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Traditional Use, Phytochemistry, Pharmacological and Toxicological Properties of *Acanthus ilicifolius*: A Review

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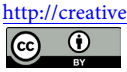


Abstract

The practice of plants for the deterrence and management of innumerable physiological states and diseases dates back to the history of humankind. Although many of today's medicinal yields are achieved synthetically, they are often modelled on the chemical composition of medicinal plants. In this accordance, Acanthus genus (Family Acanthaceae) has acknowledged considerable attention due to its wide range of secondary metabolites and its customary usage in Indian and Chinese system of medicine. It is worth to mention that *A. ilicifolius* is enormously medicinal among all the species of Acanthus genus. This plant is considered to be rich sources of steroids, triterpenoids, saponins, flavonoids, alkaloids, and tannins. Traditionally, the plant has been used for asthma, diabetes, dyspepsia, hepatitis, leprosy, neuralgia, paralysis, ringworm, skin disease, snake bite, leukemia. Toxicological investigation in mice model has showed that, the ethanolic extract of the leaves of this plant have no toxic effect up to dose of 1000 mg/kg BW, 2000 mg/kg BW dose have mild toxicity and 5000 mg/kg BW dose have caused toxic effect in some organ system like liver, heart, pancreas, lung and kidney. Different extract of this plant also exhibited Anti-inflammatory, anti-leishmanial, osteoblastic, hepatoprotective, antioxidant and anticancer activities. This review article is an endeavor to cover current expansion in phytochemical and pharmacological potential of this plant species which will be a good reference tool for investigators who wish to work on natural products.

Keywords

Acanthus, Acanthaceae, *Acanthus ilicifolius*, Anti-Cancer, Hepato-Protective Effect

1. Introduction

Serendipity and man's expedition for the drug in nature inaugurated the discovery of medicines. Nature has been an incredible cradle of medicinal agents since ages where a striking number of modern drugs have been isolated from natural sources, many of these derivations were grounded on the utilization of the agents in traditional medicine [1]. Since a long, plants have been exploited as medicines. Medicinal plant-based drug discovery continues to give new and novel therapeutics/lead compounds against various ailments like cancer, HIV/AIDS, Alzheimer, malaria, pain etc. [2]. Whole plant or plant parts basically gripped the system of crude drugs for instance tinctures, teas, poultices, powders, and other herbal formulations [3]. Traditional medicines encompass herbal medicines poised of herbs, herbal resources, herbal groundings, and finished herbal yields, that enclose as active ingredients parts of plants, or other plant supplies, or combinations thereof. Animal parts and minerals are also a part of traditional medicines [4]. The majority of the evolving world, 80% of the residents trust on these traditional medicines for major health care [5].

Acanthus that belongs to family Acanthaceae is a genus of the topmost group angiosperms (flowering plants) embracing more than 29 species extensively disseminated in the tropical and subtropical region [6]. The term "Acanthus" is picked from the Greek word "Acantha" which means thorn or thistle indicates sensitive leaves. **Acanthaceae**, one of 24 families in the mint order (Lamiales) of flowering plants, containing approximately 220 genera and nearly 4000 species distributed predominantly in tropical and subtropical regions of the world. The greater part of the Acanthaceae family are herbs or shrubs, but vines and trees occur as well [7]. The range of habitats extends from marshes and estuaries to extremely dry situations, but most of these plants are found in damp tropical forests. A diverse family, Acanthaceae has few universal characteristics among its members. Most have simple leaves arranged in opposite pairs, with cystoliths (enlarged cells containing crystals of calcium carbonate) in streaks or protuberances in the vegetative parts. The bisexual flowers are frequently bilaterally symmetrical and are usually enclosed by leaflike bracts, often colored and large. Sepals and petals number five or four each and are often fused into tubular structures [8].

Acanthus ilicifolius (**Figure 1**), also identified as sea holly, holly mangrove, or holly-leaved acanthus, are conventionally used in Indian and Chinese medicine. These mangroves belong to the Acanthaceae family and are 1.5 m tall vines. Conferring to Indian Ayurveda, the uses of *A. ilicifolius* species are convenient as nerve tonic, astringent, stimulant, and expectorant. The roots of *Acanthus ilicifolius* are highly indicated for the treatment of cough, asthma, leucorrhea, and paralysis. The roots and leaves are indicated against the bites of animals and insects. The mucilage of leaves aids in managing neuralgia and rheumatism [9].

2. Methods

Scientific literatures were searched using databases like Google Scholar, PubMed,

Figure 1. *Acanthus ilicifolius*.

ScienceDirect, Research Gate for traditional use, phytopharmacology and toxicology of the *Acanthus ilicifolius* and its pahamcological and therapeutic properties are briefly discussed in this paper.

2.1. Notable Species of Acanthus Genus

Among 29 representative species of the Acanthus genus, around six species are available in India cited *A. ebracteatus Vahl*, *A. leucostachyus Wall*, *A. carduaceus Griff*., *A. mollis L*., *A. volubilis Wall*. Asia and Australia represent the overriding variety and distribution of mangrove species. Consequently, the genus is inimitable amid all true mangrove genera where together true mangrove and terrestrial associates are accessible. The two subspecies of *A. ebracteatus A. ebracteatus* subsp. ebracteatus and *A. ebracteatus* subsp. *ebarbatus* are prevalent in Australia. Additionally, both subspecies are standing apart by few key structural features *i.e.* leaf outline, stem spines, floret shade and hairiness, etc. The genus was testified with one acknowledged species; *A. leucostachyus* from North East India which was formerly recognized by Wallich in his Numerical List of Dried Specimens (Cat. No. 2512) on the source of the assortment made by F. De Silva from Sylhet District of Bangladesh [7].

2.2. Phytochemical Work of *Acanthus ilicifolius*

Different categories of chemical constituents have been sequestered and categorized from *Acanthus ilicifolius*. Ethanolic, Methanolic, Chloroform, Hexane extracts of different parts of the plant like root, leaves, aerial parts, stem, pods have been found to encompass diverse chemical moieties e.g., alkaloids, glycosides, lignans, triterpenoid saponins, sterols, fatty acids, and coumaric acid derivatives as summarized in Table 1 & Table 2.

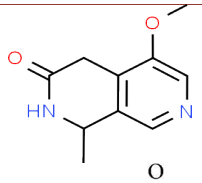
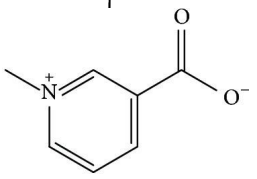
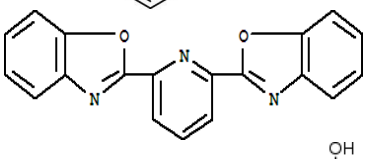
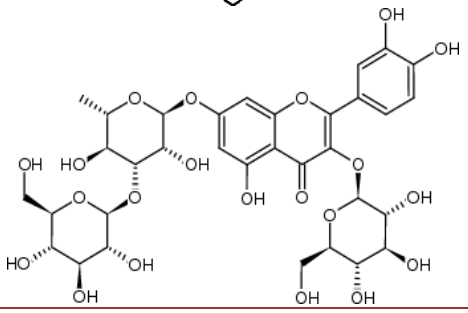
2.3. Pharmacological Potential of *Acanthus ilicifolius*

Anti-Inflammatory Activity

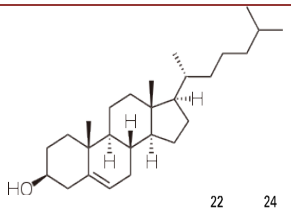
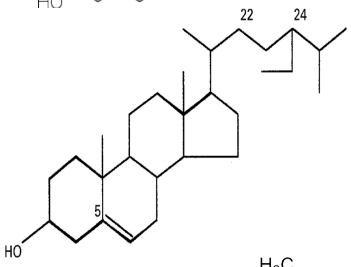
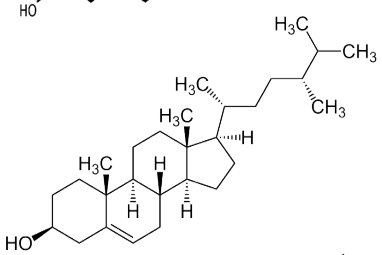
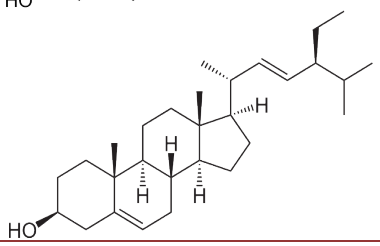
Table 1. Phytochemistry of *Acanthus ilicifolius*.

Plant part	Type of extract	Compounds isolated	Reference
Powdered plant material	Ethanolic extract	Alkaloid-Acanthicifoline	[10]
Root	Ethanolic extract	Triterpenoid saponin	[10]
Leaves	Aqueous Methanolic extract	2-benzoxazolinone	[11]
Leaves	Chloroform extract	Pentacyclic triterpenoids and sterols	[12]
Leaves	Ethanolic extract	Methyl apigenin 7-o-β-D-glucuronate-Flavone glycosides	[13] [14]
Leaves	Methanolic extract	Bisoxazolinone	[12]
Aerial part	Methanolic extract	Lignan and Cyclolignan glycosides	[14]
Pods	Methanolic extract	1,4-benzoxazinone	[15]
Dried aerial part	Methanolic extract	Benzoxazinoid glucosides	[14]
Dried aerial part	Ethanolic extract	Aliphatic alcohol glycoside-ilicifolioside C and two Z-4-coumaric acid glycosides	[16]
Stem	Hexane extract	Homologous series of 15 saturated odd and even fatty acids	[16]

Table 2. Compounds Isolated from *Acanthus ilicifolius*.

Class	Name of the phytoconstituents	Compound structure	PubChem ID	References
Alkaloids	Acanthicifoline		442503	[10]
	Trigonellin		5570	[10]
	5,5'-bis-benzoxazoline 2,2'-dione		136846167	[10]
Flavonoids	Quercetin-3-O-β-D-glucopyranoside		15959354	[10]

Continued

Steroids	Cholesterol		5997	[17]
	β–sitosterol		222284	[10]
	Campesterol		173183	[17]
	Stigmasterol		5280794	[17]

The methanolic extract of *Acanthus ilicifolius* plant leaf was tested for analgesic activity in mice in dosage of 1 to 100 mg/kg i.p. The extract showed graded analgesic activity ranging from 42.8% to 85.7% in the tail clip method. The extract displayed substantial anti-inflammatory activity in case of carrageenan-induced edema at 5 mg/kg i.p in rats. In acute toxicity test, the extract did not demonstrate any case of mortality in mice at doses up to 1 g/kg I [16].

Anti-Leishmanial Activity

A compound named 2-Benzoxazolinone (BOA) was extracted from the leaves that exposed in vitro anti-leishmanial activity against *Leishmania donovani.* There was no case of mortality in mice when BOA was administered (i.p.) in the doses ranging from 0.25 - 1 g/kg. The LC_{50} value for BOA was observed to be 40 μg/ml and compared well with pentamidine [15].

Osteoblastic Activity

A derivative of coumaric acid named acancifoliuside was secluded from the methanolic extract of the leaves. Its effects were tested on the functions of Osteoblastic MC3T3-E1 cells. It augmented the growth and differentiation of osteoblasts expressively, designating that *A. ilicifolius* leaves may aid to prevent osteoporosis [18].

Hepatoprotective Activity

A significant reduction of CCl4-induced hepatotoxicity was observed followed by the oral administration of the alcoholic extract (250 and 500 mg/kg) in rats as judged from the serum and tissue activity of marker enzymes. The results were comparable with those obtained with curcumin 100 mg/kg, P.O. [19].

Anti-Cancer Activity

According to Babu BH, alcoholic extract of *A. ilicifolius* (250, 500 mg/kg body weight) was found to be effective against tumor progression and carcinogen induced skin papilloma formation in mice. The extract was observed to exhibit cytotoxic activity towards lung fibroblasts (L-929) cells in 72 h MTT assay, and the concentration needed to cause 50% cell death was about 18 μg/ml. Furthermore, the tumor volume reduced and the life span by 75% in ascites tumor harboring animals followed by the oral administration of the extract (500 mg/kg body wt). The extract also pointedly delayed the onset of dimethyl benzanthrazene/croton oil-induced skin papilloma in mice in a dose-dependent manner [19].

Anti-Ulcer Activity

Methanol extract of *Acanthus ilicifolius* leaves in experimental rats demonstrated significant inhibition of gastric lesions induced by pylorus ligation and ethanol-induced gastric ulcers. The extract displayed significant lessening in the gastric volume, free acidity, and ulcer index as compared to control. This recommends leaf methanolic extracts were found to hold anti-ulcerogenic as well as ulcer healing properties, which might be owing to anti-secretary activity [20].

Anti-Microbial Activity

Khajure *et al* investigated the antimicrobial activity of the extracts of *Acanthus ilicifolius* demonstrated that the anti-microbial activity of alcoholic, butanolic, and chloroform extracts of leaves and roots of the plant *A. ilicifolius*. In that study, Ampicillin and clotrimazole were used as standard anti-bacterial and anti-fungal agents, respectively. The end result of the study discovered that the alcoholic and chloroform extract of the leaves unveiled robust inhibitory action against *Bacillus subtilis*, *Staphylococcus aureus*, *Candida albicans*, *Aspergillus fumigatus*, and *Aspergillus niger* and moderate inhibitory action against *Pseudomonas aeruginosa* and *Proteus vulgaris* [21].

Antioxidant Activity

Firdaus *et al.* have inspected the antioxidant properties of *A. ilicifolius* by the DPPH scavenging assay. The test was piloted on entire five extracts (methanol, acetone, acetone 70%, methanol 80% and water) of flowers where the extracted methanol exhibited maximum antiradical effectiveness (141.30%), whereas water extract of indicated lowermost (0.0037%) amid the extracts [22]. Flavonoids and phenolic compounds extracts of *A. ilicifolius* presented their good antioxidant activity on the animal model [23].

Cytotoxic Activity

Firdaus *et al.* investigated the cytotoxic action of the flower extracts of A. ilicifolius on the brine shrimp lethality. The outcomes revealed methanol extract has nethermost LC_{50} value (22 μg/ml) while water extract exposed the peak value

at 10 µg/ml amongst the extracts [22].

Table 3 summarized the pharmacological properties of *A. ilicifolius*.

Table 3. Pharmacological potential of *Acanthus ilicifolius*.

Type of activity	Part used	Extract	Dose	Model	Key result	Ref
Anti-inflammatory activity	Leaves	Methanolic extract	1 to 100 mg/kg i.p.	*In vivo*	Significant inhibition of rat paw edema.	[16]
			5 mg/kg i.p.	*In vivo*	Substantial anti-inflammatory activity in case of carrageenan-tempted edema in rats.	[16]
Anti-leishmanial activity	Leaves	2-Benzoxazolinone (BOA)	0.25 - 1 g/kg i.p.	*In vitro*	Anti-leishmanial activity against Leishmania donovani.	[15]
Osteoblastic activity	Leaves	Methanolic extract		*In vivo*	Increased the growth and differentiation of osteoblasts significantly, indicating that A. ilicifolius leaves may help to prevent osteoporosis.	[18]
Hepatoprotective activity	Leaves	Alcoholic extract	250 and 500 mg/kg	*In vivo*	Significantly reduced CCl4-induced hepatotoxicity in rats.	[19]
Anticancer activity	Leaves	Alcoholic extract	250, 500 mg/kg	*In vivo*	Effective against tumor progression and carcinogen induced skin papilloma formation in mice, in reduction of tumor volume & cytotoxic against lung fibroblast cells in mice.	[19]
Antiulcer activity	Leaves	Methanolic extracts	doses of 100, 20 mg/kg body weight	*In vivo*	Significant inhibition of gastric lesions induced by pylorus ligation and ethanol-induced gastric ulcers.	[20]
Antimicrobial activity	Leaves, stem, and root	Ethanol, methanol, and aqueous extracts	10 mg/ml	*In vitro*	Strong inhibitory action against *Bacillus subtilis*, *Staphylococcus aureus*, *Candida albicans*, *Aspergillus fumigatus*, and *Aspergillus niger* and moderate inhibitory action against *Pseudomonas aeruginosa* and *Proteus vulgaris.*	[21] [24]
Cytotoxic activity	Flowers	Methanolic crude extract	LC50 value at 60 µg/ml and LC90 value at 120 µg/ml	*In vitro*	Cytotoxic activity.	[22]
Antioxidant activity	Flowers	Methanol extract, acetone, acetone 70%, methanol 80% and water	500 µg/ml to 0.98 µg/ml. IC50 was recorded 5.1 µg/ml.	*In vitro*	free radical scavenging activity.	[23]
	Leaves	Alcoholic Extract	IC50 of 550 µg/ml, 2750 µg/ml, 600 & 670 µg/ml	*In vitro*	Inhibition of formation of oxygen derived free radicals, superoxide radicals, nitric oxide radical.	[23]

2.4. Toxicological Studies of *Acanthus ilicifolius*

Acute Toxicity

According to Husori *et al.*, all male mice groups showed no symptoms of toxicity after the administration of ethanolic extracts if *Acanthus ilicifolius* leaves at the doses of 1000, 2000 and 5000 mg/kg body weight. At the maximum dose, there was no death in the acute toxicity experimental animal. The above-mentioned dose did not change in general behavior or any clinical signs of toxicity [25].

Effect on Liver

Husori *et al.* investigated the effect on liver by histopathological examination in mice by administering the ethanolic extract of *Acanthus ilicifolius* leaves at different doses. While in the group dose of 1000, 2000, and 5000 mg/kg BW, the hepatocytes initiated to experience deviations marked by the amplified infiltration of inflammatory cells, asymmetrical sinusoidal arrangement and noticeable broadening of the cell to further cover the sinusoid, but the hepatocyte has not necrosis. Infiltration of inflammatory cells did not occur in the control group, but at a dose of 1000 mg/kg BW began to be found mild infiltration and at a dose of 2000 mg/kg BW augmented infiltration of inflammatory cells and at doses of 5000 mg/kg BW severe infiltration and had formed the thrombus [25].

Effect on Kidney

In a study of ethanolic extract of the leaves of *Acanthus ilicifolius* at the dose of 1000 mg/kg BW, showed the occurrence of mesangial cell proliferation but has not shown hypertrophy of glomerular tissue. But the dose of 2000 mg/kg BW showed hypertrophy of the glomerular tissue and at doses of 5000 mg/kg BW had increased the proliferation of mesangial cells, Bowman's capsule, narrowing of tubular lumen due to enlarged cells [25].

Effect on Pancreas

The pancreas is an essential glandular organ in the body comprising of exocrine and endocrine tissues, exocrine part consists of pancreatic acinar cells that secrete enzymes into the duodenum and the endocrine region composed of Langerhans island excrete enzymes directly into the blood [26]. In a study of the ethanolic extract of the leaves, at the dose of 2000 and 5000 mg/kg BW showed that, the glands around the Langerhans island begun to swell [25].

Effect on Heart

Ethanolic extract of the leaves of *Acanthus ilicifolius* at the dose of 1000 mg/kg BW had showed no abnormality, but at the dose of 2000 mg/kg BW, had showed necrosis in heart muscle and at the dose 5000 mg/kg BW, had occurred necrosis and fatty tissue infiltration [25].

Effect on Lung

The histologic feature of the lung after administration of ethanolic extract of the *Acanthus ilicifolius* leaves appeared normal. While the dose of 2000 mg/kg BW has begun thickening of the bronchial epithelium. While the dose of 5000 mg/kg BB occurs of epithelial cells damage. The results of this study indicated that the, dose up to 1000 mg/kg BW remains safe, dose of 2000 mg/kg BW cause

some damage in lung tissue and dose of 5000 mg/kg BW cause toxicity on the lung tissue [25].

The toxicological effect of the *Acanthus ilicifolius* is summarized in Table 4.

2.5. Ethnomedicinal Use of *Acanthus ilicifolius*

This plant is used to formulate Ayurvedic medicine known as Sahachara used to treat for rheumatic diseases. In Thai Traditional Medicine System, the plant is used as purgative and as an anti-inflammatory, the leaves are mixed with pepper (*Piper nigrum* L) as tonic pills. It is also employed as an emollient for rheumatism and neuralgia [27]. It is believed among mangrove habitats that chewing the leaves cause protect against snake bites [28]. Tea prepared from the leaves relieves pain and purifies blood [29]. A decoction of the plant with sugar candy and cumin is used in dyspepsia with acid eructation. Leaves are pounded and

Table 4. The toxicological effect of the *Acanthus ilicifolius*.

Part of the plant	Extract	Affected organ	Model	Dose	Key result	Reference
Leaves	Ethanolic Extract	Liver	*In vivo*	1000 mg/kg	Mild infiltration of inflammatory cells.	[25]
			In vivo	2000 mg/kg	Increased infiltration of inflammatory cells.	
			In vivo	5000 mg/kg	Severe infiltration of inflammatory cells.	
Leaves	Ethanolic Extract	Kidney	*In vivo*	1000 mg/kg	A dose of 1000 mg/kg BW already shows the occurrence of mesangial cell proliferation but has not shown hypertrophy of glomerular tissue.	[25]
				2000 mg/kg	The dose of 2000 mg/kg BW already shows hypertrophy of the glomerular tissue.	[25]
				5000 mg/kg BW	At doses of 5000 mg/kg BW has increased the proliferation of mesangial cells, Bowman's capsule, narrowing of tubular lumen due to enlarged cells, and visible tubular damage.	
Leaves	Ethanolic Extract	Pancreas	*In vivo*	2000 & 5000 mg/kg	In the treatment of doses of 2000 and 5000 mg/kg BW has appeared that the glands around the Langerhans island begun to swell. Cell changes caused by substances that have the cytotoxic effect are the reduction of the Langerhans islands, the reduction of β-cell counts, degranulation, and vacuolization of these cells.	[25]
Leaves	Ethanolic Extract	Heart	*In vivo*	2000 mg/kg & 5000 mg/kg	A dose of 2000 mg/kg BW has begun to show an abnormal cell nucleus that was necrosis. While at a dose of 5000 mg/kg BW has occurred of necrosis and fatty tissue infiltration.	[25]
Leaves	Ethanolic Extract	Lung	*In vivo*	1000 mg/kg, 2000 mg/kg & 5000 mg/kg	The dose of 1000 mg/kg BW still appears normal. While the dose of 2000 mg/kg BW has begun thickening of the bronchial epithelium. While the dose of 5000 mg/kg BB occurs of epithelial cells damage.	[25]

soaked in water for external application and also used as an expectorant [30]. Traditional medicinal practitioners claim that this plant is useful in the treatment of asthma, diabetes, dyspepsia, hepatitis, leprosy, neuralgia, paralysis, ringworm, skin disease, snake bite, leukemia [27].

3. Conclusion

The plants belonging the genus Acanthus are extensively sprinkled in the tropical and subtropical provinces of the globe. The methodical pharmacological studies regarding *Acanthus ilicifolius* have assumed incredible appreciation to their ethnomedicinal uses in the management of health care. Study of the literature revealed that, *Acanthus ilicifolius* is an important medicinal plant with diverse pharmacological activities. Additionally, scanty and inadequate toxicological information on the animal model is currently existing, which proposes that meticulous toxicological estimation is needed for different extracts of different parts of this plant. Furthermore, the biological efficacy studies should be conducted for the extracted secondary metabolites as well, which could validate the remedial claims of *Acanthus ilicifolius.*

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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