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Pharmacological Importance of Melia azedarach L. (Chinaberry tree): An Overview

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ABSTRACT
Ayurveda medicinal system is being practiced for thousands of years. Remarkable research on chemistry, pharmacognosy, pharmacology and clinical therapeutics has been carried out on Ayurveda medicinal plants. The present study was conducted to review the phytochemistry, as well as pharmacological value of plant Melia azedarach L. (Chinaberry tree, bead tree, Cape lilac) from Meliaceae. M. azedarach is cultivated throughout Asia as well as grown as decorative tree in most part of the world. The plant's chemistry has been reported to compose of primary (proteins, lipids and carbohydrates) metabolites as well as secondary metabolites (flavonoids, polyphenols, tannins, glycosaponins, polysaccharides, etc having salutary effects on human health). It is recorded that the fruits, leaves, seeds, roots, and bark are used as an ingredient in formulationsfor treatment of various diseases. It has potential to reduce diseases such as, infections, cancer, inflammation, urolithiasis, oxidative stress, diabetes,and ulcers. The present study may help the researchers to develop new herbal leads for the management of various disorders.

Keywords: Melia azedarach, Chinaberry tree, Phytochemistry, Pharmacology.

I. INTRODUCTION

Medicinal plants play a key role in the primary healthcare system around the globe. Based on different theories, beliefs and experiences of the indigenous people, medicinal plants are not only used in disease treatment and prevention but also used in the maintenance of good health[1]. Of 422,000 flowering plants found worldwide, more than 50,000 plants are used for traditional medicines[2]. In practice, Ayurveda (India), Acupuncture (China), Unani (Arabic countries) and folk medicines are considered as the major systems of traditional medicines[3].The records indicate that 90% of the herbal raw material used in the manufacturing of Unani, Siddha, Ayurvedic, and homeopathic medicines are obtained from natural sources[4]. More than 80% of the world's populationrelies on herbal drugs. Despite the recent advancements in science and technology, the folk knowledgeregardingmedicinal plants and some of the cultural beliefs and practices of people are irreplaceable[5]. Medicinal plants comparatively pose lesser side effects than synthetic drugs and these plants are considered as a recognized tool to find out the new sources of a drug[6]. Some plants are good source of nutrition which results in the treatment of various diseases. These plants include, green tea, ginger, walnuts, ginseng, garlic and other various plants[7].

The knowledge regarding the medicinal plants has been of great importance as a lead component for the discovery of a new single-molecule drug for the modern system of drugs[8]. To assess the chemical nature of the compound, isolation of the active component, its chemical and spectral characteristics are the requisites for creating its chemical structure[9]. However, due to recent interventions in bioinformatics (computational methods) and instrumentation, the horizons of drug discovery are now broadened[10]. Some of the drugs obtained from natural sources have been used since the immemorial time for treating various diseases. These drugs include analgesics (morphine), cardiotonic (digoxin), antimalarial (artemisinin and quinine), antihypertensive (reserpine), and antineoplastic (vincristine and vinblastine)[11]. Despite advances in combinatorial chemistry as a method to discover

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drugs, the potential of medicinal plants or their extracts is still enormous providing new and novel drugs for control of disease and prevention[12].

II. LITERATURE REVIEW OF MELIA AZEDARACH

Melia azedarach, a deciduous tree is derived from Greek words;Meliameans "flowering ash or manna ash" and azedarach means "poisonous tree"[13]. It is commonly used in Chinese, Unani, and Indian traditional medicines[14].

2.1 Botanical Description

M. azedarach is a small to medium deciduous tree attaining height up to 45m and up to 30-60cm in diameter. The bark is smooth, greenish-brown, and turning grey with age. Leaves are greenish, bipinnate, 20-40cm long and a pungent odor. Flowers are greenish-white or purple, cyclic, smooth, fragrant and generally fleshy or non-fleshy. Fruits are yellow drupe, smooth, cyclic and about 15mm in diameter [15]. The natural distribution of M. azedarach is unknown but it is thought to be indigenous to South Asia particularly in tropical and subtropical regions [16]. A study reported that M. azedarach is scattered from the Himalayan foothills of Pakistan and India, tropical China via Malesia to northern and eastern Australia and Solomon Islands [17]. In Australia, it is distributed from northern Queensland to New South Wales. It is also scattered in regions of eastern and southern Africa, United States, Croatia, France, and throughout the Middle East [18].

2.2 Vernacular/Common names

Chinaberry tree, Pride of India, Persian lilac, Pride of China (English), Lilas des Antiles, Lilas des Indes (French), Paternosterbaun, Zedarachbaum (German), Arbol del Paraiso, Paraiso (Spanish), Bakain (Hindi), Darek, Chein, Dhek (Punjabi), Persischerzedrachbaun (Malaysia), Violeta (Singapore), giant paradise (Argentina), Cinarnorno (Brazil), syringe tree (South Africa), Thamga (Burma)andZanzalacht (Jordan)[16].

2.3 Taxonomical classification[19]

Kingdom: Plantae
Phylum:Magnoliophyta
Class:Magnoliopsida
Order:Sapindales
Family:Meliaceae
Genus:MeliaL.
Species:MeliaazedarachL.

2.4 Phytochemical constituents

The different parts of M.azedarachhave been shown the presence ofphytochemicals,i.e. flavonoids, alkaloids, terpenoids, saponins, steroids, tannins, and anthraquinones which exhibit different pharmacological activities. Roots of the plant contain limonoids and terpenoids like 6-acetoxy-7□-hydroxy-3-oxo-14β, 6-acetoxy-3β-hydroxy-3-oxo-14β, 15β-epoxymeliac-1,5-diene, azecinand 15β-epoxymeliac-1,5-diene-3-O-β-D-glucopyranoside. The roots also contain flavonoids such as apigenin-5-O-β-D-galactopyranoside;steroids,e.g. β-sitosterol, 24-methylenecydoartanol, 4-campestene-3-one, and β-sitosterol-B-D-glucoside and phenolic acids such asvanillic acid and trans-cinnamic acid (derivatives of benzoic acid, which mainly serve as antioxidant activity of the plant)[20]. The stem bark was revealed to containterpenoids and limonoids,e.g. fraxinellone, amoorastatin, 12-acetoxyamoorastatin, 15β-epoxygedunan-1-ene-3-O-B-D-glucopyranoside, kulactone, methylkulonate,12-hydroxyamoorstatone [13]. It also contains steroids like, cholesterol, campesterol, stigmasterol as well as fatty acids including linolenicacid, linoleic acid, and oleic acid. The leaves contain fatty acids (i.e. palmiticacid) and terpenoids and limonoidssuch as 1-cinnamoyl-3-methacrylyl-11-hydroxy meliacarpin, 1-cinnamoyl-3-acetyl-11-hydroxy meliacarpin, deacetylsalanin, α-terpineol, α-terpinene, α- and β-pinene,kaempferolFraxinellone, amoorastatin, 12-acetoxyamoorastatin, 15β-epoxygedunan-1-ene-3-O-□-D-glucopyranoside, kulactone, methylkulonate, and 12-hydroxyamoorstatone [15, 21, 22]. The fruits contain sendanin, 3β,16β-hydroxytirucalla-7,24(25)-dien-21,23-olide, 3α-tigloylsapelin D, erythron-guaiacylglycerol-β-O-4'-coniferyl alcohol, balanophonin, (7S,8R)-3-hydroxyl-4-methoxyl-balanophoni whiletheseeds contain nimbinene□-D-glucopyranose, 6,11-diacetoxy-7-oxo-14 beta, 15 beta-epoxymeliacin, and scopoletin[15, 23-25].Moreover, Gang and his colleagues isolated compounds from barks that includedmeliavolin, usnic acid, dammarendiol II 3-O caffeate, methyl 3-formyl-2,4-dihydroxy-6 methyl benzoate,epicatechin, 24-methylenecycloartenone, 12β,20 (S)-dihydroxydammar-24-en-3-one, and 3,20-diacetyl-11-methoxy-1-tigloylmeliacarpinin[26].

2.5 Ethnopharmacological relevance

In developing as well as developed countries, medicinal plants play a vital role in the treatment of various ailments. The choice of

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medicinal plants varies between regions and cultures. Ethnopharmacological survey of medicinal plants is considered the most reliable approach to natural drug discovery[27]. Overall, 50% of natural products and their derivatives are clinically used to treat various diseases[28]. M. azedarach is a well-documentedmedicinal plant used in traditional and folk medicines. Different parts of M. azedarach possess different therapeutic potentials. The bark is used as a diuretic, deobstruent, and anti-diarrheal[15]. Bark decoction is also used in fever to relieve nausea, vomiting, thirst, loss of appetite, and stomachache[13].The root bark is also used as an anti-malarial drug before the discovery of quinine[29]. Roots are bitter, anodyne, anthelmintic, febrifuge, expectorant, astringent, and tonic in low doses[13]. Leaves are used to treat anemia, jaundice, eczema, measles, malaria, skin diseasesi.e.scabies, and diabetes[15]. They are also used as a mouthwash to treat gingivitis and also kill insects, mites, and nematodes. Fruits taste sweetish but poisonous,whileused for the formulation of tonic for purgative and emollient purposes and alsoapproved in the treatment of leprosy and scrofula. Dried ripe fruit is used as aparasiticide, the pericarp of the fruit is considered as effective phytotherapy for the treatment of diabetes. It is also useful in intestinal worms, piles, urinary diseases, etc. The seeds are bitter, laxative, expectorant, emetic and are useful in rheumatism, typhoid, and helminthiasis, hepatopathy, and dermatopathy[15]. Externally, it has stimulant, antiseptic and alterative properties and is useful in chronic syphilitic sore and indolent ulcers. Gums are deemed as a remedy for splenic enlargement. The whole plant is used to stimulate hair growth. Primary and secondary metabolites are responsible for the biological activities. The table 1 described the qualitative analysis of primary as well as secondary metabolites. The results may vary with other studies due to geographical origin of the plant.

Table 1. Qualitative analysis of Melia azedarach.

Tests	Aqueous Extract	Methanolic Extract	Chloroform Extract	N-hexane Extract
Carbohydrates	+	+++	++	+
Tannins	-	-	-	-
Proteins	-	+	+	-
Quinones	++	+++	++	+
Glycosides	+	++	+++	+
Phenols	-	+	+++	+
Alkaloids	++	+++	++	+
Saponins	+	++	++	-
Terpenoids	++	+++	+	-
Flavonoids	+	++	+++	+

-=absent, +=low, ++=moderate, +++=high.

2.6 Review of biological and pharmacological activities

2.6.1 Antidiabetic activity

Leaf extract of M. azedarach exert a hypoglycemic effect on alloxan-induced diabetes in rats and one of the possible mechanisms of action is to increase the insulin secretion and enhances the glucogenesis process [30]. Two compounds were isolated from root extracts that exert α-amylase sucrase and α-glucosidase inhibitory activities [31]. M. azedarach bark also showed significant inhibitory activities against protein tyrosine phosphatase 1B (PTP1B), which might be attributed to the antidiabetic potential of the plant [22].

2.6.2 Antibacterial activity

The fruit-seed extracts of M. azedarach exhibit potent antibacterial activity against different microorganisms such asEscherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae, Salmonellatyphimurium, and Enterobacteraerogenes[32]. Silver nanoparticles synthesized from the leaf extracts of M. azedarach showed antimicrobial activity against E. coli, K. pneumoniae, S. aureus, P. aeruginosa, and Proteus species[33].

2.6.3 Antiviral activity

A compound was isolated from the leaf of Melia azedarach that showed an antiviral property that is responsible for the inhibition of replications of several viruses such as, Mycobacterium

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tuberculosis, Herpes simplex virus (HSV), vesicular stomatitis virus (VSV), polio, and foot and mouth disease virus (FMDV)[34]. Ethyl acetate extract of M. azedarachafforded a limonoidcompound identified as 1-cinnamoyl-3,11-dihydroxilmeliacaripin that exhibit good activity against HSV and VSV[35]. Meliacin is a bioactive component isolated from M. azedarach exhibit antiviral activity against HSVtype-I [36].

2.6.4 Antifungal activity

M. azedarach possessesfungistatic property against various microfungiincludingFusariumoxysporum, F. verticllioides, F. solani, Aspergillusflavus, Sclerotiniasclerotrorium, Ascochytalabrei, and Diaporttephaseolina[37, 38].

2.6.5 **Antimalarial activity**

The methanolic extract of the leaves possess anti-malarial activity and showed positive effects against laboratory-adapted isolated of Plasmodium falciparum [39]. The methanolic extracts of bark and fruit have a significant suppression effect on parasitemia[40]. A recent study reported that M. azedarach synthesized silver nanoparticles can be employed to control young instar populations of malarial vector i.e., Anophelesstephensi[41].

2.6.6 Hepatoprotective activity

Ethanolic extract of M. azedarach plant leaves has been documented to reduce the serum enzyme including, glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvate transaminase (SGPT), which is intoxicated by carbon tetrachloride (CCL_4) in mice; thus shown significant hepatoprotective activity [42]. Liver biliary duct enzyme alkaline phosphate (ALP) and serum bilirubin are considered biomarkers for liver injury. A study reported that M. azedarach reduced the level of these mentioned parameters to normal levels after therapy [43].

2.6.7 Anti-inflammatory and analgesic activity:

M. azedarach possesses high anti-inflammatory activity against carrageenan-induced paw edema [13]. Another study reported good anti-inflammatory properties, when compared with the standard drug, indomethacin [38, 44]. Hydromethanol extract of M. azedarach leaves exhibit strong antipyretic activity using yeast-inducing pyrexia method in rabbits [45].

2.6.8 Antioxidant activity

Alcoholic extracts of M. azedarach leaves exhibit anti-oxidant activity in 1,1-diphenyl-2-picrylhydrazyl (DPHH) scavenging and ferric-reducing antioxidant power (FRAP) assays[46].It exerts high scavenging activity due to the presence of the hydroxyl group in phenolic compounds[47]. The ethyl acetate extracts also show positive effects in the metal-chelation assay[48].

2.6.9 Anti-urolithiatic activity

A study reported that the ethanolic and aqueous extracts of plants showed the promising effects against ethylene glycol-induced calcium oxalate urolithiasis in male albino rats [49]. Moreover, in another study the aqueous extract showed the anti-urolithiatic effect against ethylene glycol-induced nephrolithiasis in Wister albino rats [50].

2.6.10 Anti-ulcer activity

Alcoholic extracts of M. azedarach displayed anti-ulcer activity in albino rats [13]. The aqueous extract of the leaf also exhibits anti-ulcer property when compared with omeprazole that is used as standard drug [51].

2.6.11 Anticancer activity

Various parts of M. azedarachexerted cytotoxic and anti-proliferative property against various cancer cell lines such as human lung adenocarcinoma (A549), colorectal carcinoma (HT-29), breast cancer (MCF, SK-BR-3), cervix hepatoma (HepG-2, SMMC-7721 and Hep3B), kidney epithelial cells (KB), prostate cancer (PC3), CNS (SH, SV5V,U251,SF539), B16F10 mouse melanoma cell-line[52].A study reported that the chloroform, butanol, crude, hexane, ethyl acetate and aqueous fractions of M. azedarach exhibit good cytotoxic activities[53].The hexane layer of M. azedarachbark extract has anti-cancer activity and could improve the toxicity of cisplatin[54].

The overall pharmacological activities were discussed in Table 2.

Table 2. Review of pharmacological activities of plant Melia azedarach Linn.

References	Biological activity	Part used
[30, 31, 55, 56]	Anti-diabetic	Fruit, leaf and root

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[57-60]	Antibacterial	Fruit, seed, leaf, and flower
[34, 61, 62]	Antiviral	Leaf
[63-65]	Antifungal	Leaf and fruit
[39, 41]	Antimalarial	Bark and fruits
[43, 66]	Hepatoprotective activity	Leaf
[38, 67, 68]	Anti-inflammatory and analgesic	Leaf, flower, and root
[50]	Anti-urolithiatic	Leaf and seed
[51, 69]	Anti-ulcer	Leaf
[46, 48, 70-73]	Antioxidant	Root, leaf, fruit-seed and bark
[54, 71, 74-76]	Cytotoxic and anti-proliferative activity	Fruit, leaf, and bark

III. CONCLUSION

M. azedarach L. is a rich source of primary as well as secondary metabolites. Many studies have documented the pharmaceutical and medicinal value in the field of phytomedicine. Its antioxidant, anti-inflammatory, anticancer, anti-urolithiatic, antibacterial, anti-fungal, anti-viral and anti-diabetic properties are well documented in existing literature. The review of existing literature revealed that studies have been conducted on different parts of Melia azedarach L. Furthermore, the extracts of M. azedarach and the experimental conditions in which extracts were prepared also varied in different studies. For this reason, the reported phytochemical constituents and the properties may vary greatly. The present study may help the researchers to develop new herbal leads for the treatment and management of various disorders.

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