Ethnomedicinal uses, phytochemistry and pharmacological aspects of the genus Premna: a review

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ABSTRACT

**Context:** The genus *Premna* (Lamiaceae), distributed throughout tropical and subtropical Asia, Africa, Australia and the Pacific Islands, is used in folk medicine primarily to treat inflammation, immune-related diseases, stomach disorders, wound healing, and skin diseases.

**Objectives:** This review exhaustively gathers available information on ethnomedicinal uses, phytochemistry, and bioactivity studies on more than 20 species of *Premna* and critically analyzes the reports to provide the perspectives and directions for future research for the plants as potential source of drug leads and pharmaceutical agents.

**Methods:** A literature search was performed on *Premna* species based on books of herbal medicine, major scientific databases including Chemical Abstract, Pubmed, SciFinder, Springerlink, Science Direct, Scopus, the Web of Science, Google Scholar, and ethnobotanical databases.

**Results:** More than 250 compounds have been isolated and identified from *Premna* species, comprising of diterpenoids, iridoid glycosides, and flavonoids as the most common secondary metabolites, followed by sesquiterpenes, lignans, phenylethanoids, megastigmanes, glyceroglycolipids, and ceramides. Many in vitro and in vivo studies have been conducted to evaluate the biological and pharmacological properties of the extract, and isolated compounds of *Premna* species with antimicrobial, antioxidant, anti-inflammatory, immunomodulatory, antihyperglycaemia, and cytotoxic activities.

**Conclusion:** The bioactive compounds responsible for the bioactivities of most plants have not been well identified as the reported *in vivo* pharmacological studies were mostly carried out on the crude extracts. The isolated bioactive components should also be further subjected to more preclinical studies and elaborated toxicity study before clinical trials can be pursued.

Introduction

The genus *Premna* was previously classified within the family Verbenaceae (Munir 1984), but has been transferred into the family Lamiaceae, subfamily Viticoideae (Harley et al. 2004; Olmstead 2010, 2012). Currently, this genus contains 200 species which are mainly distributed throughout tropical and subtropical Asia, Africa, Australia, and the Pacific Islands (Harley et al. 2004). There are 46 species recognized in the *Flora of China* (Tan & Li 2014) and 14 species occurring in the *Flora Malesiana* area (de Kok 2013). The word ‘Premna’ is derived from the Greek *premonn*, meaning tree stump, which refers to the short and twisted trunks of *P. serratifolia* L., the first collected species of this genus. Based on the shape and number of calyx lobes, the genus *Premna* has been subdivided into five sections: *Holopremna* Briq. (consisting of two subsections: *Thysioideae* and *Corymbiferae*), *Odontopremna* Briq., *Gumira* (Rumph. ex Hassk.) Briq., *Prennos* Briq., and *Holochiloma* Briq. (de Kok 2013).

Morphologically most species in the genus *Premna* are small trees or shrubs and rarely found as lianas (*P. trichostoma* Miq.) and pyroherbs (*P. herbacea* Roxb.). Some species have young twigs with a series of small decussate triangular scales at the base which will fall off once the branch is older. The leaves are usually decussate and hairy. A ridge is often present between the petioles. There are two shapes of calyx types. The first one has four isomorphic lobes, the shape remaining largely intact when the flower develops and when the fruits are formed. The second type has 0–5 lobes, usually heteromorphic. There are also two fruit types: a globose drupe-like fruit consisting of four fleshy mericarps with one seed each, and a clavoid, almost single-seeded, drupe-like and consisting of one fleshy mericarp (de Kok 2013).

Our review of the genus *Premna* is based on ethnomedicinal uses, phytochemical investigations, and pharmacological attributes. This review is comprised of more than 20 species of *Premna* from 150 publications. It is noted that some species have recently been considered as synonyms based on current plant taxonomy (The Plant List 2013). For example: *P. obtusifolia* R.Br., *P. integrifolia* Willd., and *P. corymbosa* var. *obtusifolia* (R.Br.) H.R. Fletcher are synonyms to *P. serratifolia*; *P. japonica* Miq. is a synonym to *P. microphylla* Turcz.; *P. latifolia* Roxb. as a synonym to *P. mollissima* Roth. However, in order to avoid any confusion, we continue to use the species names as referred to by the author(s) of the original papers. The detailed information gathered and critically analyzed in this review should be useful as reference for phytochemists, pharmacologists, medicinal
Ethnopharmacological uses

The diversity of species of *Premna* throughout the habitat region resulted in various traditional uses by the local people. The earliest report was on ethnomedicinal values of ten species of *Premna* throughout East and Southeast Asia, notably to treat malaria, stomach disorders, headache, cough, malaria and tuberculosis (Perry & Metzger 1980). Most lately, the extensive work by Quattrocchi (2012) has recorded various ethnomedicinal uses of 29 species of *Premna* from numerous regions. Unlike other species which are endemic in certain region, *P. serratifolia* is widely distributed throughout the habitat region which explained its popularity in traditional medicine to treat various diseases or illnesses. In tropical Asia and East Africa, this species is notably used to treat neuralgia and headache, stomachic, fevers, colds and cough, and also to improve liver- and cardiac-related problems (Quattrocchi 2012). Other species, such as *P. tomentosa* Willd., are mostly used to treat stomach-related disorders by local people in Southeast Asia region. The local people in Burma, Thailand, Malay Peninsula and Indonesia use the leaves, root or the inner bark to relieve stomach ache discomfort/pain, for diarrhoea, or to treat diarrhea (Perry & Metzger 1980; Wiart 2000; Quattrocchi 2012).

Meanwhile, in Polynesian Islands, *P. serratifolia* is commonly used to treat infectious-related diseases such as leucorrhoea, genital disease, cancer sores, bad breath and white tongue (Girardi et al. 2015). It is an interesting fact that few species were used in malarial treatment in different regions. For example, bark of *P. angolensis* Gürke was among traditional plants used to treat malaria and other fevers in S. Tomé and Príncipe islands in the Gulf of Guinea (do Céu de Madureira et al. 2002). The bark and the leaves of *P. chrysoleada* (Bojer) Gürke were used in treatment of malaria by the traditional health practitioners in Kilifi District, Kenya (Gathirwa et al. 2011). Quattrocchi (2012) has listed two species of *Premna* that were used in malarial treatment in traditional medicine, *P. foetida* Reinw. Ex Blume leaves used in local communities in topical Asia, and *P. glandulosa* Hand.-Mazz. leaves used by the local community in China.

In the Philippines, the leaves of *P. odorata* Blanco are used to treat phlegm and tuberculosis (Lirio et al. 2014). In China, India, Vietnam, Burma and Thailand, a few species have been recorded to treat skin diseases such as eczema, ringworms and boils, scabies, skin’s rashes and itching (Perry & Metzger 1980; Quattrocchi 2012; Sharma et al. 2014). The mucilaginous substance of *P. ligustroides* Hems. was recorded to be used topically as a sunstrike prophylactic in China (Perry & Metzger 1980). Jeevan Ram et al. (2004) also reported the use of the stem bark of *P. latifolia* for wound healing. Khare (2004, 2007) has highlighted four species of *Premna* (*P. herbacea*, *P. integrifolia*, *P. latifolia* and *P. tomentosa*) that are used in Ayurvedic medicine, either alone or together with other plant(s), and still available as over-the-counter medicine for local people. Known as ‘agnimanta’, ‘siru thekku’, ‘ghantu bharangin’, ‘agethu’, or ‘gineri’, the decoction of the leaves, stem bark, or roots have been used to treat asthma, rheumatism, neuralgia, diarrhea and stomach disorder, hyperglycaemic, and obesity. It is also used as a post-delivery tonic for women.

The details of species, part of the plant and the ethnomedical use of the *Premna* species are detailed in Table 1. Thus, we can categorize the ethnomedicinal values of the *Premna* species (i) as anti-inflammatory – either to treat asthma, rheumatism, gout, pains, fevers; (ii) to improve immune system and treat cold and cough; (iii) for stomach disorders such as diarrhea, dysentery, febrifuge, stomachache; (iv) for wound healing and treating skin diseases; (v) to treat bacterial (for example, tuberculosis, leucorrhoea) and malarial infections; (vi) to treat migraine, headache, and neuralgia problems; and (vii) to treat hypertension, diabetes, liver-and cardiac-related problems.

Phytochemistry

**Essential oils**

The genus *Premna* is not widely known to be rich in essential oil content. Nevertheless, previous studies have reported the contents of essential oils in a range of 0.056–0.102% in some *Premna* species (i.e. *P. angolensis*, 0.056%; *P. barbata* Wall. ex Schauer, 0.08–0.1%; *P. coriacea* C.B. Clarke, 0.08%; *P. quadrifolia* Schumach. & Thonn., 0.102%; *P. integrifolia*, not determined; *P. tomentosa*, 0.073%) (Narayan & Muthana 1953; Teai et al. 1998; Chanotiya et al. 2009; Rahman et al. 2011; Sadashiva et al. 2013; Adjalian et al. 2013). Among the compounds identified, 1-octen-3-ol, limonene, α-copaene, β-elemene, β-caryophyllene, and δ-cadinene were found as among well-distributed compounds in studied species in varied concentrations.

**Hydrocarbons, fatty acids, ceramides and glyceoglycolipids**

Hydrocarbons and lipid-related constituents [1–4, 7] have been identified in *P. fulva* Craib, *P. crassa* Hand.-Mazz., *P. hainanensis* Chun & F.C.How, *P. odorata*, *P. integrifolia* and *P. serratifolia* (Wei et al. 1991; Hang et al. 2008; Dai et al. 2010; Lirio et al. 2014). A phytochemical study on *P. microphylla* leaves has led to isolation of fatty acids [5–6], glyceroglycolipids [8–10] and ceramides [11–12] (Zhan & Yue 2003). Ceramides and glyceroglycolipid are major components of chloroplast membrane of the plant, which serve mainly as precursors of important signaling compounds/pathways in various cellular processes (Kolter & Sandhoff 1999). A few studies have reported ceramides and glyceroglycolipids to have immunomodulatory activity as well as anti-tumor, anti-cancer and anti-inflammation properties (Van Veldhoven et al. 1992; Cateni et al. 2004; Ramos et al. 2006; Mboeso et al. 2012).

**Sesquiterpenoids**

Habtemariam et al. (1993) have reported the isolation of an antibacterial sesquiterpenoid, 7α-hydroxy-6,11-cyclofarnes-3(15)-en-2-one [13] from *P. oligotricha* Baker. Meanwhile, numerous monocyclofarnesanes sesquiterpenes [14–19, 23–24] were isolated from *P. microphylla* leaves (Hu et al. 2013). An eudesmane [25] and an aromadendrane [26] were reported to be isolated from *P. obtusifolia* (Salae et al. 2012). In addition, Sudo et al. (2000) reported the isolation of three megastigmane glycosides [20–22] from the leaves of *P. subsandens* Merr.

**Diterpenoids**

The genus *Premna* is mainly characterized by its diterpenoid constituents (Harley et al. 2004). One study has identified 91 skeletons of diterpenes within Lamiaceae, of which 13 skeletons were frequently identified (Vestri Alvarenga et al. 2001), and...
| Species          | Part of plant | Uses                              | Community/area                          | References                           |
|------------------|---------------|-----------------------------------|-----------------------------------------|--------------------------------------|
| *P. angolensis*  | Bark          | To treat malaria                  | S. Tome and Principe islands            | do Céu de Madureira et al. 2002      |
|                  | Leaves        | As insect repellent               | Africa & Benin                          | Adjalian et al. 2015                 |
| *P. barbata*     | Fruits        | Fever, chilblain, eczema          | India, Pakistan                         | Quattrocchi 2012                     |
|                  | Wood          | Wound healing                     | India, Pakistan                         | Quattrocchi 2012                     |
|                  | Stem bark     | In throat pain                    | India, Pakistan                         | Quattrocchi 2012                     |
| *P. bengalensis* | Leaves        | Improve immune system             | India                                   | Quattrocchi 2012                     |
|                  | Bark          | In paralysis                      | India                                   | Quattrocchi 2012                     |
| *P. chrysocolla* | Leaves, roots | Kidney diseases, venereal infections, fevers, dysentery | Tropical Africa                         | Quattrocchi 2012                     |
|                  | Roots & leaves| To treat malaria; diarrhoea       | Klifi district, Kenya                   | Gathirwa et al. 2011                 |
| *P. cordifolia*  | Leaves, roots | Febrifuge                         | Malay peninsula                         | Perry & Metzger 1980                 |
|                  | Leaves        | Anti-inflammatory, rheumatism     | Vietnam, Malay peninsula                | Quattrocchi 2012                     |
| *P. corymbosa*   | Leaves        | To treat malaria                  | China                                   | Perry & Metzger 1980                 |
|                  | –             | Applied to contusions             | Taiwan                                  | Perry & Metzger 1980                 |
|                  | Roots         | For stomach disorders             | Indo-China                              | Perry & Metzger 1980                 |
|                  | Leaves        | As galactogogue                   | Indonesia                               | Perry & Metzger 1980                 |
|                  | –             | Cough, headache                   | Philippines                             | Perry & Metzger 1980                 |
| *P. divaricata*  | Leaves        | For cold                         | Malay peninsula                         | Quattrocchi 2012                     |
| *P. esculenta*   | Root          | Urinary problem, to espel the stones | Sumatera, Indonesia; Malay peninsula | Perry & Metzger 1980; Wiart 2000     |
| *P. foetida*     | Roots         | For shortness of breath, cough    | Indonesia, Philippines                  | Perry & Metzger 1980                 |
|                  | –             | –                                 | New Guinea, Solomon Islands             | Perry & Metzger 1980                 |
| *P. glandulosa*  | Leaves        | Malaria, liver and spleen problems, worms and constipation | China                       | Quattrocchi 2012                     |
| *P. henryana*    | –             | For cough and colds               | China                                   | Quattrocchi 2012                     |
| *P. herbacea*    | Rhizome       | To treat cancer                   | Thailand                                | Itharat et al. 2004                  |
|                  | Leaves        | Headache                          | China and Tropical Asia                 | Quattrocchi 2012                     |
|                  | Leaves & roots| Rheumatic pain, cough, fever, cold | China and Tropical Asia                 | Quattrocchi 2012                     |
|                  | Roots         | Ulcers, rheumatism, gout          | China and Tropical Asia                 | Quattrocchi 2012                     |
|                  | Whole plant   | To treat sprain                   | China and Tropical Asia                 | Quattrocchi 2012                     |
|                  | Roots & rhizomes| For dropsy, cough, asthma, fever, rhematism, cholaera | China and Tropical Asia                 | Quattrocchi 2012                     |
| *P. hispida*     | Leaves        | As febrifuge                      | Malay peninsula                         | Wiart 2000                           |
| *P. latifolia*   | Stem bark     | For wound healing                 | Eastern Ghats, India                    | Jeevan Ram et al. 2004               |
| *P. mollissima*  | Root          | As a local application after parturition | Burma                                   | Perry & Metzger 1980                 |
| *P. ligustroides*| Muscillaginous substance | Used topically as sunstrike prophyllactic | China                                   | Perry & Metzger 1980                 |
| *P. maxima*      | –             | For febrifuge                     | China                                   | Quattrocchi 2012                     |
| *P. mollissima*  | Stem, stem bark, bark | Eczema, ring-worms and boils, skin diseases, itch, fever | China, tropical Asia                   | Quattrocchi 2012                     |
|                  | Leaves        | Diuretic, aromatic, dropsy, for a bath to reduce body allergy | China, tropical Asia                   | Quattrocchi 2012                     |
| *P. mucronata*   | Bark          | To treat ringworm                 | Uttarakhand, India                      | Sharma et al. 2014                   |
| *P. nauseosa*    | Leaves        | For a bath to reduce body allergy | India                                   | Quattrocchi 2012                     |
| *P. odorata*     | Leaves        | To treat tb, phlegm, stomachae, headache, cough. Also as wound healing, paracities, to cure tympanites, beri-beri and heart trouble, to relieve abdominal pain and dysentery | Albay Province, Philippine            | Lirio et al. 2014; Perry & Metzger 1980 |
|                  | Leaves, roots, flowers and fruits | Sudorific, analgesic, pectoral, carminative, headache | Philippines, Taiwan                    | Quattrocchi 2012                     |
| *P. obtusifolia* | Leaves        | Malaria, cough                    | Manus, Papua New Guinea                 | Larson et al. 2014                   |
| *P. parasitica*  | Leaves        | As tonic after confinement; for fever | Indonesia; Malay peninsula              | Perry & Metzger 1980; Wiart 2000      |
| *P. puberula*    | Stem bark     | Mouth blisters                    | China                                   | Quattrocchi 2012                     |
| *P. pyramidalata*| Shoots        | Applied externally on abdomen to treat worms | India                                   | Quattrocchi 2012                     |
abietane diterpenes were highlighted as the most abundant and widespread within Lamiaceae, followed by labdanes, pimaranes, and clerodanes. Interestingly, our current review involving 17 species revealed that icetexanes and abietanes (including nor- and seco-abietanes) were the most common diterpene types occurred in the genus Premna, followed by pimaranes (including iso- and sandaraco-pimaranes), clerodane, labdane, podocarpanes and rosane (Table 2). At one time, icetexanes were found only in three genera of Lamiaceae: Coleus, Lepechinia, and Salvia. Habtemariam et al. (1990) reported the presence of antibacterial clerodane diterpenes [29–30] from the leaves of P. schimperi Engl. A year later, two ent-labdane diterpenes [27, 28] were isolated from the aerial parts of P. oligotricha (Habtemariam et al. 1991). Another three clerodanes [31–33] were reported in P. tomentosa leaves (Chin et al. 2006). The labdane, ent-12-oxo-labda-8,13(16)-dien-15-0ic acid [27] and all clerodanes bear a free carboxylic acid unit attached to C-15 with oxygen substitution at C-12 and sp²-hybridization between C-13 and C-16. The structures of some of the diterpenes are shown in Figure 1.

Eighteen abietanes [34–51], a nor-abietane [52], two secoabietanes [54, 55] and a abietane [53] have successfully been identified in P. latifolia (Rao et al. 1978; Rao & Vijayakumar 1980), P. integrifolia (Yadav et al. 2010), P. obtusifolia (Salae et al. 2012) and P. serratifolia (Habtemariam & Varghese 2015). Oxygenated substitution at C-12 of abietane is common within this genus and sometimes the substitution may occur at C-1, C-6, C-7, C-11, C-14 and C-16. While nor-abietane [52] is characterized by loss of methyl at C-10, this methyl moves from C-10(α) to C-5(β) in a novel abietane, prenomal [56]. Additionally, two abietane derivatives [56, 57], known as podocarpanes, were isolated from P. latifolia var. cuneata C.B.Clarke which do not have iso-prenyl substitution at C-13. Two pimaranes [58, 59] with rare 1,3-dihydroxy and 2-hydroxy, respectively, were isolated from

| Table 1. Continued |
|-------------------|
| **Species**       | **Part of plant** | **Uses**                          | **Community/area** | **References** |
| P. quadrifolia Schumach. & Thonn. | Leaves | As insect repellent | Africa & Benin | Adjian & others 2015 |
| P. serratifolia L. | Leaves | As tonic after childbirth | Malay peninsula | Wiart 2000 |
| P. serratifolia L. | Leaves | Migraine | North Bougainville, Papua New Guinea | Larson & others 2014 |
|                      | Leaves | Cough, constipation | Rotuma, Pacific Islands | McClatchey 1996 |
|                      | Bark | Hypertension, cardiac insufficiency | Rotuma, Pacific Islands | McClatchey 1996 |
|                      | Bark | Dysentri, stomachache | Siwai and Buin districts, Bougainville, Papua New Guinea; tropical Asia, east Africa | Waruruai et al. 2011 |
| P. tomentosa Willd. | Leaves, bark | Headache, malaria | Siwai and Buin districts, Bougainville, Papua New Guinea | Waruruai et al. 2011 |
|                      | Leaves, twigs | Leucorrhrea, genital disease, girl’s intimate hygiene, vaginal discharge | Marquesas Islands, Polynesian Islands | Girardi et al. 2015 |
|                      | Aerial parts | Canker sores, bad breath, thrush, white tongue, oral form of epa, including bewitchment, taboo transgression, medicomagic | Marquesas Islands, Polynesian Islands | Girardi et al. 2015 |
|                      | Leaves | Diabetes/hypoglycaemic, gout | Marquesas Islands, Polynesian Islands, tropical Asia, East Africa | Quattrocchi 2012 |
|                      | Leaves | Antiparasitic against tb; to treat migraine and general pains | New Caledonian | Desrivots et al. 2007 |
|                      | Whole plants | Rheumatism, neuralgia, headache | Tropical Asia and East Africa | Quattrocchi 2012 |
|                      | Fruits | Cough | Tropical Asia and East Africa | Quattrocchi 2012 |
|                      | Leaves | Stomachic, colds, fevers, cough, headache, applied externally for body pain | Tropical Asia and East Africa | Quattrocchi 2012 |
|                      | Roots | Stomachic, tonic, liver problems, cardiac troubles | Tropical Asia and East Africa | Quattrocchi 2012 |
| P. steppicola Hand.-Mazz. | – | Skin diseases | China | Quattrocchi 2012 |
| P. sunyiensis C.Pei | – | Astringent, stomachic | China | Quattrocchi 2012 |
| P. szemaoensis C.Pei | – | Wound healing, stomachic | China | Quattrocchi 2012 |
| P. tahitensis Schauer | Bark | Tonics | Pacific | Quattrocchi 2012 |
| P. tomentosa Willd. | Root, leaves | For stomachache, to take care of worms, and as bath after childbirth | Malay peninsula | Perry & Metzger 1980; Wiart 2000 |
|                      | Inner bark | For diarrhea | Indonesia | Perry & Metzger 1980 |
|                      | Whole plants | Applied externally on caterpillar stings | Burma, Thailand | Quattrocchi 2012 |
|                      | Leaves | Diuretic, postpartum remedy, for biliousness and abdominal pains, applied locally on scabies, skin rashes, itching | Burma, Thailand | Quattrocchi 2012 |
| P. urticifolia Rehder | Oil from root | Stomach disorder | Burma, Thailand | Quattrocchi 2012 |
| – | Skin disease | China | Quattrocchi 2012 |

- not mentioned.
| Classes          | No. | Isolated compounds                                                                 | Synonym                  | Species          | References            |
|------------------|-----|-------------------------------------------------------------------------------------|--------------------------|------------------|-----------------------|
| Fatty acid       | [1] | Stearic acid                                                                        | Octadecanoid acid        | P. fulva, P. crassa | Wei et al. 1990; Wei et al. 1991 |
| Fatty acid       | [2] | Hexacosic acid                                                                      |                          | P. hainanensis    | Dai et al. 2010      |
| Fatty acid/Aldehyde | [3] | 2-Hexylenedi-3-methylsuccinic acid                                                  |                          | P. serratifolia   | Wang et al. 2011     |
| Fatty acid       | [4] | 1-Heneicosyl formate                                                                |                          | P. odorata        | Lirio et al. 2014    |
| Fatty acid       | [5] | α-Linolenic acid                                                                    |                          | P. microphylla    | Zhan & Yue 2003      |
| Fatty acid       | [6] | 1-Monolinolenin                                                                     |                          | P. microphylla    | Zhan & Yue 2003      |
| Alkana glucoside | [7] | Hexyl glucoside                                                                     |                          | P. microphylla    | Zhan & Yue 2003      |
| Glyceroglycolipid| [8] | 1-O-9Z,12Z,15Z-octadecatrienoyl-3-O-β-D-galactopyranosylglycerol                    |                          | P. microphylla    | Zhan & Yue 2003      |
| Glyceroglycolipid| [9] | Gingerglycolipid A                                                                  |                          | P. microphylla    | Zhan & Yue 2003      |
| Glyceroglycolipid| [10]| 1-O-9Z,12Z,15Z-octadecatrienoyl-3-O-β-D-galactopyranosyl-1-O-β-D-galactopyranosyl- |                          | P. microphylla    | Zhan & Yue 2003      |
| Ceramide         | [11]| (2S,3S,5R,7S,9β)-2-[2R]-2-hydroxytetracosanoylamino]-11-octadecene-1,3,4-tetrol    |                          | P. microphylla    | Zhan & Yue 2003      |
| Sesquiterpene    | [12]| 1-O-β-L-β-D-glucopyranosyl-25,35,4R,8R,2-[2R]-2-hydroxydocosanoylamino]-8-octadene-1,3,4-tetrol | | P. microphylla | Zhan & Yue 2003 |}

(continued)
| Classes | No. | Isolated compounds | Synonym | Species | References |
|---------|-----|--------------------|---------|---------|------------|
| Diterpene | [46] | 7α,12-Dihydroxy-8,12-abieta-11,14-diene | Horminone; 7α-hydroxyroyleanone | *P. serratifolia* | Razak et al. 2010; Salae et al. 2012 |
| Diterpene | [47] | Montbretrol | | | Salae et al. 2012 |
| Diterpene | [48] | 5,6,10-Trihydroxy-7-isopropyl-1,4-oxo-trimethyl-2,3,4,4α-tetrahydrophenanthren-9(1H)-one | 14-deoxycoleone; 6-hydroxy-salvinolone | *P. serratifolia* | Salae et al. 2009; Salae et al. 2012 |
| Diterpene | [49] | Taxodion | | | Salae et al. 2012 |
| Diterpene | [50] | 5α,11,12-Trihydroxy-6-oxa-abieta-8,11,13-trien-7-one | | *P. serratifolia* | Salae et al. 2012 |
| Diterpene | [51] | 5α,6,11-Trihydroxy-7,12(20)-epoxy-8,11,13-abietaatriene | | *P. serratifolia* | Salae et al. 2012 |
| Diterpene | [52] | Arucadiol | | *P. serratifolia* | Salae et al. 2012 |
| Diterpene | [53] | 11,12,16-Trihydroxy-2-oxo-5-methyl-10-demethyl-abieta-1[10],6,8,11,13-pentene | | *P. serratifolia* | Habtemariam and Varghese 2015 |
| Diterpene | [54] | 12-Hydroxy-6,7-secoabieta-8,11,13-triene-6,7-dial | | *P. serratifolia* | Salae et al. 2012 |
| Diterpene | [55] | 13-Formyl-11,14-dihydroxy-podocarpa-8,11,13-triene | Premnolal | *P. mollissima* | Rao & Vijayakumar, 1980; Rao et al. 1982 |
| Diterpene | [56] | 6,7-Dihydropremnolal | | *P. mollissima* | Rao & Rao 1978; Rao & Vijayakumar 1980; Rao et al. 1982 |
| Diterpene | [57] | 6,7-Dihydropremnolal | | *P. mollissima* | Rao & Rao 1982 |
| Diterpene | [58] | 1β[3,4]-oxyroyleanone | | *P. serratifolia* | Yadav et al. 2010 |
| Diterpene | [59] | 2α,19-Dihydroxy-royleanone-7,15-diene | | *P. serratifolia* | Yadav et al. 2010 |
| Diterpene | [60] | Isopimara-7,15-dien-1-[1β]-diol | | *P. serratifolia* | Salae et al. 2012 |
| Diterpene | [61] | Sandaracopimar-15-en-8β-ol | | *P. mollissima* | Rao & Rao 1982; Rao & Vijayakumar 1980; Rao et al. 1982 |
| Diterpene | [62] | 11-Ketosandaracopimar-15-en-1β,8β-triol | | *P. mollissima* | Rao & Rao 1978; Rao & Vijayakumar 1980; Rao et al. 1982 |
| Diterpene | [63] | Sandaracopimar-15-en-1β,8β-triol | | *P. mollissima* | Rao & Rao 1982; Rao & Vijayakumar 1980; Rao et al. 1982 |
| Diterpene | [64] | 13-epi-5,15-rosadien-3β,11β-triol | Previously sandaracopimar-15-en-1β,8β-triol | *P. mollissima* | Rao & Rao 1982; Rao & Vijayakumar 1980 |
| Diterpene | [65] | Sandaracopimar-15-en-7α,8β-triol | | *P. mollissima* | Rao & Rao 1978; Rao & Vijayakumar 1980; Rao et al. 1982 |
| Diterpene | [66] | 11,12-Dihydroxy-8,11,13-icetexatrien-1-one | | *P. mollissima* | Rao & Rao 1978; Rao & Vijayakumar 1980 |
| Diterpene | [67] | 1-Ketosandaracopimar-15-en-1β,8β-triol | | *P. mollissima* | Rao & Vijayakumar 1980 |
| Diterpene | [68] | 13-epi-5,15-rosadien-3α,11β-triol | | *P. mollissima* | Salae et al. 2012 |
| Diterpene | [69] | Obulsinone A | | *P. serratifolia* | Salae et al. 2012 |
| Diterpene | [70] | Obulsinone B | | *P. serratifolia* | Salae et al. 2012 |
| Diterpene | [71] | Obulsinone C | | *P. serratifolia* | Salae et al. 2012 |
| Diterpene | [72] | Sirutekkone | Bharangin | *P. herbeae* | Sandhya et al. 1988; Murthy et al. 2006 |
| Diterpene | [73] | 8,11,13-Icetexatriene-10,11,12,16-tetrol | Icetexane-1 | *P. tomentosa* | Hymavathi et al. 2009 |
| Diterpene | [74] | 8,11,13-Icetexatriene-10,11,12,16-tol | Icetexane-2 | *P. tomentosa* | Hymavathi et al. 2009 |
| Diterpene | [75] | 8,11,13-Icetexatriene-7,10,11,16-tol | Icetexane-3 | *P. tomentosa* | Hymavathi et al. 2009 |
| Diterpene | [76] | 7,10-Epoxy-8,11,13-Icetexatriene-11,12,16-triol | Icetexane-4 | *P. tomentosa* | Hymavathi et al. 2009 |
| Diterpene | [77] | 11,12-Dihydroxy-8,11,13-Icetexatrien-1-one | | *P. tomentosa* | Salae et al. 2012 |
| Diterpene | [78] | 11,12-Dihydroxy-8,11,13-Icetexatetraene-1-one | 11,12-dihydroxy-10β,8β,11,13-icetexapentane-1-one | *P. tomentosa* | Razak et al. 2011; Salae et al. 2012 |
| Diterpene | [79] | Salviasperanol | | *P. serratifolia* | Salae et al. 2012 |
| Diterpene | [80] | 5,6-Dihydroxy-6,6-salviasperanand | | *P. serratifolia* | Asik et al. 2010; Salae et al. 2012 |
| Diterpene | [81] | 8,11,13-Icetexatriene-10-hydroxy-11,12,16-triacetoxyl | Icetexatriene-1 | *P. tomentosa* | Ayinampudi et al. 2012 |
| Diterpene | [82] | 8,11,13-Icetexatriene-7,10-11-hydroxy-12,13-dihydoxyfuran | Icetexatriene-2 | *P. tomentosa* | Ayinampudi et al. 2012 |
| Diterpene | [83] | 10β,11-Dihydroxy-12,16-epoxy-9(10→20)-abeo-abieta-8,11,13-tetraene | Lattifolionol | *P. mollissima* | Suresh et al. 2011b |
| Diterpene | [84] | 10β,11-Dihydroxy-12,16-epoxy-9(10→20)-abeo-abieta-8,11,13-triene | Dihydrolattifolionol | *P. mollissima* | Suresh et al. 2011b |

(continued)
| Classes | No | Isolated compounds | Synonym | Species | References |
|---------|----|---------------------|---------|---------|------------|
| Diterpene | 85 | 6β,11-Dihydroxy-(10→7)β epoxy-12,16-epoxy-9(10→20) abeo-abieta-8,11,13-triene | Latiferanol | P. mollissima | Suresh et al. 2011b |
| Diterpene | 86 | Obtusinone D | P. serratifolia | Salae & Boonnak 2013 |
| Diterpene | 87 | Obtusinone E | P. serratifolia | Salae & Boonnak 2013 |
| Diterpene | 88 | Premnalatifolin A | P. mollissima | Suresh et al. 2011a |
| Triterpene | 89 | Lupeol | P. tormentosa; P. hainanensis | Hymavathi et al. 2009; Aynampudi et al. 2012; Dai et al. 2010 |
| Triterpene | 90 | Betulin | P. tormentosa | Hymavathi et al. 2009; Aynampudi et al. 2012 |
| Triterpene | 91 | Lupeol octacosanoate | P. fulva | Wei et al. 1991 |
| Triterpene | 92 | Lupeol nanocosanoate | P. fulva | Wei et al. 1991 |
| Triterpene | 93 | Lupeol melissate | P. fulva | Wei et al. 1991 |
| Triterpene | 94 | Lupeol-Jone | P. fulva | Quan et al. 1999 |
| Triterpene | 95 | Friedelin | 3-friedelanone | Quan et al. 1989; Wei et al. 1990, 1991; Dai et al. 2006, 2010 |
| Triterpene | 96 | Friedelan-3β-ol | Epifriedelanol | Quan et al. 1989; Wei et al. 1990, 1991 |
| Triterpene | 97 | Arjuncolic acid | P. microphylla | Zhan et al. 2009 |
| Triterpene | 98 | Hypstastic acid | P. microphylla | Zhan et al. 2009 |
| Triterpene | 99 | Ursolic acid | P. tormentosa, P. fulva | Chin et al. 2006, Dai et al. 2006 |
| Triterpene glycoside | 100 | Tormentic acid | P. microphylla | Hu et al. 2013 |
| Sterol | 101 | 28-O-α-L-hamnopyranosyl (1→2)-β-o-glucopyranoside tormentic acid ester | P. serratifilia | Wang et al. 2011 |
| Sterol | 102 | 2x,3β,23-trihydroxy-12,20(30)-ursadien-28-oic acid 28-O-β-glucopyranosyl ester | Actinicoside | P. fulva | Niu et al. 2013 |
| Sterol | 103 | β-Ecdysterone | P. serratifilia | Wang et al. 2011 |
| Sterol | 104 | 20S,22-2α-Epoxystigmasterol | P. serratifilia | Wang et al. 2011 |
| Sterol | 105 | Stigmasterol | P. odorata, P. mollissima | Dinda et al. 2010; Lirio et al. 2014 |
| Sterol | 106 | β-Sitosterol | P. odorata; P. mollissima; P. fulva; P. crassa | Rao & Rao 1981; Rao et al. 1981; Quan et al. 1989; Wei et al. 1990, 1991; Dai et al. 2006, 2010; Dinda et al. 2010; Lirio et al. 2014 |
| Sterol glycoside | 107 | β-Sitosterol-3-0-β-D-glucoside | P. mollissima | Rao & Rao 1981; Rao et al. 1981; Ghosh et al. 2014; Otsuka et al. 2008; Otsuka et al. 2009b |
| Sterol glycoside | 108 | (3β)-Stigmast-5-en-3β-ol-β-D-glucopyranoside | β-Daucosterol | P. hainanensis, P. fulva | Dai et al. 2006, 2010 |
| Rhamnopyranoside | 109 | 1-0-trans-p-coumaroyl-α-L-rhamnopyranoside | P. serratifilia | Hang et al. 2008 |
| Rhamnopyranoside | 110 | 2-0-trans-isofeuloyl-farnosopyranose | P. microphylla | Otsuka et al. 1991c |
| Rhamnopyranoside | 111 | 3-0-trans-isoferuloyl-farnosopyranose | P. microphylla | Otsuka et al. 1991c |
| Rhamnopyranoside | 112 | 2-0-trans-p-methoxyximacoylamide-pyrano-28-0-trans-farnosopyranose | P. microphylla | Otsuka et al. 1991c |
| Rhamnopyranoside | 113 | 3-0-trans-p-methoxyximacoylamide-pyrano-28-0-trans-farnosopyranose | P. microphylla | Otsuka et al. 1991c |
| Rhamnopyranoside | 114 | 2-0-trans-p-methoxyximacoylamide-pyrano-28-0-trans-farnosopyranose | P. microphylla | Otsuka et al. 1991c |
| Iridoid glycoside | 115 | 6-O-α-L-(2'-0-cafeoyl) rhamnopyranosyl-catalpol | P. odorata | Otsuka et al. 1989b, 1990b |
| Iridoid glycoside | 116 | 6-O-α-L-(3'-0-caffeoyl) rhamnopyranosyl-catalpol | P. odorata | Otsuka et al. 1989b, 1990b |
| Iridoid glycoside | 117 | 6-O-α-L-(2'-0-isofeuloyl) rhamnopyranosyl-catalpol | P. microphylla | Otsuka et al. 1991c |
| Iridoid glycoside | 118 | 6-O-α-L-(3'-0-isofeuloyl) rhamnopyranosyl-catalpol | P. microphylla | Otsuka et al. 1991c |
| Classes | No. | Isolated compounds | Synonym | Species | References |
|---------|-----|-------------------|---------|---------|------------|
| Iridoid glycoside | [119] | 6-O-α-L-(2''''''''-O-cafeoyl) rhamnopyranosyl catalpol | Premnoside A | P. serratifolia | Otsuka et al., 1993 |
| Iridoid glycoside | [120] | 6-O-α-L-(2''''''''-O-trans-p-coumaroyl) rhamnopyranosyl catalpol | Premnoside B | P. serratifolia | Otsuka et al., 1993 |
| Iridoid glycoside | [121] | 6-O-α-L-(2''''''''-O-cis-p-coumaroyl) rhamnopyranosyl catalpol | Premnoside C | P. serratifolia | Otsuka et al., 1993 |
| Iridoid glycoside | [122] | 6-O-α-L-(2''''''''-dicaffeoyl) rhamnopyranosyl catalpol | Otsuka et al., 1989a,b |
| Iridoid glycoside | [123] | 6-O-α-L-(2''''''''-O-tor 3''''''''-O-''''''''-O-caffeoyl, p-trans-coumaroyl) rhamnopyranosyl catalpol | Otsuka et al., 1989a,b |
| Iridoid glycoside | [124] | 6-O-α-L-(2''''''''-O-tor 3''''''''-O-''''''''-O-caffeoyl, feruloyl) rhamnopyranosyl catalpol | Otsuka et al., 1989a,b |
| Iridoid glycoside | [125] | 6-O-α-L-(2''''''''-O-tor 3''''''''-O-''''''''-O-caffeoyl, p-trans-coumaroyl) rhamnopyranosyl catalpol | Otsuka et al., 1989a,b |
| Iridoid glycoside | [126] | 6-O-α-L-(2''''''''-O-isofeacyl, 4''''''''-acetyl) rhamnopyranosyl catalpol | Otsuka et al., 1990a |
| Iridoid glycoside | [127] | 6-O-α-L-(3''''''''-O-isofeacyl, 4''''''''-acetyl) rhamnopyranosyl catalpol | Otsuka et al., 1990a |
| Iridoid glycoside | [128] | 6-O-α-L-(2''''''''-O-p-coumaroyl) rhamnopyranosyl catalpol | Saccatoside | Otsuka et al., 1990b |
| Iridoid glycoside | [129] | 6-O-α-L-(4''''''''-O-p-coumaroyl) rhamnopyranosyl catalpol | Otsuka et al., 1990b |
| Iridoid glycoside | [130] | 6-O-α-L-(2''''''''-O-methoxycinnamoyl) rhamnopyranosyl catalpol | Otsuka et al., 1991a,b |
| Iridoid glycoside | [131] | 6-O-α-L-(3''''''''-O-methoxycinnamoyl) rhamnopyranosyl catalpol | Otsuka et al., 1991a,b |
| Iridoid glycoside | [132] | 6-O-α-L-(2''''''''-O-methoxycinnamoyl-4''''''''-O-acetyl) rhamnopyranosyl catalpol | Otsuka et al., 1991a,b |
| Iridoid glycoside | [133] | 6-O-α-L-(3''''''''-O-methoxycinnamoyl-4''''''''-O-acetyl) rhamnopyranosyl catalpol | Otsuka et al., 1991a,b |
| Iridoid glycoside | [134] | 6-O-α-L-(2''''''''-O-ferulyl) rhamnopyranosyl catalpol | Otsuka et al., 1991a,b |
| Iridoid glycoside | [135] | 6-O-α-L-(3''''''''-O-ferulyl) rhamnopyranosyl catalpol | Otsuka et al., 1991a,b |
| Iridoid glycoside | [136] | 6-O-α-L-(4''''''''-O-ferulyl) rhamnopyranosyl catalpol | Otsuka et al., 1991a,b |
| Iridoid glycoside | [137] | 6-O-α-L-(2''''''''-O-trans-p-coumaroyl)-α-L-rhamnopyranosyl catalpol | Premnacorymboside A | P. serratifolia | Hang et al., 2008 |
| Iridoid glycoside | [138] | 6-O-α-L-(2''''''''-O-trans-p-coumaroyl)-α-L-rhamnopyranosyl catalpol | Premnacorymboside B | P. serratifolia | Hang et al., 2008 |
| Iridoid glycoside | [139] | 1,8-Diester of muscaenonic acid of 3,7-dimethyloctan-1,8-diol | Premnaodorside A | P. serratifolia | Otsuka et al., 1992 |
| Iridoid glycoside | [140] | 3,7-Dimethyloctan-1,8-diol esterified with one moiety each of muscaenonic acid and 8-epi-loganic acid | Premnaodorside B | P. serratifolia | Otsuka et al., 1992 |
| Iridoid glycoside | [141] | 3,7-Dimethyloctan-1,8-diol esterified with one moiety each of muscaenonic acid and 8-epi-loganic acid | Premnaodorside C | P. serratifolia | Otsuka et al., 1992 |
| Iridoid glycoside | [142] | 1,8-Diester of the 8-epi-loganic acid of 3,7-dimethyloctan-1,8-diol | Premnaodorside D | P. serratifolia | Sudo et al., 1999 |
| Iridoid glycoside | [143] | 1,8-Diester of the 8-epi-loganic acid of 3,7-dimethyloctan-1,8-diol | Premnaodorside E | P. serratifolia | Sudo et al., 1999 |
| Iridoid glycoside | [144] | Mixture of 1-gardoside-8-epi-loganic acid ester of 3,7-dimethyloctan-1,8-diol and 1-epi-loganic acid-8-gardoside ester of 3,7-dimethyloctan-1,8-diol (1:1) | Premnaodorside F | P. serratifolia | Sudo et al., 1999 |
| Iridoid glycoside | [145] | Mixture of 1-gardoside-8-muscaenonic acid of 3,7-dimethyloctan-1,8-diol and 1-muscaenonic acid-8-gardoside ester of 3,7-dimethyloctan-1,8-diol | Premnaodorside G | P. serratifolia | Sudo et al., 1999 |
| Iridoid glycoside | [146] | Bisdesoxythiodyrrohotropein | 7-deoxyloganic acid | P. mollissima | Rao et al., 1981 |
| Iridoid glycoside | [147] | Geniposidic acid | Geniposidic acid | P. mollissima | Rao et al., 1981 |
| Iridoid | [148] | Piscrosin D | Piscrosin D | P. serratifolia | Wang et al., 2011 |
| Iridoid glycoside | [149] | Aucubin | Aucubin | P. serratifolia | Otsuka et al., 1991b |
| Iridoid glycoside | [150] | Premnosidic acid | Premnosidic acid | P. serratifolia | Negi et al., 2004; Yadav et al., 2013 |
| Iridoid glycoside | [151] | 10-O-trans-p-methoxycinnamoyl catalpol | Otsuka et al., 2008; Sudo et al., 1997a,b |
| Iridoid glycoside | [152] | 10-O-cis-p-methoxy cinnamoyl catalpol | Otsuka et al., 1997a,b |
| Iridoid glycoside | [153] | 10-O-cis-p-coumaroyl catalpol | Otsuka et al., 1997a,b |
| Iridoid glycoside | [154] | 10-O-trans-p-coumaroyl catalpol | Otsuka et al., 1997a,b |
| Iridoid glycoside | [155] | 10-O-trans-caffeoyl catalpol | Sudo et al., 1997a,b |
| Iridoid glycoside | [156] | 10-O-trans-isofeacyl catalpol | Sudo et al., 1997a,b |
| Iridoid glycoside | [157] | 10-O-trans-p-methoxycinnamoylaslystasioside E | Sudo et al., 1997a,b |
| Iridoid glycoside | [158] | 10-O-cis-p-methoxy cinnamoylaslystasioside E | Sudo et al., 1997a,b |
| Iridoid glycoside | [159] | 10-O-trans-p-coumaroyslystasioside E | Sudo et al., 1997a,b |
| Iridoid glycoside | [160] | 10-O-cis-p-coumaroyslystasioside E | Sudo et al., 1997a,b |
| Iridoid glycoside | [161] | 10-O-trans-p-coumaroyl-6-O-α-L-rhamnopyranosyl catalpol | P. serratifolia | Yadav et al., 2013 |
| Classes               | No     | Isolated compounds                                                                 | Synonym          | Species          | References                  |
|----------------------|--------|-------------------------------------------------------------------------------------|------------------|------------------|-----------------------------|
| Iridoid glycoside    | [162]  | Scutellarioside II                                                                   | P. serratifolia; | Sudo et al. 1997b;      |
| Iridoid glucoside    | [163]  | 4'-Methoxy-E-glubaranin                                                             | P. subscandens;  | Hang et al. 2008    |
| Iridoid glucoside    | [164]  | 4'-Methoxy-Z-glubaranin                                                             | P. subscandens;  | Sudo et al. 1998    |
| Iridoid glucoside    | [165]  | 4'-Hydroxy-E-glubaranin                                                             | P. subscandens;  | Sudo et al. 1998;  Yadv |
| Iridoid glucoside    | [166]  | 4'-Methoxy-E-glubaranin                                                             | P. subscandens;  | Sudo et al. 1998    |
| Iridoid glucoside    | [167]  | 4'-Methoxy-Z-glubaranin                                                             | P. subscandens;  | Sudo et al. 2000    |
| Iridoid glucoside    | [168]  | 4,4-Dimethoxy-b-truxinic acid catalpd diester                                       | P. subscandens;  | Sudo et al. 2000    |
| Iridoid glucoside    | [169]  | {1-0-(3,4-dihydrophenethoxy)-3-O-α-L-6-deoxy-mannopyanosyl-4-O-[E-3-(3,4-dihydrophenyl)-prop-2-enoyl]-β-D-glucopyran-6-yl/octox-1,4,5,6,7,7-α-hexahydro-6-hydroxy-1-{β-D-glucopyranosyl}-6-methylidenecyclopenta[c]pyran-4-carboxylate} | Premfulvaoside | Otsuka et al. 1991b, 1992, Otsuka et al. 1993, 1993, Sudo et al. 1997a, Hang et al. 2008, Bose et al. 2013 |
| Phenethyl alcohol glycoside | [170]  | Cistanoside F                                                                       | P. odorata; Otsuka et al. 1991b, 1992, 1993, Sudo et al. 1997a, Hang et al. 2008, Bose et al. 2013 |
| Phenethyl alcohol glycoside | [171]  | Benzyl alcohol β-D-(2'-O-β-D-xylopyranosyl)glucopyranoside                           | P. subscandens;  | Sudo et al. 2000    |
| Phenethyl alcohol glycoside | [172]  | Phenethyl alcohol β-D-(2'-O-β-D-xylopyranosyl)glucopyranoside                       | P. subscandens;  | Sudo et al. 2000    |
| Phenethyl alcohol glycoside | [173]  | Acteoside Verbacoside                                                               | P. serratifolia; | Otsuka et al. 1991b, 1992, Otsuka et al. 1993, 1993, Sudo et al. 1997a, Hang et al. 2008, Bose et al. 2013 |
| Verbacoside iridoid glucoside | [174]  | Premcryoside                                                                        | P. serratifolia; | Otsuka et al. 1991b, 1992, Otsuka et al. 1993, 1993, Sudo et al. 1997a, Hang et al. 2008, Bose et al. 2013 |
| Phenethyl alcohol glycoside | [175]  | Isoacteoside                                                                        | P. serratifolia; | Otsuka et al. 1991b, 1992, Otsuka et al. 1993, 1993, Sudo et al. 1997a, Hang et al. 2008, Bose et al. 2013 |
| Phenethyl alcohol glycoside | [176]  | Martynoside                                                                          | P. serratifolia; | Otsuka et al. 1991b, 1992, Otsuka et al. 1993, 1993, Sudo et al. 1997a, Hang et al. 2008, Bose et al. 2013 |
| Martynoside glucoside | [177]  | 3-Hydroxy-4-methoxyphenethyl alcohol β-D-[3'-O-α-L-6-deoxy-mannopyanosyl-4'-O-[E-3-(3,4-dihydrophenyl)-prop-2-enoyl]-β-D-glucopyran-6-yl/octox-1,4,5,6,7,7-α-hexahydro-6-hydroxy-1-{β-D-glucopyranosyl}-6-methylidenecyclopenta[c]pyran-4-carboxylate} | Premafolioside | Otsuka et al. 1991b, 1992, Otsuka et al. 1993, 1993, Sudo et al. 1997a, Hang et al. 2008, Bose et al. 2013 |
| Phenethyl alcohol glycoside | [178]  | Decaffeoylverbascoside                                                               | P. subscandens;  | Sudo et al. 1997a    |
| Phenylethanoid        | [179]  | Premethanoside A                                                                    | P. subscandens;  | Sudo et al. 1997a    |
| Phenylethanoid        | [180]  | Premethanoside B                                                                    | P. subscandens;  | Sudo et al. 1997a    |
| Phenolic acid         | [181]  | p-Hydroxybenzoic acid                                                                | P. fulva; P. hainanensis | Chen et al. 2010, Dai et al. 2007, 2010, Wei et al. 1991; Dai et al. 2007; Chen et al. 2010 |
| Phenolic acid         | [182]  | Vanillic acid                                                                        | P. fulva         | Dai et al. 2007, 2010, Wei et al. 1991; Dai et al. 2007; Chen et al. 2010 |
| Aldehyde              | [183]  | 4-Hydroxybenzaldehyde                                                                | P. serratifolia; | Hang et al. 2008    |
| Aldehyde              | [184]  | 4-Hydroxy-2-methoxybenzaldehyde                                                     | P. serratifolia; | Hang et al. 2008    |
| Aldehyde              | [185]  | Syringaldehyde                                                                      | P. tomentosa; Hymavathi et al. 2009, Aynampudi et al. 2012 |
| Aldehyde              | [186]  | Acetoxy syringaldehyde                                                               | P. tomentosa; Aynampudi et al. 2012 |
| Aldehyde              | [187]  | Premalalin                                                                          | P. tomentosa; Aynampudi et al. 2013 |
| Aldehyde              | [188]  | Coniferaldehyde                                                                     | P. tomentosa; Hymavathi et al. 2009, Aynampudi et al. 2012 |
| Aldehyde              | [189]  | 2-(4-Methoxyphenyl)-2-butanone                                                      | P. tomentosa; Hymavathi et al. 2009, Aynampudi et al. 2012 |
| Phenolic glucoside    | [190]  | Leonuriside A                                                                       | P. serratifolia; | Hang et al. 2008    |
| Alkaloid (indole)     | [191]  | Indole-3-carboxylic acid                                                             | P. microphylla; Hu et al. 2013 |
| Alkaloid              | [192]  | Premine                                                                             | P. serratifolia; | Basu & Dandiya 1947 |

(continued)
| Classes     | No  | Isolated compounds                                                                 | Synonym       | Species          | References               |
|------------|-----|-------------------------------------------------------------------------------------|---------------|------------------|--------------------------|
| Alkaloid   | [193] | Ganiarine                                                                           |               | P. serratifolia² | Basu & Dandiya 1947     |
| Alkaloid   | [194] | Aphelandrine                                                                         |               | P. serratifolia³ | Dasgupta et al. 1984    |
| Lignan     | [195] | (-)-Lyoniresinol-2α-O-[β-D-glucopyranoside                                           |               | P. serratifolia² | Yuasa et al. 1993      |
| Lignan     | [196] | (4S)-4-Hydroxy-3-methoxyphenyl-2-[2-[2-formyl-(E)-vinyl]-2-methoxyphenoxy]-propan-1,3-diol |               | P. serratifolia² | Yuasa et al. 1993      |
| Lignan     | [197] | (4R)-4-Hydroxy-3-methoxyphenyl-2-[2-[2-carbonyl-(E)-vinyl]-2-methoxyphenoxy]-propana-1,3-diol |               | P. serratifolia² | Yuasa et al. 1993      |
| Lignan     | [198] | Seco-isolariciresinol                                                                |               | P. recinosa      | Habtemariam et al. 1995 |
| Lignan     | [199] | Pluchezoside D₃                                                                     |               | P. serratifolia⁴ | Yuasa et al. 1993      |
| Lignan     | [200] | (+)-Lariciresinol                                                                    |               | P. recinosa      | Habtemariam et al. 1995 |
| Lignan     | [201] | (-)-Olivill                                                                         |               | P. serratifolia⁴ | Yuasa et al. 1993      |
| Lignan     | [202] | Premnalatin                                                                          |               | P. mollissima²   | Rao & Rao 1991          |
| Lignan     | [203] | Syringaresinol                                                                       |               | P. fulva         | Dai et al. 2007; Chen et al. 2010 |
| Lignan     | [204] | (+)-1-Hydroxypinoresinol                                                             |               | P. recinosa      | Habtemariam et al. 1995 |
| Lignan     | [205] | (+)-Medioresinol                                                                     |               | P. microphylla⁶  | Hu et al. 2013          |
| Lignan     | [206] | 4-Oxopiresinol                                                                       |               | P. microphylla⁶  | Hu et al. 2013          |
| Lignan     | [207] | 4'-Hydroxy-8,3'-dimethoxy-6-acroleinylflavan-3,4-diol                                |               | P. serratifolia² | Yuasa et al. 1993      |
| Lignan     | [208] | 4'-Hydroxy-8,3'-dimethoxy-6-acroleinylflavan-3,4-diol                                |               | P. serratifolia² | Yadav et al. 2013      |
| Xanthone   | [210] | 1-Hydroxy-2,3-methylenedioxy-6-methoxybenzyl-7-acetylthanol                          |               | P. microphylla⁶  | Wang & Xu 2003          |
| Xanthone   | [211] | 3,5-Dihydroxy-2-methoxy-6-methoxybenzyl-7-acetylthanol                               |               | P. microphylla⁶  | Wang & Xu 2003          |
| Flavonoid  | [212] | 4'-Hydroxy-6,3'-dimethoxy-6-acroleinylflavan-3,4-diol                               |               | P. fulva         | Chen et al. 2010        |
| Flavonoid  | [213] | Naringenin                                                                           |               | P. fulva, P. recinosa | Habtemariam et al. 1992; Dai et al. 2007; Chen et al. 2010 |
| Flavonoid  | [214] | Eriodictyol                                                                          |               | P. recinosa      | Habtemariam et al. 1992 |
| Flavonoid  | [215] | Pinocembrin                                                                          |               | P. yunnanensis   | Yu et al. 2012          |
| Flavonoid  | [216] | Pinostrobin                                                                          |               | P. yunnanensis   | Yu et al. 2012          |
| Flavonoid  | [217] | 7-Hydroxy-flavanone                                                                  |               | P. yunnanensis   | Yu et al. 2012          |
| Flavonoid  | [218] | Apigenin                                                                             |               | P. fulva, P. pyramidal | Dai et al. 2007; Chen et al. 2010; Monprasart et al. 2011 |
| Flavonoid  | [219] | 5,7-Dihydroxy-4'-methoxy-flavone                                                    | Acacetin      | P. odorata, P. szemaoensis | Li et al. 2008; Pinzon et al. 2011 |
| Flavonoid  | [220] | Luteolin                                                                             |               | P. serratifolia², P. schimperi, P. recinosa | Habtemariam et al. 1992; Dasgupata et al. 1984 |
| Flavonoid  | [221] | 5,7,3'-Trihydroxy-4'-methoxyflavone                                                  | Diosmetin     | P. odorata; P. serratifolia | Pinzon et al. 2011; Wang et al. 2011; Hu et al. 2013; Lirio et al. 2014 |
| Flavonoid  | [222] | Selagin                                                                              |               | P. pyramidaldata | Monprasart et al. 2011 |
| Flavonoid  | [223] | 5-Hydroxy-3',4',6,7-tetramethoxyflavone                                              |               | P. pyramidaldata | Monprasart et al. 2011 |
| Flavonoid  | [224] | Quercetin                                                                            |               | P. schimperi, P. recinosa, P. serratifolia | Habtemariam et al. 1992; Wang et al. 2011 |
| Flavonoid  | [225] | Kaempferide                                                                          |               | P. schimperi     | Habtemariam et al. 1992 |
| Flavonoid  | [226] | Myricetin-3',4,7-trimethyl ether                                                     |               | P. tormentosa    | Balakrishna et al. 2003 |
| Flavonoid  | [227] | 3-Methoxy-galangin                                                                  |               | P. yunnanensis   | Yu et al. 2012          |
| Classes               | No     | Isolated compounds                                      | Synonym                                    | Species                  | References       |
|-----------------------|--------|---------------------------------------------------------|--------------------------------------------|--------------------------|------------------|
| Flavonoid             | [228]  | 3,7-Dimethoxy-galangin                                   | P. yunnanensis                            | Yu et al. 2012           |                  |
| Flavonoid             | [229]  | 5,4'-Dihydroxy-7-methoxyflavon                           | P. szemaoensis                            | Li et al. 2008           |                  |
| Flavonoid             | [230]  | 3',4',5'-Trihydroxy-3,7-dimethoxyflavone                 | P. szemaoensis                            | Li et al. 2008           |                  |
| Flavonoid             | [231]  | 5,3'-Dihydroxy-7,4'-dimethoxyflavon                      | P. szemaoensis                            | Li et al. 2008           |                  |
| Flavonoid             | [232]  | 5,4'-Dihydroxy-3,7,3'-trimethoxyflavone                  | P. szemaoensis                            | Li et al. 2008           |                  |
| Flavonoid             | [233]  | 5-Hydroxy-7,4',5'-trimethoxyflavone                      | P. szemaoensis                            | Li et al. 2008           |                  |
| Flavonoid             | [234]  | Pachypodol Trimethyl ether of quercetin                  | P. recinosa                               | Habtemarim et al. 1992   |                  |
| Flavonoid glycoside   | [235]  | Chrysosplenol-D                                         | P. recinosa                               | Habtemarim et al. 1992   |                  |
| Flavonoid glycoside   | [236]  | 3,5,7,5'-Tetrahydroxy-6,3',4'-trimethoxyflavone          | P. oligotricha                            | Habtemarim et al. 1992   |                  |
| Flavonoid glycoside   | [237]  | 3,5,5'-Trihydroxy-6,7,3',4'-tetramethoxyflavone          | P. oligotricha                            | Habtemarim et al. 1992   |                  |
| Flavonoid glycoside   | [238]  | Kaempferol-3-O-β-D-galactopyranoside                     | P. serratifolia                           | Wang et al. 2011          |                  |
| Flavonoid glycoside   | [239]  | Quercetin 3-O-β-D-xlopyranoside                          | P. serratifolia                           | Yu et al. 2012            |                  |
| Flavonoid glycoside   | [240]  | Genkwan-5-O-β-D-glucopyranin                             | P. serratifolia                           | Wang et al. 2011          |                  |
| Flavonoid glycoside   | [241]  | Vitexin                                                  | P. fulva                                  | Dai et al. 2007; Chen et al. 2010; |                  |
| Flavonoid glycoside   | [242]  | Apigenin 7-O-β-D-glucopyranoside-4'-acetate              | P. mollissima                             | Ghosh et al. 2014         |                  |
| Flavonoid glycoside   | [243]  | Apigenin 7-O-β-D-apiofuranosyl (1→2)-x-L-rhamnopyranoside| P. mollissima                             | Ghosh et al. 2014         |                  |
| Flavonoid glycoside   | [244]  | 6-C-β-D-glucopyranosyl-8-C-β-D-xlopyranosyl apigenin     | Vicenin-3                                 | Jyotsna et al. 1984       |                  |
| Flavonoid glycoside   | [245]  | Quercetin 3-rutinoside                                   | P. serratifolia                           | Hang et al. 2008          |                  |
| Flavonoid glycoside   | [246]  | 5-Hydroxy-4-methoxy-flavone-7-O-bioside                  | P. mollissima                             | Rao & Rao 1981            |                  |
| Flavonoid glycoside   | [247]  | 5-Hydroxy-4-methoxy-flavone-7-O-trioside                 | P. mollissima                             | Rao & Rao 1981            |                  |
| Flavonoid glycoside   | [248]  | 6,3'-Dihydroxy-7-methoxy-4',5'-methylene dihydroisoflavone| P. microphylla                            | Zhong & Wang 2002         |                  |
| Flavonoid glycoside   | [249]  | 6,3'-Dihydroxy-7-methoxy-4',5'-methylene dihydroisoflavone-6-O-β-D-glucopyranoside | P. microphylla | Zhong & Wang 2002 |                  |
| Flavonoid glycoside   | [250]  | 6,3'-Dihydroxy-7-methoxy-4',5'-methylene dihydroisoflavone-6-O-β-L-rhamnopyranoside | P. microphylla | Zhong & Wang 2002 |                  |
| Flavonoid glycoside   | [251]  | 6,3'-Dihydroxy-7-methoxy-4',5'-methylene dihydroisoflavone-6-O-β-L-rhamnopyranoside | P. microphylla | Zhong & Wang 2002 |                  |
| Chalcone              | [252]  | 2,4'-Dimethoxy chalcone                                  | P. yunnanensis                            | Yu et al. 2012            |                  |
| Chalcone              | [253]  | Isoliquiritigenin                                        | P. yunnanensis                            | Yu et al. 2012            |                  |
| Chalcone              | [254]  | 2-Methoxy isoliquiritigenin                              | P. yunnanensis                            | Yu et al. 2012            |                  |
| Chalcone              | [255]  | Cardamonin                                               | P. yunnanensis                            | Yu et al. 2012            |                  |

1. P. serratifolia L.
2. P. serratifolia L. (syn P. integrifolia Willd.).
3. P. serratifolia L. (syn P. obtusifolia R.Br.).
4. P. serratifolia L. (syn P. corymbosa var obtusifolia (R.Br.) H.R.Fletcher).
5. P. mollissima Roth. (syn P. latifolia Roxb.).
6. P. microphylla Turcz.
7. P. microphylla Turcz (syn P. japonica Miq.).
8. P. mollissima Turcz (syn P. latifolia var. cuneate C.B.Clarke).

Aicetexane.
**5** Aicetexane.
**6** Aicetexane.
**7** Aicetexane.
**8** Aicetexane.
Quinone methane.
Clerodane.
Labdane.
Abietane.
Nor-abietane.
Secoabietane.
Podocondane.
Pimarane.
Sandaracopimarane.
Rosane.
Figure 1. Chemical structures of some diterpenoids obtained from Premna species.
Sterols and triterpenes

Three skeleton type of pentacyclic triterpenes have been reported from the genus Premna, i.e. lupane, oleane and ursane. Three lupane-type sterols [89, 90, 94] have been identified in P. fulva (Quan et al. 1989), P. hainanensis (Dai et al. 2010) and P. tomentosa (Hymavathy et al. 2009; Ayinampudi et al. 2012) while three derivatives of lupeol [91–93] have been isolated from P. fulva (Wei et al. 1991). Further studies also reported the presence of four oleane-type triterpenes [95–98] which were distributed in P. crassa, P. fulva, P. hainanensis and P. microphylla (Wei et al. 1990, 1991; Dai et al. 2006, 2010; Zhan et al. 2009). Additionally, four ursane-type triterpenes [99–102] were identified in P. fulva (Dai et al. 2006; Niu et al. 2013), P. microphylla (Hu et al. 2013) and P. tomentosa (Chin et al. 2006). Common plant sterols, such as stigmasterol [105], and their glycosides [106,107], are widely distributed among P. crassa, P. fulva, P. hainanensis, P. latifolia and P. odorata (Rao et al. 1981; Rao & Rao 1981; Wei et al. 1991; Ghosh et al. 2013; Lirio et al. 2014). Two cholestanes [103–104] were isolated from P. serratifolia (Wang et al. 2011), and stigmastene-glycoside [108] was identified in P. fulva (Dai et al. 2006) and P. hainanensis (Dai et al. 2010).

Iridoid and iridoid glycosides

Iridoids are monopentene lactones which usually occur in plants as glycosides and sometimes are known as monopentene alkaloids. They can be found in dicotyledone angiosperms within the superorders Corniflorae, Gentianiflorae, Lamiflorae and Loasiflorae (Ghisalberti 1998). Their structures are based on cyclopentan[c]pyran skeleton represented as iridine (cis-2-oxabi-cyclo[4.3.0]nonane) and seems to be biosynthesized via alternative cyclization of geranyl diphosphate (Sampaio-Santos & Kaplan 2001). The name ‘iridoid’ itself comes from iridodial and related compounds isolated from the defense secretion of Iridomyrmex species (Tietze 1983). 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. Our current review has identified more than 53 iridoid glycosides within nine species of Premna (Table 2). Most of the isolated iridoids are catalpol derivatives [115–138, 148–168] although mussiaenosidic acid, epiloganic acid and gardoside derivatives [139–147, 169] also could be identified in quite a great number. Majority of the iridoids are linked to their glycosides at C-1 though in catalpol, the glycoside could have linked to C-6. Interesting structure was displayed by compound 168, with two catalpol glycosides formed an ester to truxinic acid. Piscrosin D [148] was the only non-glycoside iridoid isolated from P. japonica (Otsuka et al. 1991b) and P. serratifolia (Wang et al. 2011), respectively. Figure 2 shows the structures of some of the iridoid and iridoid glycosides.

Phenylethanoids, aldehydes, alkaloids and lignans

Phenylethanoid glycosides (PhGs) are natural products which are structurally a glycosidic ester consisting of cinnamic acid and hydroxyl phenethyl moieties attached to glycoside residue. Their structure may consist of monosaccharide, disaccharides, or trisaccharides, with the common glycosides being glucose, rhamnose, xylose, and apiose. They are found in many of the family Lamiaceae where acteoside or verbascoside [173] is common (Jiménez & Riguer 1994). Cistanoside F [170] and other ten PhGs [171–180] were isolated from the genus Premna (details in Table 2), of which 174 contains a iridoid moiety attached to its glucose. Phenolic acids [181, 182] were reported in P. fulva and P. hainanensis (Wei et al. 1991; Dai et al. 2007, 2010; Chen et al. 2010) and several aldehydes [183–190] were isolated from P. integrifolia (Hang et al. 2008) and P. tomentosa (Hymavathy et al. 2009; Ayinampudi et al. 2012). One indole carboxylic acid [191] was also isolated from P. microphylla (Hu et al. 2013). Some alkaloids [192–194] were only identified in P. integrifolia (Basu & Dandiya 1947; Dasgupta et al. 1984). Lignans, a phenylpropa-noid derivatives, were identified within six species of Premna and commonly found as furan lignans [199–202] (Rao & Rao 1981; Yuasa et al. 1993; Habtemariam et al. 1995) and furufuran lignans [203–209] (Yuasa et al. 1993; Habtemariam et al. 1995; Dai et al. 2007; Chen et al. 2010; Hu et al. 2013; Yadav et al. 2013) in the genus Premna except for compounds 195–198 which are dibenzylbutane lignans (Yuasa et al. 1993; Habtemariam et al. 1995) (Table 2).

Flavonoids, xanthones and chalcones

The occurrence of these flavonoids was reported from 13 species (Table 2). Most of the flavonoids were flavonols [224–239] and flavones [218–223, 240–247], although quite a number were flavonones [213–217], isoflavones [248–251] and one flavan-3-ol [212] (Dasgupta et al. 1984; Habtemariam et al. 1992; Balakrishna et al. 2003; Dai et al. 2007; Li et al. 2008; Chen et al. 2010; Monprasart et al. 2011; Pinzon et al. 2011; Wang et al. 2011; Yu et al. 2012; Hu et al. 2013; Lirio et al. 2014). A few flavonoid glycosides were also reported, identified as O-glycoside to either C-3 [238, 239], C-5, C-6 [240], C-6 [249–251], or C-7 [242, 243, 246, 247]; while two others [241, 244] attached to the glycoside residue through C-linkages at C-6 and/or C-8 (Rao & Rao 1981; Iyotsna et al. 1984; Zhong & Wang 2002; Dai et al. 2006).
2007; Hang et al. 2008; Chen et al. 2010; Wang et al. 2011; Yu et al. 2012; Ghosh et al. 2014). In addition, two xanthones \[210, 211\] were isolated from *P. microphylla* (Wang & Xu 2003) and four chalcones \[252–255\] were reported in *P. yunnanensis* W.W.Sm. (Yu et al. 2012). The structures of some of the flavonoids are shown in Figure 3. The skeleton structure resemblance of the flavonoids \((C_6-C_3-C_6)\), xanthones \((C_6-C_1-C_6)\) and chalcones \((C_6-C_3-C_6, \text{without a heterocyclic C-ring in the three-carbon} \alpha\beta\text{-unsaturated carbonyl system})\) suggested they shared a similar shikimate pathway via phenylpropanoid pathway in their biosynthesis whereas xanthones, in particular, might represent the modified shorthened forms of the \(C_6-C_3\) system (Dewick

![Figure 2. Chemical structures of some of the iridoids and iridoid glycosides.](image-url)
Figure 3. Chemical structures of some flavonoids and flavonoid glycosides found in *Premna* species.
R. DIANITA & I. JANTAN

Antimicrobial, insecticidal, antileishmanial and antimalarial activities

Many studies have been carried out to evaluate the antibacterial and antifungal activities of extracts of *Premna* species ([Table 3](#)). Several studies have identified active antimicrobial compounds, mostly found as diterpenes [27, 29, 30, 48, 51, 55, 69, 70, 72, 78, 79, 80] (Habtemariam et al. 1990, 1991; Murthy et al. 2006; Salae et al. 2012) and few sesquiterpenes [13, 25] (Habtemariam et al. 1993; Salae et al. 2012). Earlier, Kurup and Kurup (1964) has successfully isolated orange crystal substance from the alcoholic extract of the root bark of *P. integrifolia* that was active against *Micrococcus aureus*, *Bacillus subtilis* and *Streptococcus haemolyticus* (MIC 0-25 μg/mL) but inactive towards *Escherichia coli*, *Salmonella typhosa* and *B. dysentriae*.

Compound 48 (Salae et al. 2012) appeared to have potent antibacterial activity with most of their MICs were <5 μg/mL, except for *P. aeruginosa*. Interesting broad spectrum antibacterial and antifungal activities were also showed by compound 72 (MIC 5-10 μg/mL), isolated from the roots of *P. herbacea* (Murthy et al. 2006). Another study by Lirio et al. (2014) evaluated antitubercular activity against *Mycobacterium tuberculosis* of the leaves of *P. odorata* and its constituents. Although the extract showed relatively weak inhibitory activity, the fractions exhibited strong activity which eventually led to isolation of the active compound 4 (MIC<sub>90</sub> 8 μg/mL whilst rifampin 0.05 μg/mL and isoniazid 0.23 μg/mL).

The insecticidal activity of different extracts and essential oil of *P. latifolia* was tested against *Spodoptera littura* larvae, a polyphagous crop pest, by using leaf-dip method. The essential oil showed the highest growth reduction (56.83%) followed by chloroform, hexane and butanol fractions (43.93, 26.01 and 23.69%, respectively) (Kumar et al. 2011). Recent study on *P. angolensis* and *P. quadrifolia* evaluated the insecticidal and repellent effects of its essential oils against *Sitoroga cerulea*, an insect pest of rice stocks, using olfactometer and contact toxicity test (Adjalian et al. 2015). The results showed that both essential oils have insecticidal and repellent activities as indicated by rate of death of *S. cerulea*, percentage of repulsion, number of rice attacked and loss of weight of rice. The leaf extract of *P. serratifolia* showed strong activity against *Leishmania donovani* (IC<sub>50</sub> 4.4 μg/mL) but showed weak and/or no effect against *Trypanosoma brucei brucei*, *Trichomonas vaginalis* and *Caenorhabditis elegans* (Desrivost et al. 2007). It has been reported previously that clerodane diterpenes [28 and 29], isolated from *P. oligoritica* and *P. schimperi*, showed potent antileishmanial effects towards axenically cultured amastigotes of *L. aethiopica* (IC<sub>50</sub> 1.08 and 4.12 μg/mL, respectively). Both compounds also exhibited high selectivity towards *L. amastigota* than the permissive host cell line, THP-1 cells or the promastigotes stage of the parasites (Habtemariam 2003).

Although widely used traditionally in malarial treatment by the Philippines, the ethanol extract of *P. angolensis* barks only showed weak antiplasmodial activity (IC<sub>50</sub> 180–500 μg/mL) towards both chloroquine sensitive and resistant strains of *Plasmodium falciparum* (do Céu de Madureira et al. 2002). However, the leaf extract of *P. chrysocladia* revealed high activity against chloroquine sensitive and resistant strains of *P. falciparum* (IC<sub>50</sub> 7.75 and 9.02 μg/mL) while the root extract only showed moderate activity (IC<sub>50</sub> 27.63 and 52.35 μg/mL). Further investigation also revealed that the leaf extract (dose 250 mg/mL) has strong ability to reduce the parasitized erythrocyte (9.26% parasitaemia) and to inhibit the parasite growth (65.08% chemo suppression) in *Plasmodium berghei* infected mice (Gathirwa et al. 2011).

Antioxidant, anti-inflammatory and immunomodulatory activities

*Premna* species are known to have high-antioxidant capacity, such as *P. cordifolia* Roxb. (Mustafa et al. 2010; Mohd Nazri et al. 2011), *P. esculenta* Roxb. (Mahmud et al. 2011), *P. integrifolia* (Gokani et al. 2011; Nguyen & Eun 2011), *P. microphylla* (Xu et al. 2010) and *P. serratifolia* (Rajagopal et al. 2014) ([Table 3](#)). The wide distribution of flavonoids and phenolics within this genus seems to contribute to this activity. Various methods were used to measure the antioxidant capacities such as radical scavenging (diphenylpicrylhydrazyl (DPPH), superoxide, nitric oxide, hydroxyl radicals), ferric reducing ability of plasma (FRAP), ferric thiocyanate (FTC), lipid peroxidation, erythrocyte membrane stabilizing and β-carotene bleaching assays. Most of the radical scavenging capacity of the extracts has been correlated to their phenolic contents – the higher the phenolic content, the higher the antioxidant capacity. The presence of hydroxyl group (OH) and/or unsaturated bond are suggested to play the main role in capturing the radical oxygen species (ROS).

Secondary metabolites such as flavonoids, xanthones, chalcone and other phenolic compounds with high-hydroxyl group substitution are hypothetically contributing to the high antioxidant activity of the plant. For example, two flavone glycosides [213, 214] from *P. latifolia* leaves significantly inhibited oxidation of DPPH (IC<sub>50</sub> 22.5 and 16.0 μg/mL, respectively) (Ghosh et al. 2014). Furofuran lignans [208, 209] and iridoid glycosides [150, 154, 161, 165] might contribute to antioxidant activity of the stem bark of *P. integrifolia* when evaluated with radical scavenging (DPPH and NO) and ferric reducing antioxidant power (FRAP) assays (Yadav et al. 2013). Compounds 165 and 154 possessed maximum radical scavenging activity (IC<sub>50</sub> 0.29 and 0.37 μM) in DPPH assay, followed by compound 209; while compounds 150 and 161 exhibited maximum reducing power in FRAP assay. Aldehyde derivatives [186 and 187] and icetexane diterpenes [81, 82] were thought to be potential free radical scavenger constituents from *P. tomentosa* (Ayinampudi et al. 2012; Ayinampudi 2013). The higher number of hydroxyl group in compound 82 (IC<sub>50</sub> 7.01 μg/mL) than compound 81 (IC<sub>50</sub> 24.80 μg/mL) reflected the higher antioxidant capacity of the former. Interestingly, this rule was not applied for compound 187 (IC<sub>50</sub> 20.58 μg/mL) which has three hydroxyl moieties, in comparison to compound 186 (IC<sub>50</sub> 20.83 μg/mL) which only has one hydroxyl moiety. Potential antioxidant activities were also exhibited by a series of icetexanes [73-76] from *P. tomentosa* towards DPPH, NO and superoxide scavenging assays, of which compound 76 demonstrated superior activities than the others and also on par with the standards (Naidu et al. 2014). Recent study also identified an aromatic diterpene [53] as antioxidant constituent from *P. serratifolia* with IC<sub>50</sub> of 20.4 ± 1.3 μM towards DPPH assay (Habtemariam & Varghese 2015).

It is note worthy that although those studies showed some potential antioxidant capacities of some extracts of *Premna* species and its constituents, they do not necessarily reflect the molecular or *in vivo* activities. For example, the DPPH and...
Table 3. Antimicrobial and anti-inflammatory effects of the extracts of Premna species.

| Species (ref.)          | Part of plant | Pharmacological effect | Concentration/dose | Methods, findings |
|-------------------------|---------------|------------------------|--------------------|-------------------|
| *P. barbata* (Tamta et al. 2012) | Leaves       | Antimicrobial          | 33 mg/200 µL       | Agar disc diff.   |
|                         |               |                        |                    | Finding: EtOH extract showed weak to moderate activity towards *A. tumefaciens*, *Xanthomonas phaseoli*, *B. subtilis* & *E. coli* but not against *B. pseudomallei*. |
| *P. cordifolia* (Mohd Nazri et al. 2011) | Leaves       | Antimicrobial          | 10 mg/mL           | Agar disc diff.   |
|                         |               |                        |                    | Finding: EtOH extract showed weak zone inhibition (6 cm) against *E. coli*, *S. aureus*, *P. aeruginosa*, *K. pneumonia* and *B. subtilis*. |
| *P. integrifolia* (Kurup & Kurup 1964) | Root bark    | Antimicrobial          | 300 µg/disc        | Not detailed      |
|                         |               |                        |                    | Finding: Ether fraction of the alcoholic extract was showing antibacterial activity against *M. luteus*, *P. aeruginosa*, *E. coli*, *K. pneumonia* and *B. subtilis*. |
| *P. integrifolia* (Rahman et al. 2011) | Leaves       | Antimicrobial          | 1500 µg/disc       | Agar disc diff.   |
|                         |               |                        |                    | Finding: EtOH extract exhibited zone inhibition (8-10 mm) against *P. aeruginosa*, *B. subtilis*, *E. coli*, *S. aureus* and *K. pneumonia*. |
| *P. latifolia* (Jeevan Ram et al. 2004) | Leaves       | Antimicrobial          | 1500 µg/disc       | Agar disc diff.   |
|                         |               |                        |                    | Finding: EtOH extract showed zone inhibition (8-10 mm) against *P. aeruginosa*, *S. aureus*, *B. subtilis* and *C. albicans*. |
| *P. microphylla* (Xu et al. 2010) | Leaves; stem | Antimicrobial          | 100 mg/mL          | Agar disc diff.   |
|                         |               |                        |                    | Finding: MeOH extract of the leaves showed antibacterial activity against *S. aureus*, *B. subtilis*, *C. albicans*, *P. aeruginosa*, *K. pneumonia* and *E. coli*. |
| *P. serratifolia* (Rajendran & Basha 2010) | Root         | Antimicrobial          | 133 mg/mL          | Agar disk diff.   |
|                         |               |                        |                    | Finding: Various extracts (hexane, CHCl₃, EtOAc, EtOH and aqueous) showed antinociceptive activities towards bacteria (*S. aureus*, *K. pneumonia*, *P. aeruginosa*, *E. coli*, *S. typhi*, *S. paratyphi A*, *B. subtilis*, *S. typhi*, *M. luteus*, *M. roseus* and *C. albicans*). |
| *P. serratifolia* (Rajendran 2010) | Bark; wood   | Antimicrobial          | 200 µg/disc        | Agar disk diff.   |
|                         |               |                        |                    | Finding: Various extracts (hexane, CHCl₃, EtOAc, EtOH and aqueous) showed high potency of antimicrobial at against bacteria (*S. aureus*, *K. pneumonia*, *P. aeruginosa*, *E. coli*, *S. typhi*, *S. paratyphi A*, *B. subtilis*, *S. typhi*, *M. luteus*, *M. roseus* and *C. albicans*). |
| *P. corymbosa* (Karthikeyan & Deepa 2011) | EtOH ext.; leaves | Anti-inflammatory     | 200 & 400 mg/kg    | Egg albumin-induced paw edema (acute inflammation model) and cotton pellet-induced granuloma formation (chronic inflammation model); both in rats. |
|                         |               |                        |                    | Finding: The extract significantly inhibited the edema in acute inflammation model dose dependently while in chronic model the results indicated mild yet statistically significant anti-inflammatory in chronic model. |
| *P. herbacea* (Narayanan et al. 2000) | EtOH ext.; roots | Anti-inflammatory, Antipyretic, Antinociceptive | 100, 200, 400 mg/kg | Carrageenan-induced paw edema (acute inflammation model) and cotton pellet-induced granuloma formation (chronic inflammation model); both in rats. |
|                         |               |                        |                    | Finding: The extract significantly showed antipyretic and antinociceptive effects on particular animal models. |
| *P. integrifolia* (Gokani et al. 2011) | MeOH ext.; roots | Anti-inflammatory     | 300 mg/kg          | In vivo: acute inflammation models (carrageenan-induced edema, histamine-induced wheal formation, formalin-induced edema, acetic acid-induced vascular permeability) and chronic inflammation model (cotton pellet-induced granuloma). |
|                         |               |                        |                    | Finding: In vitro: COX-1 inhibitory activity using spontaneous contractions of the rat’s uterus and heat-induced hemolysis of rat’s erythrocytes. |
|                         |               |                        |                    | Finding: The extract showed significant reduced both acute and chronic edema/granuloma formation in inflammation models which were supported by significant prostaglandin synthesis inhibition (% inhibition was 30.43%) on rat’s uterus and stabilization of plasma membrane of rat’s erythrocyte (conc 50, 100 and 150 µg/mL). |

(continued)
FRAP assays are mostly based on the simple chemical reaction (Benzie & Strain 1996; Molyneux 2004). These cell-free antioxidant assays do not support the cellular physiological conditions, do not include particular biological substrates that need to be protected, may not encounter the relevant types of antioxidant at molecular level, may not describe the partition coefficient of the compounds, or other cellular factors. Cell-based antioxidant assays are considered more relevant and accurate in representing the in vivo conditions since they involve several aspects such as uptake, metabolism, and target site where the compounds might potentially worked within cells (Lü et al. 2010).

Inflammatory reaction occurs due to pathogen invasion into the body or other types of body injury which can cause injury to the tissues or cells as well. At macroscopic level, inflammation is indicated by reddened, swollen, hot, pain, and loss of function of the inflamed area. The loss of function is usually referring to simple loss of mobility in a joint due to pain or edema, or the replacement of functional tissue by the scar tissue. This inflammatory event usually will be followed by the release of mediators from the cells or plasma which modify and regulate the immune response (innate/nonspecific and specific immunological response) (Punchard et al. 2004). Hence, several studies have been conducted to evaluate the anti-inflammatory effect of the extracts of Premna species (Table 3). In addition, an extensive study by Salae et al. (2012) identified several compounds from P. obtusifolia roots that exhibited potent anti-inflammation activity. Meanwhile, megastigmane [48] only showed weak anti-inflammatory activity. Further structure-activity relationship analysis suggested that the presence of a hydroxyl group in an ortho-naphthoquinone skeleton provided stronger anti-inflammation activity. It was postulated that these active compounds might be responsible for the strong NO inhibitor activity of the hexane and dichloromethane extracts (IC_{50} 4.3 and 6.1 μg/mL, respectively). Another species, P. integrifolia, also showed significant

### Table 3. Continued

| Species (ref.) | Part of plant | Pharmacological effect | Dose, methods & findings |
|---------------|---------------|------------------------|-------------------------|
| P. integrifolia (Khatun et al. 2014) | MeOH ext.; barks | Anti-inflammatory and antinociceptive | Methods: carrageenan-induced paw edema, formalin-induced licking response and acetic acid-induced writhing reflex tests. Findings: The extract significantly reduced the writhing reflex and licking response dose dependently. At 200 mg/kg, the extract provided 71.16% inhibition of carrageenan-induced edema. |
| P. latifolia (Mahire et al. 2009) | MeOH ext.; leaves | Anti-inflammatory | Methods: carrageenan-induced paw edema, cotton pellet-induced granuloma, and acetic acid-induced vascular permeability models. Findings: The extract exhibited significant anti-inflammatory activity on those three animal models, dose dependently. |
| P. latifolia (Kumari et al. 2011) | Water ext.; leaves | Anti-inflammatory | Methods: carrageenan-induced paw edema in rats. Findings: The extract showed significant reduced in the edema after 60 min of the edema induction, and the findings showed better results than P. obtusifolia and on par with indomethacin. |
| P. obtusifolia (Kumari et al. 2011) | Water ext.; leaves | Anti-inflammatory | Methods: carrageenan-induced paw edema in rats. Findings: The extract showed significant reduced in the edema after 60 min of edema induction. |
| P. obtusifolia (Salae et al. 2012) | Hexane and CH₂Cl₂ ext.; roots | Anti-inflammatory | Methods: LPS-induced nitric oxide (NO) production by murine macrophage-like RAW 264.7 cells. The NO production was measured by using Griess assay. Findings: Both extracts significantly inhibited NO production that comparable to caffeic acid phenylester (positive standard, IC₅₀ 5.6 μg/mL), with IC₅₀ 4.3 (hexane) and 6.1 (CH₂Cl₂) μg/mL. |
| P. serratifolia (Rajendran & Krishnakumar 2010) | EtOH ext.; woods | Antiarthritus | Dose: 300 mg/kg | Methods: Freund’s adjuvant-induced arthritis rats, where suspension of killed Mycobacterium tuberculosis (0.5%) in liquid paraffin was injected into the left hind paw, and the changes in paw edema were measured. Findings: The extract inhibited the edema by 68.32% after 21 days (indomethacin showed 74.87% inhibition). In hematological parameter, treatment with the extract significantly decreased the total whole blood count (WBC) and erythrocyte & sedimentation rate (ESR), but increased the red blood count (RBC) and hemoglobin (Hb) level. |
| P. serratifolia (Rajagopal et al. 2014) | MeOH ext.; flowers | Anti-inflammatory | Concentration: various, 10-1000 μg/mL Methods: in vitro HRBC membrane stabilization, with measured parameter was inhibition of HRBC membrane lysis. Findings: Starting at concentration 100 μg/mL, the extract showed an anti-inflammatory activity with percentage inhibition at 69.41 ± 0.12 μg/mL. The percentage inhibition appeared in linearity with concentration, and at 300 μg/mL, the extract exhibited inhibition at 97.30 ± 0.59 μg/mL. |
| P. tomentosa (Alam et al. 1993) | MeOH ext.; leaves | Anti-inflammatory | Dose: 100 mg/kg | Methods: cotton pellet-induced granuloma in rats. Findings: The extract caused a reduction of granuloma by 32.21%, in comparison to phenylbutazone (positive control) which was 33.77%. There was also a decreased in serum protein, SGOT and SGPT. |

Other activities such as antioxidant, antidiabetic/antihyperglycaemic, antihyperlipidemic, hepatoprotective and cardioprotective activities are discussed in the main article.
in vivo anti-inflammatory activity in both acute and chronic inflammation models; further in vitro study suggested inhibition of prostaglandin synthase and stabilization of plasma erythrocyte membrane might play role in the in vivo activity (Gokani et al. 2011).

Only one calcification-related study has been carried out on Premma. The anticalcific activity of P. latifolia leaves and stems was evaluated in vitro by assessing oxalate crystal growth on gel medium in Hane’s tubes via single diffusion method over period of 30 days at the concentrations of 20 and 200 mg/mL (Aravindakshan & Bai 1996). The extract effectively reduced the size of oxalate crystal in comparison to negative control and further analysis by using scanning electron microscope showed development of cracks in the crystal interior and rupture tendency. These results concluded chemolysis as an anticalcific mechanism of this extract.

Interesting immunostimulant activity was exhibited by P. pubescens Blume and P. tomentosa leaves. In their in vitro studies, Devi et al. (2003a, 2004a) used rat’s splenic lymphocytes and 1770 macrophage cell culture which has been induced by using chromium, Cr(IV), to provide immunosuppressant condition. The results showed P. tomentosa inhibited the apoptosis of the Cr(IV)-induced cells by preventing the proliferation of the lymphocytes and the macrophages. At the same time, the extract has significantly reduced the ROS level by increasing the levels of the endogenous antioxidant enzymes such as glutathione (GSH), glutathione peroxide (GPx) and superoxide dismutase (SOD) enzymes, and reducing malondialdehyde (MDA) level. Meanwhile, in vivo study by Restuati et al. (2014) in the antigen sheep red blood cell (SRBC)-induced immunostimulant rats, suggested that P. pubescens stimulated the immune response by increasing the number of leukocytes, immunoglobulin IgG and IgM, and lysozyme. In addition, the methanol extract of P. integrifolia roots also produced significant immunomodulatory activity in both specific and nonspecific immune responses following hemagglutinating antibody titer, plaque forming cell assay, delayed-type hypersensitive response, carbon clearance test (phagocytic activity) and E. coli-induced abdominal sepsis parameters (Gokani et al. 2007).

Cytotoxic activities

Traditional use of P. herbasePath by the Thai to treat cancer has led to the evaluation of the rhizome extract of this species towards several cancer cell lines such as COR-L23, LS-174 T and MCF-7 (Itharat et al. 2004). The results turned out to be negative. However, another study by Dhamija et al. (2013), showed that the root nodules extract had cytotoxic activity on brine shrimp lethality test (BSLT), Ehrlich ascites carcinoma (EAC) cells (trypan blue dye exclusion assay), and MCF-7 cell lines (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay). Ethanol extract and ethyl acetate fraction exhibited the most potent cytotoxic effect and further investigation on EAC-inoculated mice and Dalton’s lymphoma ascites (DLA) mice (250 and 500 mg/kg, orally) led to significant elevation of the mean survival rate and reduction of the solid tumor weight and volume. These findings were supported by hematomatological and antioxidant parameters. The EAC-inoculated mice model was used to evaluate antitumor activity of the ethanol extract of P. integrifolia; the findings were found to be comparable to the standard, 5-flourouracil (20 mg/kg) (Sridharan et al. 2011).

About 20 years ago Habtemariam (1995) isolated diterpenes [27 and 29] from P. oligotricha and P. schimperi and suggested they possess cytotoxic property towards several cancer cell lines such as L929, RAW 264.7, HeLa, Sk.N.SH and ECV 304, with IC50 values of 1.5–35 µg/mL. Compound 30 was already known to exhibit a cytotoxic effect. Extensive phytochemical works and cytotoxicity assays on P. tomentosa (Chin et al. 2006; Hymavathi et al. 2009; Naidu et al. 2014) have led to the identification of several cytotoxic diterpenes [31–33, 99, 73–76]. Compounds [31–33] showed cytotoxic activity towards several cancer cell lines, Lul, LNCAp, and MCF-7, but only 32 and 33 were active on in vivo hollow fiber assay towards the cell lines (Chin et al. 2006). Diterpenes [83-85] from P. latifolia exhibited cytotoxic effect towards HT-29 and Hep-G29 cell lines, especially compound 83 and 84 (IC50 0.04 and 0.18 µg/mL, respectively) (Suresh et al. 2011a). Another study has identified a diterpene [53] as one of the responsible compounds for cytotoxic property of P. serratifolia (Habtemariam & Varghese 2015). A similar study by Biradi and Hullati (2015) reported the cytotoxic properties of the extract of P. integrifolia and its unidentified compounds.

Antidiabetic/antihyperglycaemic and antihyperlipidemic activities

So far, four species of Premma has been studied for their antidiabetic properties. The most common method was using a chemically-induced diabetic animal model. Alloxan-induced hyperglycemic rats have been used to evaluate antidiabetic activity of ethanol extract of P. integrifolia at a dose of 250 mg/kg, to confirm the hypoglycaemic activity of this herbal based on the Indian folk medicines (Kar et al. 2003). This activity was further evaluated by Mali (2013) using cafeteria diet induced mice (inbred) through various parameters (body-mass index, blood glucose, lipid profile, histology valuation) and comparison with a standard drug (simvastatin). The findings indicated significant protective effect of the roots of P. integrifolia at doses of 200 and 400 mg/kg. P. corymbosa Rottler & Willd., also reduced blood glucose level in both normoglycaemic and alloxan-induced hyperglycemic rats, at doses of 200 and 400 mg/kg (Dash et al. 2005). Similar studies by Ayinampudi et al. (2012) and Ayinampudi (2013) successfully identified two diterpenes [81, 82], and two aldehydes [185, 187] that were responsible for anti-hyperglycaemic activity of P. tomentosa root by inhibiting enzyme α-glucosidase in vitro (IC50 values were 22.58, 9.59, 18.41, and 12.11 µg/mL, respectively). One clinical study, based on the Ayurvedic system, evaluated the effectiveness of P. obtusifolia roots as an alternative treatment for diabetics (Ghosh et al. 2009). This 9-month study involved 50 patients with a history of obesity. The results showed significant reduction on body-mass index (BMI), atherogenic index and waist-hip ratio after 6 months while the uric acid and mid-triceps skin fold thickness were significantly reduced after 9 months.

The in vivo evaluation of antihyperlipidemic activity of herbal extract is normally done by determining the lipid profiles (LDL, HDL, triglycerides, cholesterol) and histology parameters. As mention earlier, P. tomentosa leaves extract showed antihyperlipidemic activity towards the animal model by improving lipid profile and reducing lipid metabolizing enzymes (Devi et al. 2004c). Meanwhile, Mali (2013) reported the effect of P. integrifolia roots on lipid profile parameters of caffeine-induced mice. Additionally, the antihyperlipidemic effect of the leaves and roots of P. esculenta was evaluated in vivo by using Poloxamer 407-induced hyperlipidemis mice and rats (Mahmud et al. 2011). The study was designed for single dose (mice, 500 mg/kg, i.p) and repeated dose (rats, 4 days, 250 mg/kg, p.o), and the results suggested the
extract significantly reduced the serum total triglycerides, total cholesterol, LDL and VLDL levels which were comparable to the standard drug, atorvastatin.

**Hepatoprotective and cardioprotective activities**

*Premna tomentosa* has been extensively studied for its hepatoprotective activity. Devi et al. (1998, 2004b, c, 2005) have evaluated the possible protection mechanisms of the extract of *P. tomentosa* leaves on acetaminophen-induced hepatotoxicity in rats, which suggested via (i) reducing ROS and generating endogenous antioxidant enzymes in the liver (e.g. glutathione system, superoxide dismutase, catalase); (ii) improving lipid profile and reducing the activities of lipid metabolizing enzymes; (iii) decreasing the acetoaminophen-induced membrane damage so that total membrane-bound ATPases would improve and eventually help maintaining active transport and balancing of Na⁺, Ca²⁺ and K⁺ in the liver and serum; and (iv) protecting the liver against mitochondrial damage as the mitochondrial contains enzymes that would catalyze the production of lipid peroxidation products and other toxic metabolites. Additionally, Hari Prasad et al. (2006) postulated the protective mechanism of *P. tomentosa* towards dimethyl nitrosamine (DMN)-induced hepatic fibrosis was through decreasing the activation of liver stellate cells and accumulation of collagen and other connective tissue proteins. Recently Naidu et al. (2014) reported that the *in vitro* (using HepG2 cells) and *in vivo* (using tBHP-induced hepatic damage mice) hepatoprotective activity of compound 76 increased the viability of hepatic cells and decreased the elevation of serum transferases (SGOT/SGPT) and oxidative damage, including lipid peroxidation. *P. corymbosa* and *P. serratifolia* also showed protective activity on chemically induced (carbon tetrachloride (CCL₄) and paracetamol, respectively) hepatic damage in rats (Karthikeyan & Deepa 2010; Singh et al. 2011).

Two species, *P. mucronata* Roxb. (Patel et al., 2012; Savsani et al., 2014) and *P. serratifolia* (Rajendran & Saleem 2008), are reported to have cardioprotective activity towards a myocardial infarction rat model. The extracts provided protection to the heart via several mechanisms, i.e., (i) decreasing injured cardiac marker enzymes; blood glucose; heart tissue protein; and heart tissue nucleic acids; as well as (ii) maintaining the electrocardiogram (ECG) pattern and hemodynamics changes, increasing myocardial glycogen and restoring antioxidant status. Further investigation has ruled out cardiac stimulant activities of *P. serratifolia* extracts by significantly supporting positive inotropic and negative chronotropic actions similar to that of β-adrenergic effect, decreasing membrane Na⁺K⁺ATPase and Mg²⁺ATPase and increasing Ca²⁺ATPase (Rajendran et al. 2008). There was only one study reporting the gastroprotective activity of *P. serratifolia* leaves on aspirin-induced ulcer rats (Jothi et al. 2010). The evaluation was carried out at doses of 200 and 400 mg/kg by looking at several parameters: lesion index, total- and free-acidity, and percentage of ulceration. The findings suggested that *P. serratifolia* exhibited significant antulcer and anti-secretory activities in both applied doses.

**Neuropharmacological activities**

So far, two studies have evaluated the hypnotic and the neuropharmacological effects of *Premna* species on animal models. Devi et al. (2003b) evaluated the effects of the methanol extract of *P. tomentosa* leaves as a central nervous system (CNS) depressant using potentiation of phenobarbitone-induced hypnotic and locomotor activities on rats. At doses of 400 and 500 mg/kg orally, the extract decreased the locomotor activity and moderately increased the sleeping time, that were comparable to CNS depressant, chlorpromazine (10 mg/kg, i.p) yet significantly different to CNS stimulant, ephedrine hydrochloride (10 mg/kg, i.p). A recent study also evaluated the effect of *P. integrifolia* bark on locomotor activity of the rats in the open field and hole-cross tests (Khatun et al. 2014). The findings suggested that *P. integrifolia* significantly affected locomotor activity of the rats at the doses of 250 and 500 mg/kg, orally on both methods, therefore, might act as CNS depressant.

**Discussion**

This review summarizes the phytochemical work of more than 19 species (24 species once the synonyms are considered) of *Premna* with more than 250 secondary metabolites have successfully been isolated and identified. It comprises a high number of diterpenes, iridoid glycosides and flavonoids (glycosides and glycrones), followed by sesquiterpenes, lignans, phenylethanoids, megastigmanes, glyceroglycolipids and ceramides. Xanthenes and alkaloids were rarely identified though a few studies reported their presence in this genus. Meanwhile essential oils were reported in seven species. The distribution of identified secondary metabolites within the genus *Premna* is shown in Table 3.

Although the *Premna* genus is rich in diterpenes and iridoid glycosides, they were not well distributed within the studies species. Diterpenes were abundant in three species such as *P. mollissima, P. serratifolia*, and *P. tomentosa* while iridoid glycosides were reported abundantly in *P. serratifolia, P. subscandens* and *P. microphylla*. On the contrary, flavonoids seem to be well distributed among 16 reported species despite of their low number in comparison to other groups. Only a few species such as *P. serratifolia, P. microphylla, P. mollissima, P. fulva* and *P. subscandens*, have been extensively studied for their secondary metabolites. Nonetheless, a previous review (Taskova et al. 1997) endorsed terpenoids, iridoids, and flavonoids to be used as taxonomic markers in the family Lamiaceae based on their occurrence in 39 species of 25 genera such as *Sideritis, Stachys, Lamiun, Pholmis, Ballota, Salvia, Ajuga, Teucrium*. Thus, diterpenoids (icetexane, abietane, labdane, pimarane types), iridoid glycosides (catalpol derivatives), and flavonoids (flavanols and flavones) can be very useful to characterize the taxonomic markers of the genus *Premna* (Taskova et al. 1997) and to provide the secondary metabolite fingerprint of each species through infrared (IR), thin layer chromatography (TLC), high performance liquid chromatography (HPLC), mass spectroscopy (MS), or nuclear magnetic resonance (NMR) analysis.

Some of the biological and pharmacological studies reported on the studied plants have suggested scientific evidence to justify the various plant uses in traditional medicine. However, adequate biological and pharmacological studies on most of the species in the genus *Premna* have not yet been performed because most, especially in *in vivo* studies, were carried out using their crude extracts (Table 4). For example, none of the bioactive molecules have been identified from the active antimalarial *Premna* species. Similarly, some *Premna* species showed potential *in vivo* antihyperlipidemic, cardioprotective, hepatoprotective, gastroprotective, and neuropharmacological activities which require further studies to determine the active compounds and possible mechanisms for a particular activity. While, numerous isolated compounds have been isolated and evaluated for related biological activities, they were limited to *in vitro* studies. No toxicological studies that
have been carried out, although some species, such as *P. serratifolia*, have been used in Ayurvedic medicine for a long time.

There was no effort to qualitatively and quantitatively analyze the extracts used. Standardization of the extracts should be carried out to ensure consistency of the quantitative amounts of the active chemical markers in the plants of similar species collected from different locations. The variety and distribution of active secondary metabolites from this genus are useful as bioactive chemical markers for standardization and quality control purposes. Otherwise the work on biological activities may not be

### Table 4. Summary of pharmacological activities of *Premna* species.

| Pharmacological activities                      | Species          | Part of plant                  | Type of study |
|------------------------------------------------|------------------|--------------------------------|---------------|
| Antimicrobial                                   | *P. barbata*     | Extract (leaves)               | in vitro      |
|                                                | *P. cordifolia*   | Extract (leaves)               |               |
|                                                | *P. herbacea*     | Isolated compound from roots   |               |
|                                                | *P. integrifolia* | Extract (leaves, root-barks)   |               |
|                                                | *P. latifolia*    | Essential oil (leaves)         |               |
|                                                | *P. microphylla*  | Extract (leaves, stems)        |               |
|                                                | *P. obtusifolia*  | Isolated compounds from roots  |               |
|                                                | *P. odorata*      | Extract (leaves) and isolated  |               |
|                                                | *P. serratifolia* | Extract (roots, barks, woods)  |               |
| Antileishmanial                                 | *P. oligotricha*  | Isolated compound              |               |
|                                                | *P. serratifolia* | Extract (leaves)               |               |
|                                                | *P. schimperi*    | Isolated compound              |               |
| Antimalarial                                    | *P. angolensis*   | Extract                        |               |
|                                                | *P. chrysocolla*  | Extracts (leaves, roots)       |               |
| Insecticidal                                    | *P. angolensis*   | Essential oils                 |               |
|                                                | *P. latifolia*    | Extract and essential oil      |               |
|                                                | *P. quadrophila*  | Essential oils                 |               |
| Antioxidant                                     | *P. cordifolia*   | Extract                        |               |
|                                                | *P. esculenta*    | Extract                        |               |
|                                                | *P. integrifolia* | Extract                        |               |
|                                                | P. latifolia      | Isolated compounds from stem barks |           |
|                                                | P. microphylla    | Extract                        |               |
|                                                | P. obtusifolia    | Extract and isolated compounds |               |
|                                                | P. serratifolia   | Extract                        |               |
| Anti-inflammatory (including antinociceptive and antipyretic) | *P. corymbosa* | Extract (leaves)               |               |
|                                                | *P. herbacea*     | Extract (roots)                |               |
|                                                | *P. integrifolia* | Extract (roots)                |               |
|                                                | P. latifolia      | Extract (leaves)               |               |
|                                                | *P. obtusifolia*  | Extract (leaves)               |               |
|                                                | *P. serratifolia* | Extract (roots) and isolated compounds | |
|                                                | *P. tomentosa*    | Extract                        |               |
| Anticalculogenic                                | *P. latifolia*    | Extracts (leaves, stems)       |               |
| Antiarthritis                                   | *P. serratifolia* | Extract (woods)                |               |
| Immunomodulatory                                | *P. integrifolia* | Extract (roots)                |               |
|                                                | *P. pubescens*    | Extract (leaves)               |               |
|                                                | *P. tomentosa*    | Extract (leaves)               |               |
| Cytotoxic activity                              | *P. herbacea*     | Extract (rhizome)              |               |
|                                                | *P. integrifolia* | Extract (root nodule)          |               |
|                                                | P. latifolia      | Isolated compound              |               |
|                                                | *P. oligotricha*  | Isolated compounds              |               |
|                                                | *P. schimperi*    | Isolated compounds              |               |
|                                                | *P. serratifolia* | Isolated compound              |               |
|                                                | *P. tomentosa*    | Isolated compounds              |               |
| Antidiabetic                                    | *P. corymbosa*    | Extract                        |               |
|                                                | *P. integrifolia* | Extract (roots)                |               |
|                                                | *P. obtusifolia*  | Roots                          | - Clinical trials - |
|                                                | *P. tomentosa*    | Isolated compounds              |               |
| Antihyperlipidemic                              | *P. escultenta*   | Extract (leaves, roots)        |               |
|                                                | *P. integrifolia* | Extract (roots)                |               |
|                                                | *P. tomentosa*    | Extract (leaves)               |               |
| Hepatoprotective effect                        | *P. corymbosa*    | Extract                        |               |
|                                                | *P. serratifolia* | Extract                        |               |
|                                                | *P. tomentosa*    | Extract (leaves)               |               |
|                                                | *P. obtusifolia*  | Isolated compound              |               |
| Cardioprotective effect                        | *P. mucronata*    | Extract                        |               |
|                                                | *P. serratifolia* | Extract                        |               |
| Gastroprotective effect                        | *P. serratifolia* | Extract (leaves)               |               |
| Neuropharmacological activity                  | *P. integrifolia* | Extract (barks)                |               |
|                                                | *P. tomentosa*    | Extract (leaves)               |               |
Conclusions and future prospects

Further investigations are required to transform the experience-based claims on the traditional uses of *Premna* species into evidence-based information. The present knowledge obtained mainly from experimental studies was critically assessed to provide evidence and justification for their traditional uses to propose future research prospects for this plant. Phytochemical studies on *Premna* species have led to characterization of diterpenoids, iridoid glycosides, and flavonoids as the characteristic chemical composition of the genus. The *in vitro* and *in vivo* evaluation of biological properties of the extracts and isolates from various species of *Premna* on antimicrobial, antioxidant, anti-inflammatory, immunomodulatory, cytotoxic, antihyperglycaemic, and other activities should lead to further detailed investigations to identify the bioactive compounds and their mechanisms of action. The antimalarial, hepatoprotective, cardioprotective, and gastroprotective effects of the plant extracts should encourage further studies on these plants for use as preventive agents. Toxicological evaluation should be conducted to address any adverse side effects which may occur. The roles and mechanisms of the bioactive compounds should be addressed appropriately to understand the contribution of individual compound to the activities as well as to become potential lead molecules for development into drug candidates. Attempts should be made to carry out more preclinical studies of the standardized extracts and bioactive compounds of *Premna* species, which include determination of modes or mechanisms of action in different animal models, bioavailability, pharmacokinetics and toxicological studies before submission of potential candidates to serious randomized human trials is possible. As more scientific evidences on therapeutic effects are discovered, *Premna* species will be recognized as a valuable source of drug leads and pharmaceuticals.

Disclosure statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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