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Traditional Medicinal Uses, Chemical Constituents and Biological Activities of a Mangrove Plant, *Acanthus ilicifolius* Linn. : A Brief Review

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Abstract: The medicinal value of mangrove plants is not extensively read. This review article attempts to emphasize the medicinal value of a mangrove plant, *Acanthus ilicifolius* Linn. (Acanthaceae), common names of which are holy leaved acanthus, sea holly and holy mangrove. *A.ilicifolius* is abundantly available in freshwater ecosystem of Pichavaram mangroves located in southeast coast of India. Though several research articles have been published on this mangrove plant, there is no review article pertaining to its traditional use, biological activities and chemical constituents which will be described here. Directions for future research are also addressed.

Key words:*Acanthus ilicifolius* Linn · Pichavaram mangroves · Mangrove ecosystems · Holy mangrove · Freshwater ecosystem

INTRODUCTION

Acanthus ilicifolius Linn. (Acanthaceae) is a perennial herbaceous plant, popularly recognized as "Holy leaved acanthus". The plant normally lives in areas of modest salinity, forming bush around mangrove palms. Historically, the plant is employed in traditional systems of medicine, including traditional Indian medicine or Ayurveda and traditional Chinese medicine [1, 2] for treating various ailments. Various parts of the plant have been used as crude drug for treatment of asthma, diabetes, dyspepsia, leprosy, hepatitis, paralysis, snake bite, rheumatoid arthritis and diuretic [3, 4]. Moreover, the plant possesses anti-inflammatory, antioxidant, antileishmanial, osteoblastic, hepatoprotective, anticancer, antiulcer and antimicrobial activities [5]. The literature revealed that the plant is rich in bioactive compounds. Due to its varied biological activities, the plant is continually being investigated.

Taxonomy:
Class: Dicotyledones
Subclass*:* Gamopetalae
Series*:* Bicarpellatae
Order*:* Personales
Family*:* Acanthaceae
Genus*:* *Acanthus*
Species*:* *ilicifolius*

'*Acanthus'* is derived from Greek word '*Acantha*' which means thorn or thistle, referring to spiny leaves of some species. The word '*ilicifolius*' means '*ilex'* leaves in Latin and refers to holly-like leaves. Acanthus is the only genus of family Acanthaceae which occupies mangroves habitat. The genus consists of two species namely *A. ebracteatus* and *A.ilicifolius*. Differentiation of these two species could be difficult from foliage alone, however, in general, *A. ilicifolius* has prickly leaves and stems with sharp spines and *A. ebracteatus* has

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non-prickly leaves and stems with no spines. *A.ebracteatus* is also distinguishable from *A.ilicifolius* by having white flowers lacking bracteoles ('*ebracteatus*' means without bracts in Latin). *A. ilicifolius* may possess non-prickly leaves under conditions of low sunlight or strong growth. Two subspecies of *A. ebracteatus* were recognized *viz* (*A.ebracteatus* subsp. *ebracteatus* and *A. ebracteatus* subsp. *ebarbatus,* both are native to Australia. These species are differentiated by flower color, leaf shape, stem spines and flower hairiness along upper suture. *A. ebracteatus* subsp. *ebracteatus* have flowers which are white streaked with red, leaves entire and/or spiny, stems often without spines, anthers hairy on upper suture. Flowers of *A. ebracteatus* subsp. *ebarbatus* are deep purple, leaves mostly entire (rarely spiny), stems without spines, anthers not hairy on upper suture. Few other species such as *A. volubilis, A. latisepalus, A. montanus* are recorded in mangrove habitat, but they lack consistent diagnostic features [6].

Ecology and Geographical Distribution: *A.ilicifolius* is common in estuaries throughout Asian tropics from India to Polynesia and northern Australia [7]. Asia and Australia have the greatest variety and distribution of mangrove species in the universe. In India, it is found commonly in the east and west coasts, also in Meghalaya and the Andamans. It is a true mangrove species found in the most foreshore location [8]. It normally grows on river banks or tidal canal sides or low swampy areas in mangrove forests and vicinities.

Morphological Description: Shrub up to 2 meter tall growing robust along tidal swamps in sheltered mangrove areas, landward margins and back waters; Aerial roots-stilt roots; Leaves-simple, opposite, lanceolate, narrowed at base, serrate margins armed with spines; spines longer in flowering season; petiole short, 5 to 6 mm in length, slightly winged with two sharp spurs at the base; color dark green when fresh, yellowish-brown on drying. Odor-indistinct, taste bitter. Flowers-sessile, 4 cm long, spike inflorescence, terminal, corolla light blue or violet; Fruit-capsule, ovoid–oblong, up to 3 cm long, compressed, apiculate, brown, shining [9, 10]. The color plate of *A.ilicifolius* is shown in Figure 1.

Traditional Medicinal Uses: *A.ilicifolius* is popularly recognized for its full scope of secondary metabolites and its traditional usage in Indian and Chinese systems of medicine. Folklore claims for this plant are as aphrodisiac, blood purifier, diuretic, for treatment of asthma, diabetes, dyspepsia, hepatitis, leprosy, neuralgia, paralysis, ringworm, rheumatism, skin diseases, snakebite, stomach pains, leucorrhoea, leukemia [11, 12]. The plant is used to prepare the Ayurvedic medicine known as Sahachara which is used for rheumatic complaints. In Thai traditional medicine, the plant is utilized as a purgative and as an anti-inflammatory; the leaves are dispensed with pepper (*Piper nigrum* L.) as tonic pills for longevity (aphrodisiac). It is also employed as an emollient fomentation for rheumatism and neuralgia. It is widely believed among mangrove dwellers that

Fig 1: Color plate of 1. *Acanthus ilicifolius* Linn; 2. Flowering stem; 3. Corolla with stamens and pistil; 4. Fruit.

Table 1: Phytochemicals of *A.ilicifolius*

Chemical Class	Name of the Compound
Aliphatic glycosides	Ilicifolioside B[38], Ilicifolioside C[47].
Alkaloids	Acanthicifoline[48], Trigonellin[49], 2-benzoxazolinone[29], Benzoxazin-3-one[50], 5,5'-bis-benzoxazoline-2,2'-dione[51], Benzoxazinoid glucosides[52], 4-O-b-D-glucopyranosyl-benzoxazolin-2(3H)-one[53], (2R)-2-β-D-glucopyranosyloxy-2H-1,4-benzoxazine-3(4H)-one, (2R)-2-β-glucopyranosyloxy-4-hydroxy-1,4-benzoxazine-3-one (21), 2-hydroxy-2H-1, 4-benzoxazin 3(4H) one[54].
Flavonoids	Quercetin, quercetin 3-O- β -D-glucopyranoside[49], apigenin 7-O- β -D-glucuronide, methylapigenin 7-O- β -D-glucopyranuronate[55-56], acacetin 7-O-α-L-rhamnopyranosyl-(1''' 6'')-O- β -D-glucopyranoside, vitexin[57].
Lignan glycosides	(+)-Lyoniresinol 3a-[2-(3,5-dimethoxy-4-hydroxy)-benzoyl]-O-β-glucopyranoside, dihydroxymethyl-bis (3,5-dimethoxy-4-hydroxyphenyl)tetrahydrofuran-9(or9')-*O*-β-D-gluco pyranosid, (8R,7'S,8'R)-5,5'-dimethoxylariciresinol 4-*O*-β-D-glucopyranoside, Acanfolioside, Alangilignoside C, (+)-syringaresinol-*O*-β-D-glucopyranoside[58] (+)-lyoniresinol 3α-O-β-D-glucopyranoside[41], (+)-lyoniresinol 2a-O-α-D-galactopyranosyl-3a-O-β-D-glucopyranoside, (+)-lyoniresinol 3a-O-α -D-galactopyranosyl-(1-6)-β-D-glucopyranoside[59], (-)-lyoniresinol 3α-O-β-D-glucopyranoside[60].
Megastigmane and phenolic glycosides	(Z)-4-coumaric acid 4-*O*- β -D-glucopyranoside, (Z)-4-coumaric acid 4-*O*- β -D-apiofuranosyl-(1''/2')-*O*- β -D-glucopyranoside[47], (6R,7E,9R)-9-hydroxy-megastigman-4,7-dien-3-one-9-O- β -D-glucopyranoside, (6S,7E,9S)-6,9-dihydroxymegastigman-4,7-dien-3-one-9-O-β-D-glucopyranoside[57], plucheoside B, 2,6-dimethoxy-p-hydroquinone 1-*O*- β -D-glucopyranoside, syringic acid *O*- β -D-glucopyranosyl ester[58], 5,11-epoxymegastigmane glucoside[61].
Phenylethanol glycosides.	Phenylethyl-O-b-D-glucopyranosyl-(1/2)-O-b-D-glucopyranoside, phenylethyl-O-b-D glucopyranoside [19], cistanoside F, isocistanoside F, cistanoside E, campneoside I, ilicifolioside A[38], ilicifolioside D[38,62], acteoside, isoacteoside[63].
Triterpenoids	α-L-Arabinofuranosyl-(1/4) - β -D-glucuronopyranosyl-(1_3) -3 β -hydroxylup-20(29)-ene, pentacyclic triterpenes, β –amyrin, α –amyrin[41], lupeol, oleanolic acid and ursolic acid[49,64].
Steroids	Cholesterol, campesterol, stigmasterol[50], β–sitosterol[49, 65], stigmast-7-en-3 β -ol, stigmasteryl β -D-glucopyanoside[50], 28-isofucosterol[66], octacosyl alcohol[50], β -sitosterol-3-O- β -D glucopyranoside, stigmasterol-3-O- β -D-glucopyranoside[54].
Fatty acid derivatives	Palmitic acid, octadecanoic acid, stigmasterol octadecanoate, β -sitosterol octadecanoate, tetracosanol, octacosanol[54].
Miscellaneous	(2R)-2-*O*-β-D-glucopyranosyl-4-hydroxy-*2H*-1,4-benzoxazin-3(4H)-one, (2R)-2-*O*-β-D-glucopyranosyl-7-hydroxy-*2H*-1,4-benzoxazin-3(4H)-one, 7-chloro-(2R)-2-*O*-β-D-glucopyranosyl-*2H*-1,4-benzoxazin-3(4H)-one[58], betaine, vanillic acid[63], luteolin-7-O-b-D-glucuronide, uridine, uracil[56].

chewing the leaves will protect against snake bite [13]. Tea brewed from the leaves relieves pain and purifies blood [11]. The root boiled in milk is largely used in leucorrhoea and general debility [14]. A decoction of the plant with sugar candy and cumin is used in dyspepsia with acid eructations. Leaves are bruised and soaked in water for external application and are also used as an expectorant. It is also considered to be a diuretic and it is used as a remedy for dropsy and bilious swellings [15].

Chemical Constituents: Phytochemical investigation of *A.ilicifolius* indicated the presence of glycosides, alkaloids, flavonoids, triterpenoids, steroids, fatty acid derivatives and saponins [16]. Phytochemicals of *A.ilicifolius* are shown in Table 1.

Biological Activities: Recently, many investigations on the biological activities of *A. ilicifolius* were conducted. A summary of the findings of these studies is presented below.

Anti Inflammatory Activity: Whole plant extract was reported to have analgesic and anti-inflammatory actions. Methanolic fraction of *A.ilicifolius* leaf extract produced significant and dose dependent inhibition of rat paw edema, when administered both prior to and after carrageenan administration. Its activity was similar to that of BW755C, a dual cyclooxygenase (COX) and lipoxygenase (LOX) inhibitor. Anti-inflammatory action was attributed to inhibition of COX/LOX enzymes along with significant suppression of cytokine generation. In addition, superior free radical trapping activity of components present in the leaf extract may have influenced its anti-inflammatory action [17]. Inflammation of gastrointestinal tract can affect performance of mucosal barrier, thereby compromising its protective activity. Methanolic extract of *A.ilicifolius* leaves significantly reduced formation of gastric lesions in rats caused by various ulcerogens such as acetylsalicylic acid, indomethacin, stress, ethanol and pylorus ligation. It also decreased the gastric volume, acidity and peptic activity and hence protects gastric mucosa [18]. 2-Benzoxazolinone (BOA) and benzoxazinoids [19] present in *A.ilicifolius* are identified as anti inflammatory agents [20]. Alkaloids of *A.ilicifolius* and their derivatives suppressed auricle edema induced by dimethylbenzene and reduced gastric mucosal damage in mice [21].

Antinociceptive Activity: The clinical management of chronic pain remains a challenge. Nowadays, antidepressant drugs are the first line treatment for chronic pain disorders such as diabetic neuropathy, postherpetic neuralgia, fibromyalgia, irritable bowel syndrome and interstitial cystitis [22]. Due to side effects associated with synthetic drugs, investigation of novel analgesic compounds from plant source is the inevitable outcome. Aqueous and alcoholic extracts of *A.ilicifolius* reportedly have analgesic and anti-inflammatory actions. Methanol extract of *A.ilicifolius* possess considerable antinociceptive activity on experimental laboratory animal. Analgesic activities of benzoxazolinone and its derivatives have been reported [20, 23], thus BOA may have contributed to analgesic activity of *A.ilicifolius*. Some 3-substituted BOA derivatives exhibit better analgesic activity than aspirin [20]. Alkaloids of *A.ilicifolius* significantly inhibited inflammatory pain in acetic acid induced mice model [21].

Anticancer Activity: Alcoholic extract of *A.ilicifolius* exhibited antioxidant [1, 24, 25] and anti-tumor activities [26]. It was found to be effective against tumor progression and carcinogen induced skin papilloma formation in mice. The free radical hypothesis supports that antioxidants can effectively inhibit carcinogenesis and observed properties may be attributed to antioxidant principles present in the extract [26]. Flavonoids and phenolic compounds of *A.ilicifolius* showed high anti oxidant activity in rats [27]. Aqueous leaf extract of *A.ilicifolius* prevents DNA alterations and provide chemopreventive effect on transplantable Ehrlich ascites carcinoma (EAC) - bearing murine model. It was beneficial at restoring haematological and hepatic histological profiles and at lengthening survival of animals against proliferation of ascites tumour *in vivo* [15]. Methanol extract of this plant was cytotoxic to Hela-KB cell line. Root callus of *A.ilicifolius* possessed potent chemoprotective, antimutagenic, antioxidant and anticancer effects against benzo(a)pyrene-induced cancer in Swiss albino rats. Petroleum ether and ethyl acetate fraction of the plant was effective against human carcinoma cell line-116 [28]. Methanol extract of *A.ilicifolius* flower and stem exhibited strong cytotoxicity against brine shrimp larvae [14, 25].

Hepatoprotective Activity: Methanolic extract of leaves exhibited hepatoprotective effect against acute dose of carbon tetrachloride (CCl_4) in rats [24]. 4-Hydroxy-2(3H) benzoxazolone (HBOA) is a naturally occurring compound that was isolated from *A.ilicifolius*. HBOA and its derivatives showed potent hepatoprotective effects against CCl_4-induced liver damage *in vivo* and they also protect against damage caused by oxidation of hepatic cellular membranes. This may be consequent to increased activity of antioxidant-defense system and inhibition of lipid peroxidation by phytochemicals of the plant [2].

Antiprotozoal Activity: 2-Benzoxazolinone was obtained from leaves of *A.ilicifolius* [29]. This compound exhibited significant anti-leishmanicidal activity against *Leishmania donovani* [30].

Antiasthmatic Activity: Ethanol root extract of *A.ilicifolius* was tested on isolated guinea pig tracheal-chain for its anti asthmatic activity. Histamine induced tracheal-chain was relaxed by the extract. It partially prevented anaphylactic shock induced in guinea pig by antigen injection. The extract also showed a brief, non-specific anti-spasmodic action on isolated tissues [31].

Antimicrobial Activity: *A.ilicifolius* possesses bioactive compounds that have potential for use as antibacterials [32]. Roots showed activity against leukemia virus in erythro leukemic Swiss mice. Alcoholic and chloroform extracts of leaves exhibited strong inhibitory action against *B.subtilis, S.aureus, C.albicans, A.fumigatus* and *A.niger* and moderate inhibitory action against *P.aeruginosa and P.vulgaris* [33]. Aqueous root, ethanol stem and methanol leaf extracts showed significant activity against *Bacillus megaterium, Lactobacillus plantarum, Salmonella paratyphi B, Shigella dycentreae, Escherichia coli, Streptococcus mutans, Klebsiella pneumoniae, Candida albicans, Aspergillus flavus, Staphylococcus albus, Lactobacillus acidophilus* [5]. n-Butanol fraction of *A.ilicifolius* leaves inhibited growth of *V. harveyi in vitro*. *A. ilicifolius* was potentially active against *Vibrio cholera, K. pneumonia* and *E. coli* [28]. Chloroform extract of leaves of *A. ilicifolius* showed systemic antifungal activity against *Aspergillus fumigates* infected mice [34]. Benzoate and phenylethanoid derivatives isolated from chloroform leaf extract elicited inhibitory activity against urinary tract infectious pathogens [35]. Chloroform extract showed maximum activity (MBC value: 0.5-3 mg/ml, MIC value: 2-4 mg/ml) against skin pathogens [36]. 2-Benzoxazolinone showed activity against some plant pathogens [37]. 2-Benzoxazolinone and benzoxazinium derivatives of *A.ilicifolius* exhibited phytotoxic, antimicrobial,

antifeedant, antifungal and insecticidal activities [3, 38, 39]. 6-Hydroxybenzoxazolinone, (Z)-4-coumaric acid 4-O-β-D-glucopyranoside and 3, 5-dimethoxy-4-hydroxy methyl benzoate were identified as the antibacterial compounds of *A.ilicifolius* [35].

Antidiabetic Activity: Ethanolic extract of *A.ilicifolius* has potent anti diabetic activity in Wistar rats [40]. The extract elicited significant reduction in blood glucose compared to glibenclamide. It also improved regeneration of β cells of pancreas, thus may be of value in diabetes treatment. HBOA and its derivatives have been reported as effective against Type 2 diabetes [2].

Osteoblastic Activity: Osteoblasts are bone-forming cells. MC3T3-E1 cells (osteoblast-like cell line) were used to study the effects of phytochemicals of *A.ilicifolius* leaves on differentiation of osteoblasts. These phytochemicals *viz* acteoside, isoacteoside and (+)-lyoniresinol 3a-*O*-β-glucopyranoside showed direct stimulatory effects on bone formation in cultured MC3T3-E1 osteoblast cells. Hence *A.ilicifolius* may play a role in treatment of osteoporosis [41].

Antioxidant Activity: Flavonoids and phenolic compounds that were isolated from *A.ilicifolius* showed high anti oxidant activity in rats [27]. The flower extract also showed antioxidant and cytotoxic effects [25]. Stem extract displayed significant free radical scavenging activity comparable to that of ascorbic acid [14]. Methanol flower extract showed highest efficiency at scavenging 2, 2-Diphenyl-1-picrylhydrazyl (DPPH) radicals [25]. Polysaccharides obtained from hot water extraction of *A.ilicifolius* showed good radical scavenging capacities [42]. *A.ilicifolius* was recently reported to have significantly lower antioxidant activities and condensed tannins than six other true mangrove species in mid- and low-tides in South China [8].

Hypercholesterolemic Activity: Stigmasterol is a common plant steroidal saponin which is abundantly present in *A.ilicifolius* [12]. It has structural similarity with cholesterol, thus competes with it leading to reduction of intestinal resorption of cholesterol and consequently, plasma cholesterol level [43-44].

Activity Against Neurological Disorders: Alzheimer's disease (AD) is characterized by extracellular deposition of amyloid-β (Aβ) in brain. Cholesterol increases Aβ generation by directly activating β - and γ-secretase enzyme activity and by elevating gene expression of β - and γ –secretase. Stigmasterol reduces amyloidogenic processing of amyloid precursor protein, suggesting that stigmasterol might be beneficial for AD [44]. Since stigmasterol is abundantly present in *A.ilicifolius,* the plant offers promise for management of AD. BOA is used extensively as a central nervous system depressant, it exhibits hypnotic activity. 2-Amino-5-chlorobenzoxazole is a potential spinal cord depressant agent [45].

Future Research Directions: Compound Sea Holly Capsules (*A.ebracteatus*) is a certified product of Ministry of Public Health Thailand and has been indicated for relief of allergies and rashes. However, there is a scarcity of scientific evidence to establish safety or to support folklore claims for this mangrove plant. Structural analogs of 2-benzoxazolinone, a phytochemical of *A.ilicifolius,* have been claimed for weight loss, anoretic, mood enhancing property and as adjunctive in therapy for arthritis, sleep dysfunction, fibromyalgia and hyperglycemia [46]. Development of single herb formulations consisting of a full spectrum standardized herbal extract with established safety and efficacy studies conducted in accordance with scientific principles for above disorders could integrate use of this mangrove plant into clinical practice.

CONCLUSION

A survey of the literature revealed that *A.ilicifolius* is an important medicinal plant with diverse pharmacological effects. This plant shows presence of many phytochemicals which are responsible for pharmacological and medicinal activities. Further studies on *A.ilicifolius* are warranted to explore concealed areas to support clinical applications for betterment of health and to uncover bnefits of a hithertho undiscovered mangrove plant.

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