Raktavikara* (Blood disorders), *Hridaya Daurbalya* (Strengthen the cardiac muscle), and edema.
***Shwasana Sansthana*:** As it is *Kaphaghna* used in *Kaphaja* diseases.
***Mutravaha Sansthana*:** It acts as *Pramehaghna* (Urinary disorders including diabetes) used in *Prameha Roga* (Urinary diseases including diabetes).
***Tapakrama*:** It is *Jwaraghna* (Anti pyretic) therefore used in *Jwara* (Fever).
***Satmikarana*:** As it is *Katu Pausthika*, it is advised in post fever general debility, *Pandu* (Anemia).
Part used: *Patra Swarasa* (Leaves juice), *Twak* (Bark), *Moola* (Root), *Moola Twak* (Root bark).
Dosage: Leaf juice 10-20ml, Churna (Powder)-1-3 grams, *Kwatha* (Decoction)-50-100 ml.
***Bheda*-(Types):** *Kshudra Agnimantha* and *Brihat Agnimatha*

Pharmacological actions according to modern
- **Analgesic Activity:** Analgesic activity was evaluated by using ethanolic extract of leaves of *P. integrifolia* [25]. Analgesic activity was also evaluated using methanolic extract of *Premna integrifolia* (MEPI) bark by writhing test in rats at doses 100 and 200 mg/kg body weight [26].
- **Anti-arthritic activity:** Anti-arthritic activity was evaluated using ethanol extract of *P. serratifolia* wood by Freund's adjuvant induced arthritis model [27].
- **Anti-bacterial activity:** Antibacterial activity of ethanolic extract of leaves of *Premna integrifolia* was tested by using the disc diffusion method. The extract showed significant antibacterial activity against both gram positive and gram negative bacteria. Alcoholic extract of the root bark of *P. integrifolia* showed good antibacterial activity against gram-positive organisms during preliminary screening [28, 29].
- **Anti-cancer/ anti-tumour/ cytotoxicity/tumour suppression activity:** Anticancer activity of biosynthesized silver nanoparticles (AgNps) using the ethanolic leaf extract of *P. serratifolia* was evaluated against carbon tetra chloride (CCl4) induced liver cancer in Swiss albino mice (Balb/c) [31, 32]. The methanolic extracts of leaves, root barks (RB) and root wood of *P. serratifolia* for cytotoxic activity against two cancer cell lines [33]. The alcoholic extract of leaves of *P. serratifolia* possessed significant antitumor activity [34]**.** The cytotoxicity screening system validates anticancer use of the plant by traditional healers and literature claims [35].
- **Anti-inflammatory activity:** Anti-inflammatory activity of methanolic extract of *Premna integrifolia* (MEPI) bark was evaluated using carrageenan induced inflammatory model in rats at doses 100 and 200 mg/kg

b. w [37]. The administration of the root extract inhibited the carrageenan induced acute paw oedema and formalin induced chronic paw oedema in a dose dependent manner [38]. The root and root callus extracts of *P. serratifolia* augments its anti-inflammatory activity against carrageenan induced paw edema. The results of a study proved the anti-inflammatory effect of callus derived luteolin through its biologically active components, which may worth for further investigation and elucidation [39]. Anti-inflammatory activity was evaluated by pretreatment with a single dose of methanolic extract of *P. integrifolia* (PIM) (300 mg/kg b.w.). The extract also showed significant inhibition of cyclo-oxygenase (COX-I) activity on rat uterus and plasma membrane stabilization. The results scientifically demonstrated the anti-inflammatory activity of P. integrifolia roots in various experimental models probably through their antihistaminic, antikinin, COX-inhibitory and antioxidant action [40].

- **Anti-microbial activity-** Antimicrobial activity was evaluated against the selected human pathogens (*Bacillus* sp., *Enterococcus faecalis*, *E. coli*, *Klebsiella pneumoniae*, Non-haemolytic *Streptococci*, *Streptococcus epidermidis*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*) by using natural leaves, roots and its respective calli induced with help of various plant growth regulators. Results revealed increased inhibitory activities of callus extracts. The activities were found to be better when compared to the natural plant material extracts [41]. *P. serratifolia* was screened to evaluate *in-vitro* antimicrobial activity against the selected human pathogenic organisms [42]. The antimicrobial activity of different extracts of bark and wood of *P. serratifolia* was also studied against nine bacterial and four fungal organisms by disc diffusion method [43].
- **Anti-obesity or hypolipidemic activity:** Anti-obesity activity of chloroform-methanol (1:1) extract of *P. integrifolia* (CMPI) in mice fed with cafeteria diet was evaluated [44]. The effect of aqueous enriched fraction of *P. integrifolia* root (AEFPIR) against cafeteria diet induced obesity in Swiss Albino Mice was studied. There was a significant decrease in body weight, BMI, food consumption and in the levels of serum glucose, triglyceride, total cholesterol, LDL, and VLDL with a significant increase in the level of HDL in mice treated with simvastatin and AEFPIR groups compared with cafeteria diet group [45] Hypolipidemic activity was also evaluated using hypercholesterolemic rabbit model in comparison to the established hypolipidemic drug atorvastatin [46]. Anti-hyperlipidemic activity of *P. integrifolia* was evaluated in an experimental animal model. High fat diet caused significant increase in serum cholesterol, triglyceride, VLDL, LDL and significant reduction in HDL level. Both P. integrifolia and atorvastatin treatment showed significant prevention in increased in serum cholesterol, triglyceride, LDL as compared to cholesterol control group. HDL level was significantly increased in both treated and standard control group as compared to cholesterol control group [47] Anti-hyperlipidaemic activity of *P. integrifolia* on nicotine induced hyperlipidaemia was evaluated. From the above results, it is clear that *P. integrifolia* is an effective anti-hyperlipidemic agent [48].
- **Anti-oxidant activity:** Ethanolic extract of root and root derived callus extracts of *P. serratifolia* were investigated against paracetamol induced oxidative stress in blood of male albino rats. This investigation concluded that, ethanolic extract of root callus possess significant antioxidant activity, which can help to overcome paracetamol induced toxicity [49]. *P. serratifolia* possessed radical scavenging activity [50]. The free radical scavenging activity of *P. serratifolia* leaf has been evaluated in various *in-vitro* model systems. The study showed that the methanolic extract of plant has free radical scavenging activity against superoxide radical, nitric oxide radical, hydroxyl radical, DPPH radical, ABTS radical and inhibition of lipid peroxidation [51]. The isolated compound, 11, 12, 16-trihydroxy-2-oxo-5-methyl-10-demethyl-abieta-1, 10, 6, 8, 11, 13-pentene that appears to be a novel compound based on a new diterpene skeleton also possesses *in-vitro* antioxidant effects [52]. Antioxidant properties of the plants were analyzed by determining the scavenging effects of free radicals such as superoxide, hydroxyl, nitric oxide and lipid peroxidation generated with *in-vitro* assay systems [53]. Methanolic extract of *P. integrifolia* showed significant anti-oxidant activity [54] Antioxidant activity was evaluated by using methanolic extract of *P. serratifolia* leaf in paracetamol intoxicated rats. The study revealed that the methanolic extract of *P. serratifolia* was found to have potential antioxidant activity in the animal model system [55]. Antioxidant effect was monitored using the DPPH radical scavenging assay. Through the use of comprehensive spectroscopy studies, the isolated active antioxidant principle was identified as acteoside (verbacoside) which is about four times more active than the crude root wood extract [56]. Significant scavenging activity was observed in DPPH and NO assays. IC_{50} values of compounds 10-O-trans-p-coumaroylcatalpol and 4-hdroxy-E-globularinin were 0.37 and 0.29 M/mL in DPPH free radical scavenging assay, respectively [57]. Antioxidant activity of the oil and various organic extracts of *P. integrifolia* leaves were examined using DPPH and superoxide radical scavenging activities assay. The amount of total phenolic compounds was also determined as gallic acid equivalent. The results of this study suggest that the natural products derived from *P. integrifolia* may have potential use in food, pharmaceutical and/or cosmetic industries [58]. The extract showed significant anti-oxidant activity which is scientifically demonstrated the use of *P. integrifolia* as a potential source of natural antioxidant [59]. The extracts of *P. integrifolia* root possesses beneficial effect on human leucocytes and erythrocytes against H_2O_2 induced oxidative damage which substantiates their use in ethnomedicine as an antioxidant. Observed effect can be attributed to the flavonoid and phenol contents in the plant [60].
- **Anti-parasitic activity:** Antiparasitic activity of a few New Caledonian medicinal plants were studied **[61]**. Among the selected plants, *Scaevola balansae* and *P. serratifolia* were the most active against *Leishmania donovani* with IC_{50} values between 5 and 10 g/ml
- **Anti-ulcer and gastroprotective activity:** Antiulcer activity of ethanolic extract of leaves of *P. serratifolia* using aspirin induced ulcers at dose levels of 200 and 400 mg/kg compared with ranitidine as a standard drug. Results showed dose dependent decrease in ulcer index,

gastric acid secretion, free acidity, total acidity and increased the pH of gastric juice in aspirin and extract treated group of animals. Histopathological studies revealed that high doses of *P. serratifolia* leaves prevented ulcer formation [62].

- **Cardiac stimulant or cardioprotective activity:** Cardiac stimulant activity of stem bark and stem-wood of *P. integrifolia* was evaluated by using Isolated Frog Heart Perfusion Technique [63]. Cardioprotective effect of ethanol extract of stem-bark and stem-wood of *P. serratifolia* were tested on isoproterenol induced experimental myocardial infarction in rats. The cardioprotective effect of ethanol extract of stem-bark and stem-wood of *P. serratifolia* on isoproterenol induced myocardial infarction in rats. The protective myocardial effect may be due to the phytoconstituents such as iridoid glycosides, alkaloids, flavonoids and phenolic compounds [64].
- **CNS depressant activity:** CNS depressant activity of methanolic extract of *P. integrifolia* (MEPI) bark was evaluated using hole cross and open field test in rats at doses 250 and 500 mg/kg b. w. The depressing effect in hole-cross test was most intense during the second (60 min) and third (90 min) observation periods [65].
- **Hepatoprotective activity:** Hepatoprotective activity of alcoholic extract of leaves of *P. serratifolia* using carbon tetrachloride was studied. The degree of protection in hepatoprotective activity was measured by using biochemical parameters such as SGOT, SGPT, ALP, bilirubin and total protein. The results suggest that the alcoholic extract at the dose level of 250 mg/kg produced significant hepatoprotection by decreasing the activity of serum enzymes, bilirubin, and lipid peroxidation which is comparable to that of standard drug silymarine [66] Hepatotoxicity induced by paracetamol (800 mg/kg) administration was studied. The effects of root callus extracts were comparable to that of standard drug, silymarine. Histopathological findings also suggested the root callus extracts of *P. serratifolia* preventing the development of chronic damage [67].
- **Hypoglycemic activity:** Hypoglycemic activity was evaluated using streptozotocin induced type 1 and type 2 diabetic rats [68]. Hypoglycemic activity was also evaluated using 95% ethanolic extract of leaves in alloxan induced diabetic rats. Steady diabetes was confirmed by noting urine sugar regularly and then measuring blood glucose values before starting the experiment. To confirm definite hypoglycemic effect, final blood glucose values of each sample were brought down closer to normal fasting level using different doses of the ethanolic extract. The results indicate that *P. integrifolia* showed definite blood glucose lowering effect within 1 week using 250 mg/kg double dose [69].
- **Immunomodulatory activity:** Immunomodulatory activity was evaluated by using methanol extract of root of *P. integrifolia* in BALB/c mice [70].
- **Anti-ageing or life promoting or anti-oxidant activity:** In modern times, there has been an increase in the use of plants or herbal constituents for the prevention of age-related disorders. 4-Hydroxy-E-globularinin (4-HEG) is an iridoid and a major component of *P. integrifolia*. The discovery of this component represents a break-through in geriatrics because of its longevity-promoting activity of 4-HEG in an animal model. 4-HEG may serve as a lead compound for the development of important nutraceuticals preventing the aging process **[71]** Aging, the major cause of several ailments has led to intense exploration of potential drugs that delay aging and its associated effects [72].
- **Neuroprotective activity:** Neuroprotective effects were evaluated by using roots of *P. serratifolia* in the experimental model of febrile seizure [73].

Aims and Objectives

- To provide brief introduction and pharmacological actions, its traditional uses, modern research activities and also discussed the botanical description, chemical composition, biological activities on the basis of digital scientific database
- To provide comprehensive information on the pharmacological activities of various parts of *Premna integrifolia* Linn. All the relevant universally accepted electronic databases were searched with respect to the terms *Agnimantha*, *Premna integrifolia* Linn, *Premna obtusifolia* Linn, *Premna serratifolia* Linn including Indian classical texts, pharmacopoeias, journals.

Materials and Methods

- A survey was done by online as well as *Ayurvedic* classical texts books and the data were obtained by several electronic scientific databases and the additional information is obtained from the various *Ayurvedic* texts.

Conclusion

The present review reveals *P. integrifolia* to possess analgesic/antinociceptive, anti-arthritic, antibacterial, anticancer/antitumor/cytotoxic/tumor suppression, anti-inflammatory, antimicrobial, anti-obesity/hypolipidemic, antioxidant, antiparasitic, antiulcer/gastro-protective, cardiac stimulant/cardioprotective, CNS depressant, hepatoprotective, hypoglycemic, immunomodulatory, longevity-promoting and neuroprotective activities. According to the literature, most of the pharmacological activities of *P. integrifolia* is investigated by using methanol and ethanol as extractive solvents. The activities may be due to the presence of these phytocompounds in the extracts. The present information will be useful for setting up of research protocols for modern drug and Ayurvedic formulation development in curing and treating various diseases, which can prove its efficacy as a novel source for new drug development. The information collected here will be useful to set-up research protocols for modern drugs and *Ayurvedic* formulation development.

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