REVIEW ARTICLE

Phytochemistry, traditional uses, and pharmacological activities of *Azima tetracantha* Lam. (Salvadoraceae) - An updated review

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Abstract

Plants form an integral part of daily life of human beings. The term ethnobotany refers to relationships and interactions between people and plants. Worldwide, plants are being used as sources of food, medicine, dyes, and timber. Traditional medicinal practitioners and indigenous systems of medicine (such as Ayurveda, Siddha and Unani) make use of several plant species to treat a range of ailments of humans and livestock. The therapeutic potential of plants lies in the presence of secondary metabolites such as alkaloids, terpenes, and polyphenolic compounds. *Azima tetracantha* Lam., belonging to the family Salvadoraceae, is a small, armed shrub with quadrangular branches. The present review is a compilation of available data on the ethnomedicinal uses, phytochemistry, and pharmacological activities of *A. tetracantha*. Phytochemical investigations on the plant revealed the presence of chemicals such friedelin, euphanol, gallic acid, genstisic acid, cinnamate, ferulic acid, azimine, azcarpine, and carpaine. An extensive literature survey was carried out to compile data on traditional uses, phytochemicals, and the pharmacological activities shown by *A. tetracantha*. It is evident from the literatures that the plant is versatile with respect to its traditional uses as a remedy for various illnesses and disorders in humans and animals. The plant is used for treatment of asthma, cold, cough, rheumatism, diabetes, dysentery, fever, toothache, dog bite, snake bite, and liver diseases. It is experimentally shown that the plant exhibits pharmacological activities such as antimicrobial, antioxidant, anti-inflammatory, cytotoxic, antivenom, hepatoprotective, antiepileptic, diuretic, antiulcer, antiasthmatic, antidiarrheal, analgesic, nephroprotective, antipyretic, and insecticidal activity. The nanoparticles synthesized from *A. tetracantha* have shown antimicrobial, antioxidant, and insecticidal properties. A pentacyclic triterpenoid friedelin isolated from the plant is shown to exhibit many bioactivities such as antimicrobial, hypolipidemic, antidiarrheal, anti-inflammatory, antipyretic, insecticidal, gastroprotective and antiradical activity. The therapeutic potential and pharmacological properties of *A. tetracantha* could be ascribed to the presence of a wide array of phytochemicals in it. The pharmacological activities of the plant reported justify the traditional use of *A. tetracantha* in treating several diseases or disorders.

Key words: *Azima tetracantha*, ethnobotany, pharmacological activities, phytochemistry, secondary metabolites, traditional uses

INTRODUCTION

Since time immemorial, plants have been used by people for various purposes such as food, medicine, timber, dyes, clothes, certain ritual practices, and for income generation. Parts such as leaves, tubers, fruits, seeds, stems, and flowers of some plant species have been utilized as main ingredients in some foods. Some plant species are utilized as they contribute to aroma and flavor. Plants form an integral part of traditional medicine which mainly focuses on the utilization of medicinal plants for therapy against dreadful diseases. It is estimated that around 70–80% of world's population (in developing and underdeveloping countries and especially those living in

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remote areas) depends on traditional medicine for primary healthcare. The term ethnobotany refers to relationship between man and plants and is a rising subject now. Often, most of the ethnic tribes use plants as indicator for predicting annual seasons. Traditional medicinal practitioners possess a vast knowledge on the medicinal uses of plants which are passed orally from one generation to next generation. Plants, singly or in certain formulations, are widely used in many indigenous systems of medicine such as Ayurveda, Siddha, and Unani and information on the role of plants in the treatment of diseases is mentioned in several classical texts. Plants are known to be rich reservoirs of a variety of chemicals (termed as phytochemicals) and provide leads for synthesis of numerous drugs. Bioactive compounds such as morphine, vincristine, vinblastine, taxol, quinine, colchicine, caffeine, camptothecin, artemisinin, nicotine, reserpine, digoxin, atropine, berberine, codeine, and solamargine are from plant origin. It is shown that extracts and purified metabolites (such as polyphenolic compounds, alkaloids, and terpenes) from plants exhibit a range of bioactivities such as antimicrobial, antioxidant, anti-inflammatory, and anticancer activity.[1-19] The genus *Azima* Lamarck (Salvadoraceae) includes shrubs with axillary thorns. In the present review, an attempt is being made for compiling data on the phytochemistry, ethnomedicinal uses, and biological activities of *Azima tetracantha* Lam.

DISTRIBUTION AND BOTANICAL DESCRIPTION

A. tetracantha [Figure 1] is a scandent, armed, small shrub (reaching about 2 m) with quadrangular branches. Thorns are four in number, axillary, strong, and straight. Leaves are simple, opposite, 2.5–4.0 × 1.5–2.0 cm, subsessile, elliptic-ovate with acute apex and entire margin. Flowers are unisexual, pale yellow, in axillary cluster, passing into terminal interrupted spike. Calyx, corolla, and stamens are 4 in number and free. Fruit is a berry, globose in shape, 6 mm across, 1–2 seeded, and edible. Flowering and fruiting occur between March and August. The plant is found distributed in India, tropical Africa, Madagascar, Philippines, and Sri Lanka. In India, the plant is distributed in states such as Karnataka, Kerala, Maharashtra, Tamil Nadu, Orissa, and West Bengal. The plant is frequent in drier parts of Karnataka such as Bengaluru, Kodagu, Tumkur, Kolar, Davangere, Kolar, Gulbarga, Bellary, Chitradurga, Hassan, and Mysore. The plant is known by names such as Mistletoe berrythorn and Needle bush in English, Kundali in Sanskrit, kantagurkamai in Hindi, Mulchangan in Siddha/Tamil, Shankunkuppi in Malayalam, tella uppi in Telugu, and Yessagale and Biliuppina gida in Kannada. It is often grown for medicinal and ornamental purposes and also as a fence. The plant is reported to have many medicinal uses as evidenced by its use in several parts of the world. Root is diuretic and is used in Siddha medicine for rheumatism and dropsy. Leaves are stimulants, expectorant and used in cough, asthma, and rheumatism. Bark is astringent, expectorant, and antiperiodic.[20-24]

Figure 1: (a and b) *Azima tetracantha* Lam.

PHYTOCHEMISTRY OF *A. TETRACANTHA*

The chemical compounds present in plants are known phytochemicals and their study is called phytochemistry. The plant *A. tetracantha* is shown to contain a variety of phytochemicals which are distributed in various parts of the plant. Techniques such as standard phytochemical tests, gas chromatography-mass spectrometry (MS), High-performance liquid chromatography, liquid chromatography–MS and other chromatographic techniques, spectral analyses such as nuclear magnetic resonance and infrared have been employed by various researchers to identify chemicals or phytochemical groups present in different parts of the plant. The seed oil is shown to contain ricinoleic acid and cyclopropenoid fatty acids along with normal fatty acids.[25] It is shown that roots and seeds contain high concentrations of N-methoxy-3-indolylmethyl-glucosinolate while its content is lower in the stems and young leaves. The roots also contain another indole glucosinolate (N-hydroxy-3-indolymethyl-glucosinolate). The roots, stems, and leaves contain neoascorbigen, a condensation product of N-methoxy-indole-3-carbinol and ascorbic acid. The seeds contain a complex mixture of 26 flavonoids predominantly as glycosides and acyl-glycosides, with traces of aglycones. The dimeric piperidine alkaloids azimine, azcarpine, and carpaine were detected in all tissues.[26] Gayathri *et al*.[27] isolated a triterpenoid compound from hexane fraction of methanol extract of leaves of *A. tetracantha*. On the basis of spectral data, the compound was identified as friedelin. In another study, Kavitha and Sandhiya[28] isolated a triterpene compound from chloroform extract of leaves of *A. tetracantha* by column chromatographic technique. The spectral details identified the compound as euphol. Table 1 shows phytochemicals that have been detected by various methods in different parts of *A. tetracantha*. Structures of some of the compounds isolated from *A. tetracantha* are shown in Figure 2.

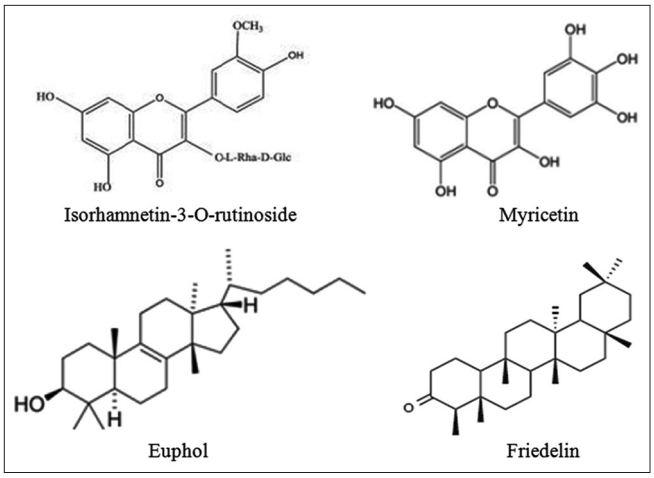

Figure 2: Structures of some compounds identified in *Azima tetracantha*

NUTRITIVE COMPOSITION OF LEAVES OF *A. TETRACANTHA*

Gayathri *et al*.[45] evaluated nutritional composition of leaves of *A. tetracantha*. Potassium and manganese were detected in highest quantity among major and minor elements. An appreciable quantity of carbohydrates, proteins, and lipids were detected in the leaf material. The content of Vitamin C was highest when compared to Vitamin E.

A. TETRACANTHA AS FOOD FOR ANIMALS

Studies have shown that certain parts such as fruits and leaves of *A. tetracantha* are consumed by some animals. The fruits of *A. tetracantha* are consumed as food by yellow baboon *Papio cynocephalus* in Amboseli National Park, Kenya.[46] The study of Rao *et al*.[47] revealed that the leaves of *A. tetracantha* formed one of the food sources for grizzled giant squirrel *Ratufa macroura*.

ETHNOMEDICINAL USES OF *A. TETRACANTHA*

A. tetracantha is a versatile plant with respect to its extensive use for the treatment of human as well as veterinary illnesses. Studies have shown that various parts of the plant, in particular leaf and root, have been used for the preparation of formulations that have been used in traditional medicine. The root of *A. tetracantha* is used by herbal vendors in South India as a component in the herbal formulation called Pilavaikkalimbu which is applied externally on the tumors.[48] In Siddha system of medicine, the plant is indicated for respiratory illness including pulmonary tuberculosis.[49] The root of *A. tetracantha* is a component in a Siddha polyherbal formulation Parangichakkai Choornam which is used to treat several ailments.[50] The leaves of *A. tetracantha* are used traditionally for medicinal purposes by rural households in the Mahafaly region of semi-arid SW-Madagascar.[51] In Dharwad district of Karnataka, India, the plant is used in the treatment of treatment of toothache.[52] Table 2 shows the ethnomedicinal uses of different parts of *A. tetracantha* to treat several human and veterinary ailments.

BIOLOGICAL ACTIVITIES OF *A. TETRACANTHA*

The plant *A. tetracantha* is shown to exhibit a wide range of biological activities such as antimicrobial, hepatoprotective, anti-arthritic, nephroprotective, antiulcer, hypolipidemic, antioxidant, analgesic, anti-inflammatory, antipyretic, diuretic, antiepileptic, and antivenom activity. A brief description on the biological activities displayed by various parts of the plant is shown below.

Antiquorum Sensing Activity

Tilton *et al*.[78] studied antiquorum-sensing potential of hexane, ethyl acetate, and ethanol extract of leaves of *A. tetracantha* by inhibition of the violace in the production of *Chromobacterium violaceum*. Hexane and ethyl acetate extracts were shown to exhibit antiquorum-sensing property while ethanol extract lacked the property.

Antiepileptic Activity

Eerike *et al*.[79] evaluated antiepileptic activity of ethanol extract of root of *A. tetracantha* by maximal electroshock and pentylenetetrazole-induced seizures in mice. In maximal electroshock model, the extract caused reduction in the duration of hind limb extension and showed marked seizure protection. In pentylenetetrazole-induced seizure model, the extract caused delay in the onset of clonic phase and prevented death in 50% of animals in the group treated with 500 mg/kg extract.

Hepatoprotective Activity

Ekbote *et al*.[80] determined hepatoprotective activity of chloroform and ethanol extract of *A. tetracantha* leaves by CCl_4-induced hepatotoxicity in rat model. It was observed that oral administration of extracts for 12 days significantly restored normalization of serum enzyme levels. The hepatoprotection was also supported by histopathology of treated animals. Overall, ethanolic extract was shown to exhibit significant hepatoprotective activity. The study carried out by Sowmya and Nagarajan[81] revealed hepatoprotective activity of *A. tetracantha* leaf powder on ferrous sulfate-induced liver toxicity in albino rats. Prakash *et al*.[82] screened aqueous extract of *A. tetracantha* leaf for

Table 1: Chemicals/phytochemical groups detected in *A. tetracantha*

Plant part	Solvent extract	Type of analysis	Some of the compounds/ phytochemical groups identified	Reference
Leaf	Methanol	GC-MS	Myristic acid, cis-13-eicosenoic acid, ascorbic acid, heptadecanoic acid, icosanoic acid, pentadecanoic acid, oleic acid and others	Rani and Murugaiah[29]
Leaf	Ethanol	GC-MS	5-methyl-2-furancarboxaldehyde, maltol, benzyl chloride, benzoic acid and others	Abirami *et al*.[30]
Leaf	Methanol	GC-MS	Friedelan-3-one, hexatriacontane, linoleic acid, n-hexadecanoic acid, vomifoliol, trans-phytol, gamma-sitosterol, and others	Gayathri *et al*.[31]
Leaf	Hexane	GC-MS	n-hexadecanoic acid, oleic acid and others	Hariharan *et al*.[32]
Leaf	Water	UHPLC-ESI MS/MS	Isorhamnetin-3-O-rutinoside, myricetin, friedelin	Natarajan *et al*.[33]
Leaf	Various solvents	Standard tests	Flavonoids, tannins, glycosides, alkaloids, phenolic compounds	Hepsibha *et al*.[34]
Root	Various solvents	Standard tests	Alkaloids, glycosides, saponins, phenolic compounds, flavonoids, terpenoids, tannins	Vinoth *et al*.[35]
Leaf	Methanol, ethanol	TLC	Alkaloids, flavonoids, sterols	Gowthami *et al*.[36]
Leaf	Water	Standard tests	Alkaloids, tannins, flavonoids, saponins	Begum *et al*.[37]
Leaf	Various solvents	Standard tests	Terpenoids, alkaloids, saponins, tannins, flavonoids	Regalakshmi *et al*.[38]
Leaf	Various solvents	Standard tests	Glycoside, terpenoid, saponin, flavonoid, steroil, alkaloid	Anbukumaran *et al*.[39]
Leaf	Ethanol	Standard tests	Alkaloids, saponins, tannins	Hema *et al*[40]
Flower	Various solvents	Standard tests	Alkaloid, tannin, flavonoid, phenolic compound, saponin	Jaganthan *et al*.[41]
Leaf	Various solvents	Standard tests	Alkaloid, tannin, flavonoid, phenol, saponin, sterol, glycosides, tannins, terpenoids	Vinoth *et al*.[42]
Leaf	Various solvents	Standard tests	Alkaloids, flavonoids, steroids, oil	Muthuswamy *et al*.[43]
Leaf	Methanol	HPLC	Benzoic acid derivatives (gentisic acid, benzoic acid, gallic acid, salicylic acid, vanillin), cinnamic acid derivatives (cinnamate, rosmarinic acid, ferulic acid)	Gayathri *et al*.[44]

HPLC: High-performance liquid chromatography, GC-MS: Gas chromatography- mass spectrometry, TLC: Thin-layer chromatography, *A. tetracantha: Azima tetracantha*

hepatoprotective activity in isolated hepatocytes treated with CCl_4 under *in vitro* conditions. Treatment of medium with extract resulted in better survival of hepatocytes as indicated by an increase in the viability of cells on increasing the concentration of extract. The extract treatment resulted in significant restoration in the level of GOT, GPT, and alkaline phosphatase.

Antivenom Activity

In a study, Janardhan *et al*.[83] screened various solvent extract of leaves of *A. tetracantha* for antivenom activity in terms of inhibition of venom enzymes from *Bungarus caeruleus* and *Vipera russelli* venoms. The study revealed that the ethyl acetate extract produced a significant inhibitory effect on the phosphomonoesterase, phosphodiesterase, phospholipase A_2, and acetylcholinesterase enzymes.

Radical Scavenging and Antioxidant Activity

Ekbote *et al*.[80] studied the effect of oral administration of chloroform and ethanol extract of *A. tetracantha* leaf on the activity of enzymatic and non-enzymatic antioxidant defenses in animals challenged with CCl_4. The extract

Table 2: Ethnomedicinal uses of *A. tetracantha* in different countries

Region	Uses	References
Ariyalur District, Tamil Nadu, India	Decoction made from leaves is taken orally to treat cold and cough	Sathishpandiyan *et al*[53]
Rayalaseema Region, Andhra Pradesh, India	Leaves are used to treat asthma	Anjaneyulu and Sudarsanam[54]
Pudukkottai District, Tamil Nadu, India	Treatment of bronchitis, cough, asthma, diabetes, diarrhea and arthritis	Nandagopalan *et al*.[55]
Chikmagalur Taluk, Karnataka, India	Leaves are used against anthrax in cattle	Raveesha and Sudhama[56]
Sivagangai district, Tamil Nadu, India	Leaf juice is given in cough and cold. Leaf paste applied for skin to cure itch	Suresh *et al*.[57]
Adilabad district, Andhra Pradesh, India	Crushed roots and leaves are mildly heated and gently massaged on the affected parts twice a day till cure of rheumatoid arthritis	Swamy and Reddi[58]
Puducherry, India	Leaf juice is mixed with honey and given to cure cold in children. The leaves are grind with red chili, tamarind, garlic, and salt to paste which is as a side dish and to control cold	Vimalavady and Kadavul[59]
Sriharikota Island, Andhra Pradesh, India	Fresh twigs and turmeric are ground into paste and the paste is applied on affected area to get relief from skin diseases	Kumar and Suryanarayana[60]
Kalrayan hill, Tamil Nadu, India	Paste made from root is used to treat wounds	Natarajan *et al*.[61]
Eastern Cape Province, South Africa	The dried root is ground and bottled in cold water and given to cows to treat dystocia	Dold and Cocks[62]
Kawal wildlife sanctuary, Telangana, India	Stem bark is used to treat infant diseases and rheumatism	Mohan *et al*.[63]
Kollihills, Tamil Nadu, India	Leaf is used as digestive; leaf paste is applied on externally to treat dog bite	Suresh *et al*.[64]
Vizianagaram district, Andhra Pradesh	Leaf and stem are used to treat food and mouth disease	Rao *et al*.[65]
Kalrayan hills, Tamil Nadu, India	Leaf and twig are used to treat fever in livestock	Kannan *et al*.[66]
Thalamalai hills, Tamil Nadu, India	Leaves juice with *Piper longum* is used to cure cold and cough. Root paste is applied to wound	Deepakkumar *et al*.[67]
Sirumalai hills, Tamil Nadu, India	Leaf juice is used to arrest vomiting	Vikneshwaran *et al*.[68]
KwaNibela Peninsula, St Lucia, South Africa	The root is used to treat toothache	Corrigan *et al*.[69]
Khammam district, Telangana, India	Roots ground with the roots of *Abrus precatorius* and *Piper nigrum* is administered orally till cure of asthma	Rao *et al*.[70]
Polavaram Mandal, Andhra Pradesh, India	Powdered root is mixed with gum of Acasia, applied on the swollen joint to treat arthritis	Kumari and Vishnuvardhan[71]
Kalrayan hills, Tamil Nadu, India	Root is used for snakebites	Senthil *et al*.[72]
Vellore district, Tamil Nadu, India	Whole plant along with other plants is administered in chronic liver diseases	Thirunarayanan and Rajkumar[73]
Tiruchirapalli district, Tamil Nadu, India	Leaf juice is used to relieve gas problem	Ganesan *et al*.[74]
Andhra Pradesh, India	Fruit is edible	Reddy *et al*.[75]
Pallapatti village, Tamil Nadu, India	Leaf is used in dyspepsia, swellings, and cold	Ganesan *et al*.[76]
Salem district, Tamil Nadu, India	The plant is used in the treatment of dysentery	Sivakami *et al*.[77]

A. tetracantha: Azima tetracantha

administration resulted in clear elevation in the antioxidant defense system. An increase in the level of GSH, total thiols and catalase was observed in extract treated animals. A significant reduction in the level of MDA was observed in ethanol extract treated group of animals. The study of Muthuswamy *et al*.[43] was carried out to investigate antiradical activity of methanol and ethyl acetate extracts of leaves of *A. tetracantha*. Overall, methanol extract was effective in scavenging 2,2-diphenyl-1-picrylhydrazyl radicals, superoxide radicals, and hydroxyl radicals. Both extracts scavenged radicals dose dependently. Gayathri *et al*.[44] evaluated antioxidant potential of methanolic extract of *A. tetracantha* leaves by total antioxidant capacity, ABTS scavenging, hydrogen peroxide scavenging, and hydroxyl radical scavenging activity. The extract was shown to display concentration-dependent scavenging of radicals. Study also revealed a positive correlation between the scavenging activity and the total phenolic content of methanol extract. Table 3 shows the radical scavenging and antioxidant potential of *A. tetracantha* revealed by other literatures.

Antimicrobial Activity

Compounds, namely, alkaloids, flavonoids, and sterols, isolated from leaves of *A. tetracantha*, were shown to exhibit inhibitory activity against a panel of Gram-positive and Gram-negative bacteria. It was observed that sterols exhibited marked antibacterial activity when compared to alkaloids and flavonoids.[36] The study of Natarajan *et al*.[33] evaluated the antimicrobial potential of aqueous extract prepared from the leaves of *A. tetracantha* by disk diffusion assay and showed the potential of extract to inhibit reference strains of bacteria and fungi and clinical isolates of bacteria and fungi (from diabetic foot infection). More recently, Regalakshmi *et al*.[38] evaluated the antimicrobial potential of chloroform and methanol extract of leaves of *A. tetracantha* to inhibit Gram-positive and Gram-negative bacteria and three *Aspergillus* spp. Both extracts displayed concentration-dependent antimicrobial activity with marked activity observed in case of methanol extract when compared to chloroform extract. Table 4 shows the result of antimicrobial activity of *A. tetracantha* being revealed by other literatures.

Cytotoxic and Anticancer Activity

Begum *et al*.[96] determined *in vivo* anticancer activity of ethanolic extract of leaves of *A. tetracantha* on Ehrlich ascites carcinoma in mice. It was shown that the oral administration of extract increased the survival time and reduced the solid tumor volume, viable tumor cells count, and increased the non-viable tumor cells count. Veni and Pushpanathan[97] evaluated cytotoxic activity of various solvent extracts of *A. tetracantha* leaves against *Artemia salina* and *A. fransiscana*. All extracts were effective in causing dose-dependent mortality of the nauplii of both *Artemia* species. Among extracts, chloroform extracts exhibited stronger cytotoxic effect with LC_{50} value of 187.6 µg/ml. In a study, Gopalakrishnan *et al*.[98] screened methanolic extract of *A. tetracantha* leaves for cytotoxic activity against cancer cell line HeLa and normal cell line HPL by MTT assay. The extract was shown to exhibit cytotoxicity against HeLa cell line (IC_{50} value of <100 µg/ml). The extract was shown to be less toxic to HPL. Sundaresan *et al*.[99] screened anticancer activity of hexane and ethanolic extract of stem and leaf of *A. tetracantha* against MCF-7 cell line. The extracts exhibited concentration-dependent inhibitory activity against cell lines. Ethanolic extract from leaf was shown to exhibit cytotoxicity even at nanogram range.

Diuretic Activity

The study carried out by Kumarasamyraja *et al*.[100] evaluated the diuretic potential of methanolic extract of

Table 3: Free radical scavenging and antioxidant activity of *A. tetracantha*

Plant part	Extract	Activity	References
Leaf	Ethanol	DPPH scavenging, superoxide anion radical scavenging, metal chelation, reducing activity, total antioxidant assay	Rani *et al*.[84]
Leaf	Petroleum ether, hexane, ethyl acetate, methanol	DPPH, nitric oxide radical, superoxide anion and hydroxyl radical scavenging assays, lipid peroxidation inhibition assay	Hepsibha *et al*.[34]
Root	Ethanol	DPPH, nitric oxide, hydrogen peroxide, FRAP scavenging activity	Konda *et al*.[85]
Leaf	Ethanol	DPPH, ABTS, and hydrogen peroxide scavenging assay	Salomi *et al*.[86]
Leaf	Ethanol	Superoxide, nitric oxide radical scavenging and reducing power assay	Muthukumaran *et al*.[87]
Root	Methanol, hexane, chloroform, ethyl acetate	DPPH, ABTS, hydroxyl radical, superoxide scavenging assay, ferric reducing assay	Vinoth *et al*.[35]

DPPH: 2,2-diphenyl-1-picrylhydrazyl, FRAP: Fluorescence recovery after photobleaching, *A. tetracantha: Azima tetracantha*

Table 4: Antimicrobial activity of various parts of *A. tetracantha*

Plant part	Extract	Test organisms	References
Leaf	Ethanol, methanol and water	Gram-positive and Gram-negative bacteria	Anbukumaran *et al*.[39]
Leaf	Ethanol	Gram-positive and Gram-negative bacteria from diabetic foot infection	Josephinol *et al*.[88]
Leaf	Hexane, ethyl acetate, methanol	Dermatophytes, plant pathogens, yeast	Duraipandiyan *et al*.[89]
Root	Hexane, chloroform, ethyl acetate, methanol	Gram-positive and Gram-negative bacteria and *Aspergillus* species	Vinoth and Manivasagaperumal[90]
Leaf	Hexane, chloroform, ethyl acetate, ethanol, water	*C. albicans*	Sandhiya and Kavitha[91]
Leaf	Hexane, ethyl acetate, methanol	Dermatophytes, plant pathogens and yeast	Duraipandiyan and Ignacimuthu[92]
Flower	Ethanol, methanol, water	Gram-positive and Gram-negative bacteria	Jaganthan *et al*.[41]
Leaf	Ethanol, methanol, acetone, chloroform, water	Gram-positive and Gram-negative clinical pathogens	Hema *et al*.[40]
Leaf	Chloroform, methanol	Gram-positive and Gram-negative bacteria, yeasts, molds	Gayathri *et al*.[93]
Leaf	Methanol	Seed-borne fungi	Pushpavathi *et al*.[94]
Fruit	Dichloromethane, methanol, water	Yeasts and hyphomycetes	Al-Fatimi *et al*.[95]

A. tetracantha: Azima tetracantha, C. albicans: Candida albicans

A. tetracantha leaf in albino rats. The extract was found to exhibit dose-dependent diuretic activity as revealed by an increase in the urine output with an increase in the concentration of extract.

Antiasthmatic Activity

In a study, Hepsibha[101] screened the potential of various solvent extracts of *A. tetracantha* leaf to inhibit mast cell degranulation. The extracts significantly inhibited mast cell degranulation in a dose-dependent manner. Comparatively, methanol extract produced significant inhibition of mast cell degranulation when compared to ethyl acetate and petroleum ether extracts. It is inferred that the extracts possess mast cell-stabilizing effect which can be useful in developing drugs with anti-allergic potential.

Antiulcer Activity

The ethanolic extract of *A. tetracantha* leaves was evaluated for antiulcer activity using aspirin and pylorus ligation and cold restraint stress-induced ulcer models by Muthusamy *et al*.[102] The 90% alcoholic precipitate of gastric juice was examined for various biochemical parameters, and histopathological sections were examined. It was found that the extract at a concentration of 200 and 400 mg/kg exhibited a dose-dependent protective effect which was comparable with the standard drugs ranitidine and omeprazole.

Nephroprotective Activity

Manikandaselvi *et al*.[103] determined antinephrotoxic potential of leaf powder of *A. tetracantha* by ferrous sulfate-induced renal injury model in rats. Ferrous sulfate was found to cause a rise in the level of electrolytes and kidney markers. Administration of the leaf powder significantly restored the levels of potassium, chloride, bicarbonate, creatinine, urea, and CGT indicating nephroprotective potential of the plant. Konda *et al*.[85] screened ethanolic extract of *A. tetracantha* root in glycerol-induced acute renal failure in Wistar albino rats. It was shown that the rats treated with root extract revealed significant improvement in the biochemical parameters and histopathological changes compared to glycerol-treated group of rats. A highly significant protective effect was observed at 500 mg/kg.

Anti-arthritic Activity

Sridharan *et al*.[104] screened for ethanolic extract obtained from whole plant of *A. tetracantha* for antiarthritic activity by Freund's complete adjuvant (FCA)-induced arthritis method. The extract was shown to possess anti-arthritic activity. It was observed that the Rheumatoid factor and C-reactive protein levels were decreased when compared with FCA group.

Antipyretic Activity

Begum *et al*.[105] evaluated antipyretic activity of leaf extract of *A. tetracantha* using Brewer's yeast-induced pyrexia.

Treatment with leaf extract at a dose of 100 and 200 mg/kg decreased the rectal temperature of the rats in dose-dependent manner. At the dose of 200 mg/kg, the extract caused significant lowering of body temperature up to 4 h after its administration.

Insecticidal Activity

Manimegalai and Velavan[106] screened larvicidal potential of different concentrations of aqueous extract of *A. tetracantha* leaves against 4th instar larvae of Anopheles stephensi. It was observed that the extract exerted a concentration-dependent mortality of larvae. After 96 h, a mortality of 100% was observed at extract concentration of 8%.

Analgesic Activity

The benzene, chloroform, and aqueous extracts of leaves of *A. tetracantha* were screened for analgesic activity in mice using hot plate method by Nandgude *et al*.[107] The extracts displayed marked analgesic potential with significant analgesic activity at a dose of 100 mg/kg body weight. Marked analgesic activity observed at 30 min after extract administration which was near equivalent to that of morphine sulfate. In a study, Begum and Anand[108] evaluated analgesic activity of ethanolic extract of leaves by hot plate method using mice. A significant analgesic activity of extract was found at 120 s which was compared to the standard drug Pentazocine.

Antidiarrheal Activity

Begum *et al*.[37] evaluated antidiarrheal activity of aqueous extract of *A. tetracantha* by castor oil-induced diarrhea and castor oil-induced enteropooling in rats. The extract was shown to cause significant protection against castor oil-induced diarrhea and castor oil-induced enteropooling at concentration 100 mg/kg.

Anti-inflammatory Activity

The anti-inflammatory activity of *A. tetracantha* leaf powder was assayed in male albino rats using carrageenan-induced rat paw edema (to study acute inflammation) and cotton pellet granuloma (to study chronic inflammation) methods by Ismail *et al*.[109] It was observed that the crude drug exhibited maximum activity at a dose of 1000 mg/kg. In the cotton pellet granuloma assay, the drug was shown to suppress the transudative, exudative, and proliferative components of chronic inflammation. In addition, the drug was able to lower the lipid peroxide content of exudate and liver, γ-glutamyl transpeptidase activity in the exudate of cotton pellet granuloma. Sridharan *et al*.[104] screened for ethanolic extract obtained from whole plant of *A. tetracantha* for anti-inflammatory activity by carrageenan-induced paw edema method. The extract at 250–500 mg/kg dose suppressed the paw edema significantly at 3–4 h.

BIOACTIVITIES OF NANOPARTICLES SYNTHESIZED USING *A. TETRACANTHA*

Studies have shown that nanoparticles can be synthesized using the extracts of *A. tetracantha*. The nanoparticles that are synthesized using *A. tetracantha* have been shown to exhibit certain bioactivities. Manimegalai and Velavan[106] synthesized silver nanoparticles from aqueous extract of leaves of *A. tetracantha* and evaluated their antibacterial and antioxidant activity. The nanoparticles were effective against *Escherichia coli*, *Bacillus subtilis,* and *Staphylococcus aureus*. The nanoparticles also exhibited scavenging potential against DPPH and superoxide radicals. The study of Veni *et al*.[110] revealed the synthesis of silver nanoparticles from aqueous extract of *A. tetracantha* leaf and the larvicidal efficacy of nanoparticles against larvae of *Anopheles stephensi* and *Culex quinquefasciatus*. The nanoparticles were effective against both larvae to more or less similar extent. Hariharan *et al*.[111] synthesized gold nanoparticles using aqueous extract of *A. tetracantha* leaves. The synthesized nanoparticles were evaluated for antimicrobial activity against bacteria, yeasts and dermatophytes. The nanoparticles were shown to be effective against test microbes.

FRIEDELIN AND ITS BIOACTIVITIES

Friedelin is a bioactive pentacyclic triterpenoid compound [Figure 2] found in *A. tetracantha* and few other plants. The compound is found in the leaves of *A. tetracantha*. The compound is shown to exhibit a wide array of biological activities such as antimicrobial, anti-inflammatory, antioxidant, gastroprotective, anti-diarrheal, and others. Some of the bioactivities of friedelin, isolated from *A. tetracantha*, have been discussed here. Friedelin, isolated from hexane extract of leaves of *A. tetracantha*, was shown to exhibit moderate-to-good antifungal activity against a panel of fungi that included dermatophytes, plant pathogens, and a yeast.[89]

Antonisamy *et al*.[112] evaluated anti-inflammatory effect of friedelin using carrageenan-induced hind paw edema, croton oil-induced ear edema, acetic acid-induced vascular permeability, and cotton pellet-induced granuloma. In the acute phase of inflammation, a significant inhibition of 52.5% and 68.7% was observed with 40 mg/kg friedelin in carrageenan-induced paw edema and croton oil-induced ear edema, respectively. Administration of friedelin (40 mg/kg) was shown to significantly decrease the formation of granuloma tissue induced by cotton pellet. In addition, friedelin was found to inhibit acetic acid-induced vascular permeability in mice.

In a study, Antonisamy *et al*.[112] determined antipyretic effect of friedelin by yeast-induced hyperthermia in rats. It was observed that the treatment with friedelin resulted in a significant and dose-dependent reduction in the pyrexia in rats.

Antonisamy *et al*.[112] determined analgesic activity of friedelin using the acetic acid-induced abdominal constriction response, formalin-induced paw licking response, and the hot-plate test. Friedelin was shown to produce significant analgesic activity in the acetic acid-induced abdominal constriction response and formalin-induced paw licking response. However, in the hot-plate test, friedelin did not show significant results when compared with control.

In a study, Sunil *et al*.[113] isolated friedelin from leaves and showed that friedelin possesses potent *in vitro* antioxidant and free radical scavenging activity as evaluated by assays, namely, DPPH, hydroxyl, nitric oxide, and superoxide radical scavenging activities. Friedelin was also found to suppress lipid peroxidation. Friedelin was also shown to display *in vivo* antioxidant activity in rats. It was shown that rats pretreated with friedelin revealed restoration serum enzymes, glutathione, and antioxidant enzymes catalase and superoxide dismutase.

The triterpenoid friedelin, isolated from hexane extract of *A. tetracantha* leaves, was evaluated for insecticidal activity by Baskar *et al*.[114] against *Helicoverpa armigera* and *Spodoptera litura* at 125, 250, 500, and 1000 ppm concentration. Friedelin was shown to exhibit marked antifeedant, larvicidal, and pupicidal activities against both pests.

Antonisamy *et al*.[115] investigated gastroprotective activity of friedelin isolated from hexane extract by ethanol-induced gastric ulcer in albino rats. Friedelin pretreatment of animals resulted in protection against the deleterious role of ethanol. Antioxidant enzyme activities, anti-inflammatory cytokines, prostaglandin E_2, constitutive nitric oxide synthase, and mucus weight increased significantly while the vascular permeability, pro-inflammatory cytokines, inducible nitric oxide synthase, caspase-3, and apoptosis level decreased significantly after friedelin ingestion indicating the possible therapeutic role of friedelin as a natural gastroprotective tool against gastric ulcer.

Antonisamy *et al*.[116] studied the antidiarrheal effect of friedelin using castor oil-induced diarrhea, gastrointestinal motility test, magnesium sulfate-induced diarrhea, and castor oil-induced enteropooling in rats. Friedelin, at concentration 20 mg/kg, showed significant reduction of intestinal transit and gastric emptying which were similar to the antimotility activity of atropine. Friedelin, at concentration 20 mg/kg, was shown to exert significant anti-enteropooling effects, against castor oil-induced enteropooling in rats. A significant reduction in the defecation frequencies and the fecal droppings wetness was observed. In addition, friedelin also revealed significant inhibition of castor oil-induced diarrhea.

Friedelin was screened for its hypolipidemic potential in Triton WR-1339 and high-fat-diet-induced hyperlipidemic rats.[117] In Triton WR-1339-induced hyperlipidemic rats, treatment with friedelin showed a significant lipid-lowering effect as assessed by reversal of plasma levels of total cholesterol, triacylglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. In high-fat diet-fed hyperlipidemic rats, treatment with friedelin caused lowering of lipid levels in plasma and liver.

CONCLUSIONS

Interest in medicinal plants has been intensified nowadays due to many facts such as high cost of available drugs, several side effects that are associated with the use of drugs such as antibiotics, anticancer agents, and other chemotherapeutic agents and emergence of antibiotic-resistant strains. Plants are considered to be cost-effective and promising alternatives. Many plant species are being in used worldwide for the treatment of infectious and non-infectious diseases and several disorders. An extensive literature survey conducted on *A. tetracantha* clearly indicates the potential utilization of the plant singly or in certain formulations to treat several diseases or disorders of humans and livestock. The plant *A. tetracantha* can be grown in available area for medicinal purposes. Methods such as tissue and cell culture can be applied to achieve rapid propagation and conservation of the plant and to obtain bioactive principles from the plant.

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