

Review Article

COMPREHENSIVE REVIEW ON ETHANOBOTANICAL USES, PHYTOCHEMISTRY AND PHARMACOLOGICAL PROPERTIES OF *MELIA AZEDARACH* LINN.SABIRA SULTANA^{*1}, HAFIZ MUHAMMAD ASIF², NAVEED AKHTAR¹, MUHAMMAD WAQAS³, SAIF UR REHMAN⁴

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This paper is available online at www.jprhc.in**ABSTRACT**

Medicinal plants, since times immemorial, have been used in virtually all cultures for therapeutic purposes. The widespread use of herbal remedies and healthcare preparations obtained from commonly used traditional herbs and medicinal plants have been traced to the occurrence of natural products with medicinal properties. In the present review, an attempt has been made to collect the botanical, phytochemical, ethnomedicinal, pharmacological and toxicological information on *Melia azedarach* L. which is used traditionally as an anthelmintic, diuretic, emmenagogue, expectorant, vermifuge, used in piles, used as astringent, used in hysteria, leprosy, and in scrofula. Medicinally it has been shown to possess various pharmacological activities like antifungal, anti-malarial, antibacterial, hepatoprotective, anti-oxidant, anti-fertility, anthelmintic, antipyretic and cytotoxic activities. The available literature on the *M. azedarach* L. revealed that this plant contains many phytochemical constituents including alkaloids, terpenoids, saponins, glycosides, phenolic compounds, flavonoids and rutins. The aim of this article is to review those medicinal and pharmacological properties of *M. azedarach* which have been or still are being learned. The present review is therefore, an effort to give a detailed survey of the literature on its traditional, phytochemical and pharmacological properties.

KEY WORDS: *Melia azedarach*, medicinal properties, phytochemical constituents, pharmacological activities**INTRODUCTION**

Melia azedarach L. (*M. azedarach*) is a small to medium size deciduous tree or shrub of 5-15 meter in height, a close relative of Neem, from the Meliaceae family widely distributed in tropical and subtropical countries, contains phytochemical constituents which makes it candidate in pest control. It has been shown to possess antimicrobial, insecticidal and nematocidal properties. It is also known for its anti-fertility, anti-inflammatory, antipyretic, spermicidal and antiulcer activities¹.

Taxonomic Classification

Kingdom	Plantae
Order	Sapindales
Family	Maliaceae
Genus	Melia
Species	<i>Melia azedarach</i>
Binomial name	<i>Melia azedarach</i> Linn.

Vernacular names

Chinaberry, Persian lilac, pride of India, china tree, Indian lilac and breed tree (English); Bakain, Drek, Pejri, Padric (India); Bakainu (Nepal); Thamga (Burma); Inia (Hawaii); Alelaila (Peurto Rice); Jacino (Panama); Aleli (Venzulea); West Indian Lilak, Lilac (West Indies); Lilas (Haiti, French); Cinnamumo (Brazili) and Zanzalacht(Jordan)².

Distribution

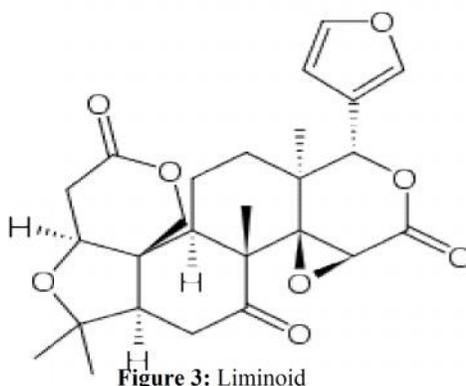
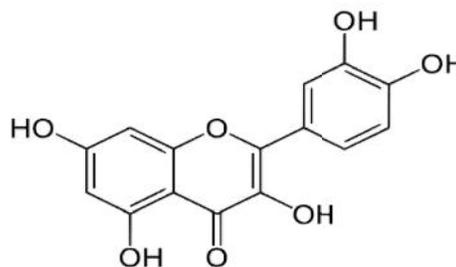
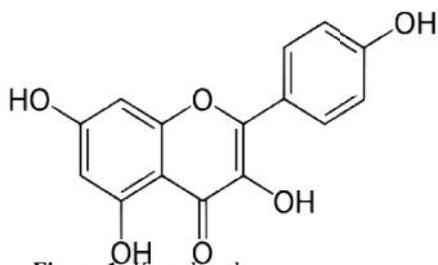
M. azedarach is native to tropical Asia. It is widely distributed in Pakistan, India, Indonesia, Southeast Asia and Australia. It has become naturalized in Philippines, United States of America, Brazil, Argentine and many African and Arab countries ².

Botanical description

M. azedarach is a small to medium size deciduous tree or shrub of 5-15 meter in height. Branches are stout, with purplish bark and dotted with buff-colored lenticels. Leaves are compound, alternate, and puberulent to glabrous. Leaves are long, serrate, dark green above, often with sparse hair along the veins and lighter green and generally smooth below. Inflorescence is a panicle, flowers are 5-parted. Sepals are green. Petals are pinkish lavender, lingulate with ten anthers. Fruit is drupe, one seeded, stalked greenish yellow to yellowish tan, globose and 1-1.5 cm in diameter ³.

Phytochemistry

The *M. azedarach* contains a number of organic molecules *i.e.* flavonoids, terpenoids, steroids, acids and anthraquinones. A variety of compounds have been detected in *M. azedarach* leaf extract including Kampherol, Quercetin (Flavonoids), stigmasterol, Campesterol (phytosterols), -sitosterol, Pyhtol (Diterpene), 3-Methyldecane, Heptadecane (alkane hydrocarbon), hexadecanic acid, Pentadecanoic acid (n-alkanoic acids), -Carotene, tocopherol (Vitamin-E) and saqulene, 1-Eicosanol (triterpene), 3,5,11,15- Tetramethyl-2-hexadecen-1-ol (Terpene alcohol) ⁴.



Chemical constituents of seeds including -sitosterol, vanillin, benzoic acid, vanillic acid, daucosterol, -D- glucopyranose, liminoid glycoside viz 6,11-diacetoxy-7-oxo-14 beta-epoxymeliacin (1,5-diene-3-O-beta-D-glucopyranoside) and melianol meliacin, meliacarpin, meliartenin vanillin, hydroxyl-3-methoxycinnamaldehyde and (\pm) pinoresinol ⁵. Stem bark contain liminoids such as 7 - Acetoxy-14 , 15 -epoxygedunan-1-ene-3-O- -D-glucopyranoside . Anthraquinone such as 1, 3, 5, 8- Tetrahydroxy-2-methylanthraquinone; 8-Me ether, 3-O- -L- rhamnopyranoside.

Root bark contains terpenoids such as Azedarachtin-A, Azedarachtin-B ¹. The methanolic extract of the *M. azedarach* showed 48 constituents, the major constituents are Quercetin (16.47%- Flavanoids), Phytol (11.04%-Diterpene), Palmitic acid (15.49%-

saturated fatty acid). 9,12,15- Octadecatrienoic acid (3.43%-n-alkanoic acids) work as an anti inflammatory, hypocholesterolemic cancer preventive, nematocide, insecticide, hepatoprotective, antihistaminic properties ⁶. Some minor components like 2,3-Dihydro-3,5-Dihydroxy-6-Methyl-4H-pyran-4-One (0.31%-flavoring agent) and 4-Methyl-2-hexanone (2.25%-flavoring agent) consider as a novel potent aroma compound in a dairy product ⁷. The compound 2, 3- Dihydrobenzofuran (0.22%) is an essential oil used in the treatment of diabetic retinopathy and arthritis ⁸. 5-hydroxypipicolic acid (0.52%-imino acid) showed platelet aggregation inhibition and larvicidal activity Limonene (0.68%) acts as natural food flavorings, used in fragrances and aromatherapy ⁹. Pyrazol-5(2H)-one (0.26%- flavonoids) possessed extensive biological activities, such as anti inflammatory, antipyretic, analgesic ¹⁰.

ETHANOBOTANICAL USES

The exuded gum obtained from *M. azedarach* trunk is considered useful in spleen enlargement, wood extract given in asthma ¹¹. Decoction of bark is prescribed in paroxysmal fever to relieve thirst, nausea, vomiting and general debility, and loss of appetite and skin diseases ¹¹.

Poultice of the leaves are applied to relieve nerve headache and to cure eruption on the scalp. Leaf juice is act as anthelmintic, diuretic, emmenagogue, expectorant, vermifuge and their decoction is astringent, stomachic, used in hysteria, leprosy, scrofula ^{11,12}. Flowers have astringent, anodyne, refrigerant, emmenagogue, diuretic, resolvent, deobsturent properties ¹³.

Fruits are considered anthelmintic, diuretic, emollient and purgative also, prescribed internally in indigestion, colic and intestinal catarrh ¹⁴.

Seeds are considered anthelmintic, expectorant, aphrodisiac and are useful in typhoid fever, helminthiasis, pain in the pelvic region and scrofula, also prescribed in rheumatism. Seed oil is used in skin diseases. Roots are astringent, emmenagogue, anodyne, febrifuge, expectorant, constipating. These are useful in sciatica, lumbago, piles, cough, asthma, ulcers, wounds, diabetes, intermittent fever, post labor pain in uterus, amenorrhea and in leuoderma ¹³.

PHARMACOLOGICAL ACTIVITIES

Hepatoprotective activity

The liver can be injured by various chemicals and drugs. In the study conducting by Ahmed et al in the year 2012, revealed the hepatoprotective activity against CCl₄ induced liver injury. Parameters like SGOT, SGPT, ALP and serum bilirubin were measured and histopathological evaluation was conducted. Biochemical parameters have improved after treatment and histological changes such as steatosis (fatty changes in hepatocytes) and fibrosis which were observed in CCl₄ intoxicated group were totally reduced to normal levels. Further investigations are in progress to determine the exact phytoconstituents responsible for hepataprotective effect ¹⁵.

Anti-fertility activity

Rapid increase in population has caused severe problem in economic growth and human progression. Several methods of contraception have been promoted, but due to their serious adverse effects, such as hormonal imbalance, hypertension, and increased risk of cancer and weight gain, therefore, search for new antifertility molecule with minimum side effects continues. Vishnukanta and Rana in the year 2009 studied hydro-alcoholic extract of *M. azedarach* roots for anti-implantation, estrogenic/anti-estrogenic and progestational/anti-progestational activities. It was found that the extract exhibited significant anti-implantation and anti-progestational activity and devoid of estrogenic/anti-estrogenic activity. It is therefore assumed that a certain substance was present in the extract which impairs the synthesis, secretion and functions of ovarian steroids and also blocks the implantation process by hindering the development of oocyte and graffian follicle as well as the endometrial epithelium ¹⁶.

Folliculogenesis inhibition

Roop et al in 2005 conducted a study to investigate the quantitative aspects of follicular development in cyclic female albino rats (135 ± 10 g; 8 groups with 6 animals in each group) after oral administration of polar (PF) and non-polar (NPF) fractions of *M. azedarach* Linn. (dharek) seed extract at 24 mg/kg body weight-1 day-1 for 18 days. There was a significant reduction ($p < 0.05$) in the number of normal single layered follicles (*M. azedarach*: 0.60 ± 0.40 and 1.80 ± 1.2 after 24 mg/kg PF and NPF, respectively, vs control: 73.40 ± 7.02) and follicles in various stages (I-VII) of follicular development in all treatment groups. These extracts also significantly reduced ($p < 0.05$) the total number of normal follicles in dharek (13.00 ± 3.58 and 14.60 ± 2.25 after 24 mg/kg NPF and PF) treatments compared to control (216.00 ± 15.72 and 222.20 ± 19.52, respectively). Thus, the present study is an attempt to investigate the effects of *M. azedarach* seed extracts on reproduction of albino rats ¹⁷.

Antioxidant activity

A study was designed by Munir et al in the year 2012 to demonstrate the antioxidant activity of *M. azedarach*. The TPC (Total Phenolic Contents) and TFC (Total Flavonoid Contents) contents in different parts of sun dried extracts of *M. azedarach* were found to be in the range of 74.43-112.10 mg GAE/g DW and 13.32-28.11 mg CE/g DW, while in ambient dried TPC (Total Phenolic Contents) and TFC (Total Flavonoid Contents) found to be in the range of 66.89-103.34 mg GAE/g DW and 10.67-23.45 mg CE/g DW, respectively. The DPPH scavenging activity and linoleic inhibition capability of sun dried was found to be in the range of 55.43-63.86% and 35.57-52.11%, respectively while for ambient dried was in the range of 48.54-61.00% and 33.87-50.33%, correspondingly. The reducing potential of sun dried and ambient dried at concentration of 10.0 mg/mL was in the

range of 0.727-1.211 and 0.601-0.890, respectively. The result of the study, therefore, showed the sun dried extracts of *M. azedarach* had higher antioxidant activity whereas, among the plant parts, the stem bark was found to be proved better antioxidant activity¹⁸. Ahmed et al in 2012 conducted a research study and concluded that phenols are responsible for the variation in the antioxidant activity of the plant. The high DPPH scavenging activity of *M. azedarach* may be due to hydroxyl groups present in the phenolic compounds. They possess antioxidant effect by inactivating lipid free radicals or preventing decomposition of hydroperoxides into free radicals. One of the major plant compounds with antioxidant activity is polyphenols. The -OH groups in phenolic compounds are considered have a significant role in antioxidant activity. It is reported, the antioxidant activity of phenolic compounds is be mainly due to their redox properties¹⁹.

Antipyretic activity

Recently in 2013, we conducted a trial in which hydro-methanolic extract of *M. azedarach* leaves exhibited significant ($p < 0.0001$) antipyretic effects at 500 mg/kg dose. The extract showed significant ($p < 0.0001$) reduction in yeast-induced elevated temperature as compared with that of standard drug paracetamol whereas the extract dose 250 mg/kg was less effective when compared with higher dose ($p < 0.05$) against baker yeast induced pyrexia method in experimental animals. Antipyretic activity of *M. azedarach* might be due to the flavonoids and or the alkaloidal components of the plants extracts²⁰.

Cytotoxicity activity

Jafari et al in the year 2013 conducted a study to evaluate the anticancer activity of *M. azedarach* in comparison with *A. indica* on cancer cell lines and also to evaluate their safety in humans by testing them on normal cell line. The study also aimed to determine the active chemical constituents that are responsible for therapeutic effects of *M. azedarach* in traditional usages. In this study, the cytotoxic activity of crude extracts from *M. azedarach* and *A. indica* leaves, pulps and seeds as well as three main fractions of their leaf extracts were determined against HT-29, A-549, MCF-7 and HepG-2 and MDBK cell lines. MTT assay was used to find their cytotoxic activities. Methanol leaf fraction of *M. azedarach* was subjected for phytochemical study. Results of the present study showed that seed kernel extract of *M. azedarach* exhibited the highest cytotoxic activity and selectivity to cancer cell lines (IC₅₀ range of 8.18- 60.10 $\mu\text{g mL}^{-1}$). *A. indica*, crude pulp and crude leaf extracts of this plant showed remarkably stronger anti-proliferative activity (IC₅₀ ranges of 83.45-212.16 $\mu\text{g/mL}^{-1}$ and 34.11-95.51 $\mu\text{g/mL}^{-1}$ respectively) than those of *M. azedarach* (all IC₅₀ values of both plants $> 650 \mu\text{g/mL}^{-1}$). Four flavonol 3-O-glycosides including rutin, kaempferol-3-O-robinobioside, kaempferol-3-O-rutinoside and isoquercetin along with a purin nucleoside, -adenosine were isolated in phytochemical analysis. Methanol leaf fraction of *M. azedarach* seems to be safer in terms of cytotoxicity. Flavonols are abundant in the leaves of *M. azedarach* and these compounds seem to be responsible for many of medicinal effects exploited in the traditional uses²¹.

Effect of *M. azedarach* against bacterial infections

The flower extract of *M. azedarach* was prepared and used to treat bacterial skin infection in children by Saleem and his colleagues in 2002²². Cream was prepared by methanol flower extract of *M. azedarach*. Neomycin was used as a standard drug. The result showed that cream possesses significant cure in several cases. In another study by Saleem et al in 2008 in which extract of *M. azedarach* flower showed potential in curing rabbits suffering from skin infection produced by *Staphylococcus aureus*²³. The effect was compare with standard drug neomycin.

Antiviral activity

A peptide "Meliacine" isolated from *M. azedarach* leaves was found to inhibit the multiplication of foot and mouth disease viruses reported in a previous study by Wachsmann in 1998²⁴.

Alche and his colleagues in 2001 reported that another compound "Meliacarpin" found in the purified extract of *M. azedarach* leaves inhibits the Vascular stomatitis and Herpes simplex virus multiplication *in vitro* when added after infection with no cytotoxic effects²⁵.

Antibacterial activity

Rhaymah in the year 2006 studied the antibacterial activity of the crude leaf extract of (methanol, ethanol, dichloromethane, ethyl acetate and aqueous) of *M. azedarach* against Gram negative and Gram positive bacterial strains using disk diffusion method. Significant inhibition showed ethyl acetate and aqueous extracts of *M. azedarach* against bacteria tested²⁶.

Another study was conducted by Khan et al in 2011 on antibacterial potential of the polar and non-polar extracts of the seeds of *M. azedarach* against eighteen hospital isolated human pathogenic bacterial strains. Petrol, benzene, ethyl acetate, methanol, and aqueous extracts at five different concentrations (1, 2, 5, 10 and 15 mg/ml) were evaluated using disk diffusion method. All extracts of the seeds showed significant antibacterial activity against tested pathogens. However, ethyl acetate extract revealed the highest inhibition comparatively among all other extracts. Therefore, this study also favored the traditional uses of *M. azedarach* reported earlier²⁷.

Anti-nephrolithiasis

In vivo study was conducted by Christina et al in 2006 on rats to determine the effect of aqueous extract of *M. azedarach* on ethylene glycol-induced nephrolithiasis²⁸. The result of the study showed that *M. azedarach* extract reduced the urinary calcium, oxalate and phosphate levels. Thus *M. azedarach* possesses inhibitory potential on induced nephrolithiasis judged by serum and urine levels of creatinine.

Suppression of inducible nitric oxide synthase (iNOS)

Lee et al in the year 2004 reported that two B- carboline alkaloids isolated from *M. azedarach*, 4, 8-dimethoxy-1-vinyl-B-carboline and 4-methoxy-1-vinyl- B-carboline inhibits inducible nitric oxide synthase in lipopolysaccharide/interferon-activated RAW 264.7 cells through the inhibition of (iNOS) protein expression due to decreased mRNA transcription. Furthermore, the inhibition of mRNA transcription of iNOS is, at least in part, associated with the inhibition of NF- κ B activation²⁹.

Antimalarial activity

Antimalarial effect of methanol extract of fruit, bark and leaves of *M. azedarach* was studied by Charturvedi in 2006 on mice against the malaria parasite *Plasmodium berghei*. The study showed that fruit and bark extracts have significant suppression effect on parasitaemia. It was concluded *M. azedarach* has significant anti-malarial effect but less significant than chloroquine³⁰.

Antiulcer activity

Some active constituents present in the lipid fraction of *M. azedarach* extracts were experimented on rats under Gipsing-restrain stress to induce ulcers by Moursi in 1994. The result demonstrated that lipid component of *M. azedarach* which is mainly phytosterol fraction was capable to reduce the free and total HCl combined with reduction of total acidity, and significant increases the volume of gastric juice thus showing its antiulcer potential³¹.

Antiprotozoal activity

Lee and his fellows in the year 2007 reported that *M. azedarach* extract possesses the antiprotozoal effect on *Trichomonas vaginalis* cells through the inhibition of cell multiplication as well as the impairment of protein synthesis³².

Anthelmintic activity

The ethanol extract of *M. azedarach* was tested for its anthelmintic activity against the Tapworm *Taenia solium* and the earthworm *Pheretima posthuma* using Piperazine phosphate as the standard drug in a study by Szewezuk et al in 2003. It was showed by the result that the extract was found active against both the tapworm and the earthworm, also the result was better against Tapworm than Piperazine phosphate³³.

Anti-complementary activity

The aqueous fruit extracts of *M. azedarach* and *Cotoneaster prostratae* were examined on rat complement by Kayastha in 1985. Both extract showed significant anti-complementary activities on rat serum but total inhibition was achieved at higher *M. azedarach* extract concentrations when compared with those of *Cotoneaster prostratae*³⁴.

Wound healing activity

Wound healing potential of *M. azedarach* leaves in alloxan induced diabetic rats was evaluated in 2011 by Vidya. Result showed that the topical application of methanol leaf extract of *M. azedarach* possesses significant wound healing activity in alloxan induced diabetic rats. Delay in wound healing process in diabetes mellitus believed to be largely caused by some basic mechanisms, such as increased blood sugar that impairs blood flow and the release of oxygen, impaired local immune and cell defenses and microbial infections. In this study it has been shown that the topical application of *M. azedarach* leaf extract encourages wound healing in diabetic rats and its effect was analogous with standard povidone iodine. *M. azedarach* leaf extract enhanced the wound healing in diabetic rats which may be due to its antimicrobial activity³⁵.

Toxicological evaluation

Toxicological study of *M. azedarach* flowers and berries was carried out by Rahman et al in 1991 on laboratory animals, i.e. rats and mice by oral and intravenous routes. Aqueous and alcoholic extracts were found to be non-toxic at a dose of 1500 mg/kg orally in mice and rats. LD50 was 395, 500mg/kg (flowers) and 700, 925mg/kg (berries) respectively when injected aqueous extract intravenously, in mice and rats. Alcoholic and aqueous extracts of *M. azedarach* also showed a mild CNS sedative effect. It was found in this study that the flowers and berries of *M. azedarach* are toxic to lower laboratory animals, i.e. rats and mice. Toxicity depends on dose and on route of administration. Higher dose quantity of the extracts depresses markedly the respiratory centre by both routes, oral as well as parenteral. This may be due to the direct action on the respiratory centers because in doses where mortality was observed it was noted that death occurs due to the respiratory cessation. In doses of extracts where animal survived beside respiratory depression, analgesic activity was also observed without the loss of consciousness³⁶.

CONCLUSION

Research in medicinal plants based remedies has gained a renewed focus recently. The reason is that other system of medicine although effective but possesses number of side effects that often lead to hazardous effects. *M. azedarach* though known for its pesticide value also possesses significant medicinal properties. Most of the work carried out on the various extracts of the different parts of the plant. Chemical studies on *M. azedarach* revealed that typical constituents of this plant are alkaloids, terpenoids, anthraquinones and flavonoids. Among them, some exhibit strong bioactivities, especially antifungal, antiviral, anti-implantation and antimicrobial activities. Though *M. azedarach* has various medicinal applications, but it is need of hour to explore its medicinal values at molecular level with the help of various techniques. Further studies should be conducted on *M. azedarach* to evaluate the molecular mechanism of interaction of various plant based drugs with human body in different diseases.

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