A Review on a Mangrove Species from the Sunderbans, Bangladesh: *Barringtonia racemosa* (L.) Roxb.


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**ABSTRACT**

*Barringtonia racemosa* is considered a mangrove associated species and found in various regions of Southeast and East Asia, as well as Micronesian and Polynesian islands and northern Australia. Important chemicals that have been found in the plant include betulinic acid, ellagic acid, gallic acid, germanicol, germanicone, lupeol, stigmasterol and taraxerol. Antibacterial, antifungal and antinociceptive activities have been reported for extracts from the plant. Traditional medicine practices include the whole plant as a remedy for itch; the roots are considered to be antimalarial, the bark and/or leaves are used in case of boils, snake bites, rat poisonings, gastric ulcer, high blood pressure, chicken pox and as a depurative, the fruits are used as remedy for cough, asthma and diarrhea, while the seeds are used for cancer like diseases and for eye inflammation.

**Key words:** Barringtonia racemosa, Sunderbans, medicinal, Bangladesh

**INTRODUCTION**

*Barringtonia racemosa* is considered a mangrove associated species and found in various regions of Southeast and East Asia, as well as Micronesian and Polynesian islands and northern Australia.

Kingdom: Plantae
Phylum: Tracheophyta
Class: Magnoliopsida
Family: Lecythidaceae
Genus: Barringtonia
Species: *racemosa* (L.) Spreng.

Other species belonging to this genus are

*Barringtonia asiatica*, *Barrington acutangula*,
*Barringtonia edulis*, *Barringtonia lanceolata*,
*Barringtonia macrostachya*, and *Barringtonia spicata*.

**Scientific synonyms:**
*Barringtonia racemosa* (L.) Spreng
*Barringtonia racemosa* (L.) Blume
*Eugenia racemosa* L.
*Bulonica apiculata* Miers
*Barringtonia insignis* Miq.
*Barringtonia pallida* (Miers) Koord. & Valeton
*Barringtonia salomonensis* Rech.

**Other names:**
Fish-killer tree, fish-poison tree, fish-poison wood, freshwater mangrove, small-leaved barringtonia, powder-puff tree, wild guava, brackwater mangrove, common putat, hippo apple (English), Godamidella (Sri Lanka / Sinhala), Arattam (Tamil), Kye-bin, ky (Burmese), Putat ayam, putat ayer, putat aying, putat kampong (Malay), Chik ban, chik suan (Thai), Apalang (Filipino), Butan darat, butun darat, penggung, putat sungai (Indonesian), Samudraphala (Sanskrit), Ingar (Hindi), Mtomondo (Swahili).
Distribution:
B. racemosa, which is considered a mangrove associate, can also be found in tropical rainforest areas, open lowlands and thickets. It occurs always near water: along riverbanks and in freshwater swamps, and occasionally in the less saline areas of mangrove swamps, where it may develop pneumatophores. The species cannot tolerate even light frost. It favours the wet tropical, moist topical and wet subtropical climatic zones. It is distributed from eastern Africa and Madagascar to Bangladesh (Sundarbans), Sri Lanka, India, Myanmar, southern China, Taiwan, the Ryukyu Islands (Japan), Thailand, the Andaman and Nicobar Islands (India), throughout the Malaysian region towards Micronesia, Polynesia (east to Fiji and Samoa) and northern Australia.

Botanical features:
Barringtonia racemosa is a small tree of mangrove associate type, capable of reaching 20 m or more with leaves tufted at the ends of stout twigs. The leaves can be up to 40 cm long and 15 cm wide, are pointed at the tip, have slightly toothed edges and very pronounced veins. Flowers are arranged in long spikes coming out of the centre of leaf groups, and have four white petals surrounded by a profusion of white filaments. The fruit is egg shaped and about 9 cm long. The bark is generally grey and smooth.

Chemical constituents and their reported pharmacological activities:
Two new triterpenoids, olean-18-en-3beta-O-E-coumaroyl ester and olean-18-en-3beta-O-Z-coumaroyl ester, were isolated from the stem bark along with 5 known compounds, germanicol, germanicone, betulinic acid, lupeol, and taraxerol [143].
Germanicone

Ethyl acetate extract of the stem bark of the plant yielded 3,3’-dimethoxy ellagic acid, dihydromyticetin, gallic acid, bartogenic acid, and stigmasterol [127].

Gallic acid

An ethanolic extract of the roots afforded two novel neo-clerodane-type diterpenoids, methyl-15,16-epoxy-12-oxo-3,13(16),14-neo-clerodatrien-18,19-olide-17-carboxylate (nasimalun A) and dimethyl-15,16-epoxy-3,13(16),14-neo-clerodatrien-17,18-dicarboxylate (17-carboxy methylhardwickiic acid Me ester, nasimalun B) [40].

Saponin namely bhattanin and sapogenins such as R1-barrigenol, barrantogenol and barrantogenic acid have been isolated from the fruit [73,4].

Similar saponins and sapogenins were also found in the seeds [60].
Nasimalun B

Barringtogenic acid

Barringtogenol
Germanicol:

Germanicol may have anti-inflammatory [96] and anti-bacterial potentials [89]. Germanicol and derivatives are also present in the following plants as described below. Germanicol acetate has been isolated from the roots of *Euphorbia nematocypcha* (along with nematocyp, nepheolin acetate, euphol, tanaxastanol, 24-methyleneoctanol, and nepheolin; Cao *et al*, [15]). The compound has also been isolated from methanol insoluble extract of *Araujia sericifera* [78]; methanolic extract of the twigs of *Celtis sinensis* (along with epifriedelanol, trans-N-caffeoyltyramine, cis-N-coumaroyltyramine, pinoresinol glycoside, pinoresinol rutinoside, and steroids; Kim *et al*, [59]); *Festuca argentina* (along with pentacyclic triterpenols such as beta-amyrin, isobaurenol, lupeol, hopenol-α, hopeol, and low amounts of sterols like cholesterol, campesterol, stigmasterol, sitosterol, and dihydrositosterol; Casabunno and Pomilio, [16]); aerial parts of *Koelpinia linearis* (along with koelpinin A (28-nor-lup-12,17-dien-3beta,16alpha-diol), koelpinin B (3beta-acetoxy-28-nor-lup-12,17-dien-16alpha-ol), koelpinin C (28-nor-lup-12,17-dien-3beta-o1-16-one), 30-nor-lup-3beta-ol-20-one, and taraxeryl acetate; Koul *et al*, [62]; hexane extract of *Marsypianthes chamaedrys*, a common herb found in the north and northeast regions of Brazil (along with alpha-amyrin, beta-amyrin, lupeol, chamaedydiol, castanospol, 2alpha-hydroxylupeol, and epigermanidiol; de Sousa Menezes *et al*, [29]); alpha-germanicol from aerial parts of the medicinal plant, *Phoradendron reichenbachianum* (along with moronic acid, 3,4-seco-olean-18-ene-3,28-dioic acid, squalene, glycerol trilinoleate, morolic acid, betulonaldehyde, betulinaldehyde, lupeol, beta-sitosterol, and beta-sitosteril glucopyranoside; Rios *et al*, [113]); and hexane extract from leaves of *Vernonia brasiliiana* (along with lupeol and beta-amyrin; Alves *et al*, [3]).

Taraxerol:

Besides *Barringtonia racemosa*, taraxerol has also been isolated from the plants *Acanthopanax sciadophyloides* (higher fatty acid esters of taraxerol, Yasue *et al*, [145]); leaves of *Acanthopanax trifoliatu* (along with nevadensin, kaur-16-en-19-oic acid, and taraxerol acetate; Du and Gao, [31]); from the chloroform leaf extract of *Alchornea latifolia* [along with taraxerone, friedelin, epifriedelinol, seco-3,4-friedelin (dihydrophtanrijvic acid), and seco-3,4-taraxerone; Setzer *et al*, [120]; taraxerol acetate from dichloromethane extracts of the roots of *Ambrosia artemisifolia* (Bilodeaux *et al*, [12]); 3alpha- and 3beta-taraxerol (along with 3alpha-E-feruloyltaraxerol, 3beta-Z-feruloyltaraxerol, 3beta-E-feruloyltaraxerol, 3beta-Z-feruloyltaraxerol, 3alpha-E-coumaroyltaraxerol, and 3alpha-Z-coumaroyltaraxerol from the fruits of *Bruguiera cylindrica* (Laphookhieo *et al*, [66]); from the twigs and buds of *Calophyllum cordatoooblongum* - methyl ether of cordatolide B, cordatoblongic acid, friedelin, canophyllol, and sitosterol (Dharomatne *et al*, [30]); *Careya arborea* (Mahato *et al*, [85]); *Clerodendrum bungei* (along with beta-sitosterol, glochidone, glochiadonol, and glochidiol; Gao *et al*, [34]); *Clitoria ternatea* [6]; *Codonopsis pilosula* (along with friedelin, alpha-spinasterol, alpha-spinasterol-beta-D-glucopyranoside, n-butylyl-alpha-D-fructofuranoside, and n-butylyl-beta-D-fructopyranoside; Chen *et al*, [19]); *Crossoptephiun chinense* [118]; taraxerol-3-beta-O-tridecyl ether from the aerial part of *Derris trifoliata* [142]; ethyl acetate extract of *Embelia schimperi* leaves [along with 3beta,16alpha-di-O-acetyl-13beta,28-epoxyleanane, 3beta-acetyl-16-oxo-13beta,28-epoxyleanane, 3beta-acetyl-16alpha-hydroxy-13beta,28-epoxyleanane, 3beta-acetyl-16alpha-hydroxyoleanane-13beta,28-olide, 3beta-acetyl-28-hydroxy-16-oxo-12oleanene, 3beta,28-di-O-acetyl-16alpha-hydroxy-12-oleanene, 3beta-acetyl-11alpha,28-dihydroxy-16-oxo-12-oleanene, 3beta,11alpha,16alpha,28-tetrahydroxy-12-oleanene, 3beta-acetyl-16alpha,28alpha-dihydroxy-13beta,28-oxydooleanane, 3beta,28alpha-dihydroxy-16-oxo-13beta,28-oxydooleanane, 3beta,16alpha-dihydroxy-13beta,28-epoxyleanane (protopimulagenin A), 3beta-hydroxy-16-oxo-13beta,28-epoxoyxleanane
(aegischerin), 3,16-dioxo-13beta,28-epoxyoleanane (embilinone), 3beta,28-dihydroxy-16-oxo-12-oleanene (schimperinone), taraxerone, and stigmastanol; Mangroo et al., [86]; leaves of *Macaranga triloba* (along with 4,5-dihydro-5’-alpha-hydroxy-4’-alpha-methoxy-6a,12a-dehydro-alpha-tocixcarol, (+)-covan-2beta,9alpha-diol, ferulic acid, 3,7,3’,4’-tertamethylquercetin, 3,7,3’-trimethylquercetin, 3,7-dimethylquercetin, abscisic acid, 3beta,6alpha-dihydroxy-4(15)-eudesmenes, 3beta-hydroxy-24-ethylcholest-5-en-7-one, loliolide, scoptolein, and 3-epi-taraxerol; Jang et al., [47]); leaves of *Mangifera persiciflora* (along with friedelin, beta-sitosterol, mangiferin, and quercetin; Si et al., [123]); ethyl acetate and butanol-soluble portions of the ethanol extract from the bark of *Mitragyna rotundifolia* (along with dauricine, 3,4-dihydroxybenzoic acid, beta-sitosterol, scopleton, 3,4,5-trimethoxyphenol-1-glucopyranoside, 4-hydroxy-3-methoxybenzoic acid, 3-hydroxy-4-methoxybenzoic acid, caffeic acid, gambirine, gambireine, and 1,1-dimethyl-2-acetyl-diethyl ether; Kang et al., [53]); root bark of *Myrica cerifera* [104]; stems of *Opuntia dillenii* (along with opuntisterol, opuntisteroside, beta-sitosterol, friedelin, methyl linoleate, 7-oxostossterol, 6beta-hydroxystigmast-4-ene-3-one, daucosterol, methyl eucomate, and eucomic acid; Jiang et al., [49]); *Pachyandra terminalis* [58]; *Rhizophora mangle* [139]; root of *Rhododendron molle* (along with rhodojaponin-III and beta-sitosterol; Xiang et al., [141]); *Rhododendron ovatum* (along with 3,5,7-trihydroxychromone 3-O-beta-D-xylpyranoside, beta-sitosterol, betulinic acid, quercetin, quercetin-3-O-alpha-L-rhamnopyranoside, and D-glucose; Feng et al., [32]); *Sageretia theezans* (along with friedelin, syringic acid, beta-sitosterol, daucosterol, and gluco-syringic acid; Xu et al., [142]); leaves of *Sasitienia adenanthera* (along with 3-beta-amyrin, beta-amyrinone, 3-epi-lupeol, lupenone, and taraxerone; Macias-Rubalcava et al., [82]); taraxer-14-en-3beta-ol from the leaves of *Sterculia foetida* (Naik et al., 2004); 95% ethanol extract, benzene fraction of *Strobilanthes callosus* (Singh et al., [125]); ethyl acetate soluble fraction of stem bark of *Styrax japonica* (along with styraxlignolide B, styraxlignolides C-F, syringin, and (-)-pinoresinol glucoside; Min et al., [91]); roots of *Taraxacum japonicum* (along with taraxasterol and other triterpenoids; Takasaki et al., [130]); *Tetraugoniwm hemsleyanum* (along with taraxerone, beta-sitosterol, and ergosterol; Liu and Yang, [74]); hexane and ethyl acetate extracts of *Uvaria hookeri* and *Uvaria narum* (along with glutinol, glutinone, beta-sitosterol, uvariamics I-III, isodesacetylvaricin, squamocin-28-one, narumicins I and II stereoisomeric mixture, squamocin, and panalicin; Padmaja et al., [97]); methanolic extract of twigs of *Vaccinium oldhami* (along with scopoletin; Lee et al., [69]); *Ventilago leiocarpa* (along with lupeol, chrysophansol, hispanicin, parietin, emodin, catenarin, skyrin, (+)-aromadendrin, ventiloquinone K, ventiloquinone I, and stigmastanol; Lin et al., [72]); and wood of *Vepris punctata* (along with glechomanolide, isogermafurenolide, (E,E)-germacra-1(10),4,7(11)-triene, alpha-amyrin, lupeol, lupeyl acetate, and 3-epi-taraxerol; Chaturvedula et al., [18]).

Taraxerol has been reported to exhibit significant inhibitory effects on Epstein-Barr virus early antigen (EBV-EA) induced by the tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA) in Raji cells. Furthermore, taraxerol exhibited potent antitumor-promoting activity in the two-stage carcinogenesis tests of mouse skin using 7,12-dimethylbenz[a]anthracene (DMBA) as an initiator and TPA as a promoter [130].

Taraxerol has been reported to significantly reduce carrageenan-induced paw edema and exhibit low anti-microbial activity [125]. Taraxerol-14-en-3beta-ol, its acetate and ketone also demonstrated anti-inflammatory activity against TPA-induced mouse ear edema [94].

Taraxerol exhibited significant inhibition of acetylcholinesterase (AchE) activity with an IC50 value of 79 microM [69].

**Bartogenic acid:**

Bartogenic acid is isolated from fruits of *Barringtonia racemosa* which has been shown to have antiarthritic activity [102]. The acid, isolated from seeds of the plant reportedly showed alpha-glucosidase and amylase inhibitory activities [37]. The latter two activities can be important for treatment of diabetes. A number of acids like chlorogenic acid, betulinic acid, syringic acid, vanillic acid, bartogenic acid, oleanolic acid, dehydrotrametenolic acid, corosolic acid, ellagic acid, ursolic acid, and gallic acid have been identified as alpha-glucosidase inhibitors and so can prove useful in treatment of diabetes [9].

**Gallic acid:**

Gallic acid (3,4,5-trihydroxy benzoic acid) along with other phenolic compounds like methyl gallate, ethyl gallate, m-digallic acid and other gallic acid derivatives are potent antioxidants. Their medicinal properties have been extensively studied and cover a wide range from anti-microbial to cytotoxic and other properties.

The anti-diabetic effects of gallic acid have been reported. Gallic acid reportedly protected RINm5F beta-cells from glucolipotoxicity by its antiapoptotic and insulin-secretagogue actions [116]. The antihyperglycemic, antilipid peroxidative, and antioxidant effects of the compound have been demonstrated in streptozotocin-induced diabetic Wistar rats [105]. Insulin-secretagogue and anti hyperlipidemic effects of gallic acid isolated from *Terminalia bellerica* Roxb. have been demonstrated in streptozotocin-induced diabetic rats [67]. Unripe *Carissa carandas* L. fruit extract has
been shown to exhibit antidiabetic potential, which has been attributed to some extent to gallic acid present in the extract [45]. The protective action of gallic acid has been shown on hepatic lipid peroxide metabolism in streptozotocin-induced type II diabetic Wistar rats [106]. Gallic acid also showed cardioprotective effects in diabetes-induced myocardial dysfunction in rats [10]. In vivo and in vitro antidiabetic effect of Cistus laurifolius L. has been shown; a major phenolic compound present in the extract was gallic acid [95]. The bark of Terminalia paniculata Roth has also been shown to reduce blood glucose levels in in vivo and in vitro diabetic model; one of the responsible phytochemical for the antidiabetic action has been postulated to be gallic acid [111]. Gallic acid reportedly also demonstrated protective effect in oxidative stress-linked streptozotocin-induced pancreatic dysfunction in diabetic rats [52].

Lupeol:
The anticancer, cancer chemo-preventive, cardioprotective, hepatoprotective, antimicrobial, antiprotozoal, anti-inflammatory, antiurolithic, antidiabetic, anti-snake venom, gastroprotective, and anticonvulsant activities of lupeol, and to some extent betulinic acid has been reviewed [33]. Since then, the results of some further studies on lupeol and betulinic acid are described (below).

It has been shown that lupeol specifically targets Wnt/beta-catenin signaling in human melanoma cells and so inhibit cell proliferation [131]. A similar observation has been made with colorectal cancer cells [132]. In human hepatocellular carcinoma cells, lupeol has been shown to inhibit growth and induce apoptosis [41]. Lupeol has been postulated to be useful for treatment of prostate cancer because of its inhibitory ability of the androgen receptor [124]. Lupeol has been found to prevent tumor formation during 7, 12-dimethylbenz(a)anthracene-induced oral carcinogenesis [100]. The enhanced effect of lupeol on the destruction of gastric cancer cells by NK cells has been described [140].

The anti-inflammatory effect of lupeol, isolated from Himatanthus drasticus (Mart.) Plumel has been described [80]. Lupeol, isolated from Calotropis gigantea (L.) Ait. latex, has been shown to ameliorate primary and secondary complications of Freund’s Complete Adjuvant induced adjuvant disease in experimental rats [117]. Lupeol also have antinoceceptive properties, which may be due to inhibition of cytokines [27]. Balanophora spicata Hayata and one of its phytochemical constituents, lupeol acetate, has been shown to possess antinoceceptive and anti-inflammatory activities in vivo and in vitro [20].

The antioxidant and antidiabetic property of lupeol has been demonstrated in experimental hyperglycemia [39]. Lupeol supplementation has also been shown to improve blood pressure and lipid metabolism in stroke-prone spontaneously hypertensive rats [5]. Lupeol has been shown to protect against acetaminophen-induced oxidative stress and cell death in rat primary hepatocytes [63]. The protection has been attributed to altering the Bax/Bcl-2 ratio and altering oxidative stress-mediated mitochondrial signaling cascade [64].

Extract of Rhinacanthus nasutus (L.) Kurz has been shown to prevent glutamate and amyloid-beta neurotoxicity in HT-22 mouse hippocampal cells; this protection has been attributed to presence of lupeol in the extract along with stigmastanol and beta-sitosterol [14], these compounds being also present in Barringtonia racemosa.

Betulinic acid:
Betulinic acid has been shown to protect against cerebral ischemia-reperfusion injury in mice by reducing oxidative and nitrosative stress [79]. Antidepressant activity has been described for betulinic acid, isolated from Rosmarinus officinalis L. [81]. The compound has been reported to regulate generation of neuroinflammatory mediators responsible for tissue destruction in multiple sclerosis in vitro [13]. Hepatoprotective activity of betulinic acid has been demonstrated through its prevention of d-galactosamine/lipopolysaccharide-induced liver toxicity, which has been shown to be triggered by activation of Bcl-2 and antioxidant mechanisms [146]. The hepatoprotective potential of Tecomella undulata (Roxb.) Seem stem bark has been partially attributed to the presence of betulinic acid in the stem bark [46]. The anti-inflammatory effect of betulinic acid has been reported [134]. In other experiments, betulinic acid inhibited superoxide anion-mediated impairment of endothelium-dependent relaxation in rat aortas [107]. Betulinic acid has further been shown to have beneficial effect in chemically induced hypothyroidism [1].

The anti-obesity effect of betulinic acid has been reported. It has been shown that combined treatment with betulinic acid and extract of Orthosiphon stamineus Benth. can lead to decreased body weight in high fat-fed mice [22]. Betulinic acid has further been reported to alleviate non-alcoholic fatty liver by inhibiting sterol regulatory element-binding protein 1 (SREBP1) via the AMPK-mTOR-SREBP signaling pathway [108]. SREBPs are transcription factors that bind to the sterol regulatory element DNA sequence TCACNCCAC. Notably, the adenosine monophosphate-activated protein kinase (AMPK)-SREBP1 pathway has been implicated in orotic acid induced development of fatty liver [51]. It has also been reported that betulinic acid ameliorates acute ethanol-induced fatty liver via Toll-like receptor 4 (TLR4) and signal transducer and activator of transcription 3 (STAT3) in vivo and in vitro [137].

The anticancer effects of betulinic acid against different cancer cell lines have been well established.
Betulinic acid reportedly inhibited proliferation, migration, and cell cycle and stimulated apoptosis of pancreatic cancer cells [50]. A combination of betulinic acid and mithramycin A has been shown to effectively suppress pancreatic cancer by inhibiting proliferation, invasion, and angiogenesis [35]. Lamin proteins are thought to be involved in nuclear stability, chromatin structure and gene expression. It has recently been shown that Lamin b1 is a therapeutic target of betulinic acid in pancreatic cancer [71].

In in vitro experiments, betulinic acid inhibited growth of cultured vascular smooth muscle cells by inducing G1 arrest and apoptosis [135]. The anti-angiogenic activity of betulinic acid has been reported in hypoxic PC-3 prostate cancer cells, and has been shown to be mediated through suppression of STAT3 and HIF-1 alpha [122]. In prostate cancer cells, betulinic acid selectively increased protein degradation and enhanced prostate cancer-specific apoptosis, possibly through inhibition of deubiquitinase activity [112]. Polyubiquitin conjugation of key pro- and anti-apoptotic molecules can play a role in regulating apoptosis [68]. In other human cancer cells, co-treatment with ginsenoside Rh2 and betulinic acid reportedly induced apoptosis along with enhanced caspase-8 activation, bax translocation, and cytochrome c release [70]. In HCT 116 colorectal carcinoma cells, alpha-mangostin has been shown to enhance betulinic acid cytotoxicity [2]. Betulinic acid has been shown to exert an antitumor effect on cervical carcinoma (U14) tumor-bearing mice [138].

In colon cancer cells, betulinic acid inhibited cancer cell and tumor growth and induced proteasome-dependent and independent downregulation of specificity proteins (Sp) transcription factors [21]. Notably, Sp1 transcription factor is a zinc finger transcription factor that binds to GC-rich motifs of many promoters, and is involved in many cellular processes including cell growth and apoptosis. Inhibition of lung cancer growth by betulinic acid has been attributed to decreases in Sp1 levels via increasing the sumoylation of Sp1 [43]. SUMO proteins are a family of small proteins that are covalently attached to and detached from other proteins in cells to modify their function, and sumoylation is a post-translational modification involved in various cellular processes like nuclear-cytosolic transport, transcriptional regulation, apoptosis, protein stability, response to stress, and progression through the cell cycle.

Betulinic acid has been shown to decrease ER (endocrine receptor)-negative breast cancer cell growth in vivo and in vitro; a role of Sp transcription factors and microRNA-27a:ZBTB10 has been reported [88]. The microRNA-27a:ZBTB10-specificity protein pathway is also involved in follicle stimulating hormone-induced vascular endothelial growth factor (VEGF), Cox2 and survivin expression in ovarian epithelial cancer cells [65]. Thus betulinic acid may have possibly beneficial effects in cases of ovarian epithelial carcinoma. Notably, betulinic acid has also been shown to target YY1 (a ubiquitously distributed transcription factor belonging to the GLI-Kruppel class of zinc finger proteins) and ErbB2 [a member of the epidermal growth factor receptor (EGFR/ErbB) family; amplification or over-expression of this gene has been shown to play an important role in the development and progression of certain aggressive types of breast cancer] through cannabinoid receptor-dependent disruption of microRNA-27a:ZBTB10 in breast cancer [75]. Microencapsulated betulinic acid, obtained from sour jujube fruits, has been shown to induce apoptosis of human breast cancer cells through the mitochondria transduction pathway [128]. Anticancer activity has been reported for betulinic acid against MCF-7 (human breast cancer cell line) tumors in nude mice [24].

In human multiple myeloma cells, in vitro, betulinic acid has been shown to inhibit autophagic flux and induce apoptosis [144]. Betulinic acid has been shown to suppress neutrophil gelatinase associated lipocalin (NGAL)-induced epithelial to mesenchymal transition in melanoma [36]. NGAL is also known as oncogene 24p3, urocalcin, siderocalin or lipocalin 2 and plays multiple roles in inflammation and cancer [17]. In 7,12-dimethybenz(a)anthracene-treated Sprague Dawley rats, administration of betulinic acid has been shown to play a role in modulating the activities of xenobiotic and antioxidative enzymes that have putative roles in cancer initiation and proliferation [55].

A possible influence of betulinic acid in the clearance of human papilloma virus has been reported [119]. The virus can cause serious health problems, including genital warts and certain cancers. Induction of Bax/Bak-independent cytochrome c release has been noted with betulinic acid in human nasopharyngeal carcinoma cells; such induction would inhibit cell growth through promoting apoptosis [76]. Taken together, betulinic acid has important therapeutic effects against various cancers, including pancreatic cancer, against which cancer there being no effective allopathic treatments.

Ethnomedicinal uses:

Roots are claimed to be as good as cinchona in terms of medicinal value. Fruits are effective in cough, asthma and diarrhea. The seeds are aromatic and useful in colics and ophthalmia [57].

In Bagerhat district of Bangladesh, the plant is used as an insect repellent and for alleviation of pain (including headache, toothache, and muscle pain) [92]. The root of the plant is used to treat diarrhea by folk medicinal practitioners of Bangladesh [25].
In Sri Lanka, the plant is widely used in traditional medical practices in the form of decoction. The bark and leaves are used to treat snake-bites, rat poisoning and in boil; the seeds along with some other ingredients are used in the preparation to treat itch, piles and typhoid fever; the bark is claimed to have specific uses in gastric ulcers [28,48].

In some villages of Kerala (India), the seeds are used to treat cancer like diseases [133]. The plant is used against jaundice in Kannur district, Kerala, India [126]. The plant is used against dog bite wounds by different communities of Uttara Kannada district, Karnataka, India [11].

Root, bark and juice are used medicinally in the East; the Zulu tribe of South Africa uses the fruit as a remedy for malaria. The fruit is used to treat cough, asthma and diarrhea; pulverized fruit is used as snuff.

Seeds are used to treat eye inflammation and by midwives for parturition. In Malaysia, the leaves traditionally are used to treat high blood pressure and as a deppurative. Pounded leaves are said to treat chicken pox [http://www.worldagroforestrycentre.org/sea/Products/AFDbases/af/asp/SpeciesInfo.asp?SpID=307].

The plant has multiple uses in Micronesian islands (Palaau, Yap, Chuuk, Pohnpei, Kosrae and the Marshall islands), which include to treat soumwahu en kau (sickness caused by sorcery), to treat soumwahu en nansapw (sickness from the cultivated fields, to reduce the need to go to the bathroom when a person will be attending a big funeral part and there will be too many people around, to stop diarrhea, to treat back pain, to treat headache, to treat poisoning caused by eating food and drink that may have been hexed by sorcerers, to treat soumwahu en ohl, to reduce a high fever, to treat or clean the uterus, to treat salengamat (ear infection) in babies (symptoms include a bad smell from the painful ear accompanied by copious amounts of white sticky fluid coming from the ear), to treat babies with cracked skin where the ears join the head (there is no local name for this illness), to treat rash similar to chicken pox, to treat a rash on a child, to treat a bad rash given by a sorcerer due to jealousy, to treat skin rash, to treat itchiness, to treat soumeahu en ohl (men’s sickness), and to treat a fungal infection [People and Plants of Micronesia, quoted from the website: http://manoa.hawaii.edu/botany/plants_of_micronesia/index.php/scientific-names/288-barringtonia-racemosa-0].

In some parts of Australasia, the plant is used to treat itchiness [http://www.aseanbiodiversity.org/medicinal_plants/page2.htm].

Reported biological activities of Barringtonia racemosa:

The ethanol extract of root, its chloroform soluble fraction and isolated triterpenoids exhibited in vitro antibacterial activity [57]. The plant reportedly inhibited Staphylococcus aureus in vitro [84]. Antifungal activity has been observed with different extracts of leaves, sticks, and barks of the plant, which activity has been attributed to several isolated compounds from the plant, namely, gallic acid, ferrulic acid, naringin, rutin, luteolin, and kaempferol [44]. The methanol extract of the bark exhibited significant activity against plant pathogenic fungi Curvularia sp., Colletotrichum gloeosporioides, Cylindrocladium quinqueseptatum and Rigidioporus lignosus [99].

Seed kernel extract showed toxicity against the golden apple snail, Pomacea canaliculata [93].

The aqueous bark extract was found to have significant antinociceptive activity when screened in rat model when evaluated with the hot plate and formalin test and such activity was supposed to be mediated via opioid mechanism [28]. Ethanol extract of bark showed significant antioxidant, analgesic and antidiarrheal activity [114]. Ethanolic extract of fruits also demonstrated anti-inflammatory and analgesic activities Shikha et al., [121]. Extract of leaves of the plant has been shown to have antioxidant and anti-inflammatory properties [8]. The antioxidant activity of various solvent extracts of aerial parts of the plant has been reported [87,61].

The protein fraction isolated from the stem bark has been shown to have high mitogenic activity in mouse lymphocytes [129] whilst the ethanol extract of leaves was found to be cytotoxic against HeLa (human cervix carcinoma) cell line with a CD50 value of 10 microg/ml [83]. Intraperitoneal administration of 50% methanol extract of seeds to mice challenged with 1 million Dalton’s Lymphoma Ascite (DLA) cells resulted in remarkable dose-dependent anti-DLA activity and this study validated the ethnomedical use of the same to treat some forms of tumor [133]. Quercetin 3-O-rutinoside, isolated from the plant has shown promising results against acute lymphoblastic leukemia [115].

Hydroalcoholic extract of fruits showed immunomodulatory activity in albino Wistar rats when evaluated in delayed type hypersensitivity reaction and humoral antibody response assays [103].

Some reported phytochemicals, biological activities, and ethnomedicinal uses of other Barringtonia species:

Some reported phytochemical constituents and biological activities of other Barringtonia species are discussed below. An aqueous extract of the bark of Barrington acutangula yielded nine triterpene saponins, acutangulosides A-F and acutanguloside D-F methyl esters and a single triterpene aglycone [90]. Crude extracts and VLC fractions from the stem bark of B. acutangula (particularly the petroleum ether extract) showed good activity against two Gram-positive bacteria, two Gram-negative bacteria and two fungi. The VLC fraction PE16 was found to be very effective against Bacillus subtilis (MIC = 25
and diarrhea by the Santhal tribe of Mayurbhanj district, Orissa, India [25]. The plant is also reportedly used by other tribes in Mayurbhanj district to treat diarrhea and dysentery [54]. The stem bark of the plant is used to treat boils and wounds in Kutchum district, Yasothon Province, Thailand [23].

Barringtonia asiatica has medicinal and poisonous properties; the fresh leaves are applied externally to relieve rheumatism and when heated used to remedy stomach pain; the seeds are used in regulated doses against intestinal parasites; in Indonesia the plant is used as a remedy against scabies.

Barringtonia macrostachya is used to counter ringworm. Barringtonia spicata is used against itchiness [http://www.aseanbiodiversity.org/medicinal_plants/page2.htm]. Barringtonia acutangula is used for its analgesic properties by the aborigines from Western Australia [http://www.gu.edu.au/research/stories/health/content_pain_relief_mangroves.html]. The fruits of Barringtonia edulis (local name, kinu) are eaten by the people of Savo island (an island in the Solomon Islands archipelago).

**Other uses of Barringtonia racemosa:**

Young leaves are eaten as a vegetable; seeds are pounded to extract the starchy content, which is made into cakes. It provides suitable firewood. It has been applied in various kinds of wood-based panels such as hardboard, particleboard and blockboard, and has been used for the production of pulp. In Kenya, the bark is utilized as cordage. Barringtonia racemosa yields a medium-weight hardwood with a density of 480-815 kg/m³ at 15% mc. The wood is light and soft and is used for light work that does not require great strength. The wood is utilized for temporary construction, local house building (posts and beams), general planking, flooring, boat building, mouldings, interior finish, handles of non-striking tools, household utensils, agricultural implements, boxes and crates and wooden pallets. It is suitable for veneer and plywood manufacturing. In India, it is used additionally for carts, rice pounders and cabinetwork. In the Philippines, it has been reported that when treated with preservatives, the timber can be used to make good ties and paving blocks. In the Pacific region, the wood has additionally been used for carving and turnery. The bark yields tannin. Seeds of the species contain saponins, which are used as a fish poison; the whole fruit, bark, wood and root can be used. Extracts of the plant have proved effective against Citrus aphis; in Bengal the seed is used as an insecticide, and to poison people; coconut is said to be the antidote [http://www.worldagroforestrycentre.org/sea/Products/AFDbases/af/asp/SpeciesInfo.asp?SpID=307].

**Drug discovery potential:**

The importance of some triterpenoids such as lupeol, betulinic acid and taraxerol (present in the
References


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