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Review on Phyto-chemistry and pharmacological activity of *Melia azedarach*

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Abstract: Medicinal plants as essential additives in foods, beverages, and medications have been a part of human culture since the dawn of time. Medicinal plants' nutritional, pharmacological, biological, and toxicological characteristics have numerous applications in numerous industries. Nowadays, most people rely on complementary and alternative therapies to treat various illnesses derived from natural sources. *Melia azedarach* is one of the plants (Meliaceae family) grown in numerous Indian states. The entire plant or its parts (leaves, stem and roots) have medicinal characteristics and have been used by native and tribal people in various parts of India for a very long time. This plant has traditionally been used to cure various conditions, including piles, itching, asthma, leprosy, and cough. The current study includes a comprehensive analysis of its systematic botanical position, phytochemical analysis, research on the plant's pharmacological activity, and medicinal applications.

Introduction

Overpopulation is one of the extreme issues with the growing international locations like India & which could be extended to nearly 9.2 billion population will be the reach year 2050 (Kaur et al., 2011). Now a day's, human beings depend upon natural as well as ayurvedic treatment (Singh et al., 2020). The natural remedy has developed in the Global scenario over the past few decades. Since the beginning of time, people from practically every civilization have sought to heal benefits from various plants by employing their medicinal properties. It is possible to trace the widespread usage of herbal medicines and healthcare preparations made from traditionally used herbs and medicinal plants back to the emergence of natural products with medicinal characteristics (Sultana et al., 2013).

Melia azedarach Linn may be found in practically every country and is very similar to the Neem tree in appearance. The inner bark primarily consists of alkaloids, which are the components that are responsible for an thelmintic activity. This plant also exhibits features such as anti-cancer activity, anti-malarial activity, anti-bacterial activity and anti-fertility activity (Ervina and Sukardiman, 2018; Efe et al., 2018; Malar et al., 2020). The World Health Organization (WHO) has established a Task Force on Plant Research to control fertility to locate new oral non-steroidal contraceptive pills (Kaur et al., 2011).

Phytopharmaceutical products have a very long history in India, despite the fact that appropriate scientific rationalization is a recent development. As antifertility treatments, various medicinal herbs have been employed. Although only a few contraceptives made from plant extracts have been discovered, their potential is no longer there. There are many issues with plant extracts, one of which could be the loss of the precise active component utilised to improve natural contraceptives (Abbasi et al., 2010). A thorough analysis of its systematic botanical position, phytochemical analysis, pharmacological activity research, and medicinal applications are included in the current paper.

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Botanical description

A native of tropical Asia, *Melia azedarach* (Meliaceae family) is widely distributed in Australia, Southeast Asia, Pakistan, India, and Indonesia. The Philippines, United States of America, Brazil, Argentina, and many other African and Arab nations have lower availability of it (Sultana et al., 2014) (Fig. 1a & 1b).

A variety knows the plant of local names throughout India and abroad, including Sanskrit (Himadruma, vraksha, Mahanimba, Paratanimba), Bengali (Ghora neem), Hindi (Bakayan, Bakain, Mahanimb), Kannada (Bevu), Telgu (Taraka vepa), Tamil (Malai veppam), Gujrati (Bakan, limbodo), Malyalam (Mullay vaempu), Panjabi (Drek), English (Persian lilac), Pride of China and Pride of Asian nation common bead tree (Vishnukanta et al., 2008; Qarabadeen et al., 2005; Azam et al., 2013).

Figure 1a. Whole plant of *Melia azedarach*.

Figure 1b. Leaves & Fruits of *Melia azedarach*.

Description of the plant

The *Melia azedarach* is a medium-sized deciduous tree that may grow up to 45 metres tall, with a spreading crown, and moderately branching limbs. Under normal circumstances, this plant reproduces unrestrictedly from seeds throughout the rain. Direct planting, cutting, and root suckers are further methods of artificial propagation. Smooth, greenish-brown barks mature to a fissured, grey colour. The leaves are compound or bipinnate, alternating, and 20–40 cm long. Leaflets 3–11, serrated, unseasoned, black on the side, lighter underneath. When crushed, they release an unpleasant smell. The inflorescence is a 20 cm long, long axillary raceme. Flowers range from white to lavender to purple and are fragrant. Sepals are separated into five lobes, each about 1 cm long. Petal length is 9 cm and it has five lobes and is pubescent. The staminal tube is deep purple, blue, and brown. Fruit or berries are small, nearly spherical, yellow stone fruits that are smooth, heavy as a stone, and contain four to five black seeds. They have a diameter of 15 metric linear units. The seed has a smooth, brown surface and is surrounded by pulp. Its dimensions are 3.5 mm x 1.6 mm (Sharma et al., 2013; Vishnukanta et al., 2008).

Therapeutic uses

In Ayurvedic medicine, preparations of *Melia azedarach* are used to treat various conditions, including the common cold, inflammation, headaches, stomach issues, diabetes, several types of poisoning, and malaria. In spleen enlargement cases, the gum secreted from the *Melia azedarach* is thought to be useful, and an extract of the timber is used to treat bronchial allergies. Bark decoctions are administered to patients suffering from paroxysmal fever to alleviate symptoms such as thirst, vomiting, lack of appetite, nausea and skin illnesses. The decoction of the plant's leaves is used to treat hysteria, scrofula and leprosy. The juice of the plant's leaves acts as an anthelmintic, emmenagogue, diuretic, expectorant and vermifuge. The juice of the plant's leaves also acts as an emmenagogue. Astringent, refrigerant, emmenagogue, anodyne and diuretic properties can be found in flowers. The consumption of fruits is thought to have anthelmintic, emollient, diuretic and purgative effects. The seeds have several medicinal applications, including as an aphrodisiac, anthelmintic, expectorant, and an aid in treating typhoid fever. In treating various skin conditions, seed oil is frequently applied. The roots are used as an expectorant, astringent and febrifuge in treating constipation. In addition, these plants can be utilized in various contexts, including but not limited to treating conditions such as sciatica, lumbago, piles, cough, bronchial allergies, ulcers, wounds, diabetes, intermittent fever, etc. (Sultana et al., 2014).

Phytochemical Constituents

Initial phytochemical analysis of *Melia azedarach* revealed the presence of a wide range of naturally occurring compounds, including flavonoids, steroids, terpenoids, acids, alkaloids, saponins, anthraquinones and tannins, among others (Fig. 2) (Sharma et al., 2013).

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Leaves

Terpenoids and limonoids are found in the leaves, such as l-Cinnamoyl 3-acetyl-11-hydroxy Meliacarpin, l-Cinnamoyl-3-methacrylate-l1-hydroxy meliacarpin, Deacetylsalannin, 1,3- dicinnamoyl-l1-hydroxy-rneliacarpin, β-Pinene, α-Terpinene, Kaempferol-3-O-β-rutinoside, Rutin. They also contain acids such as palmitic acid and hexadecanoic acid, among others (Sharma et al., 2013; Rishi et al., 2003; Suresh et al., 2008; Asadujjaman et al.,2013).

Fruits

Fruits contain terpenoids and limonoids like 15-epoxy-3, 6-Acetoxy-14, 5-diene-7-one, Amoorastatin, Amorastatone, 11-dihydroxymeliaca-l, Azadirachtin-A, Cinnamoylmelianolone, l-Cinnamoylmelianone, l-Cinnamoyl-3,11-dihydroxy-meliacarpinin, Composite id,1-O-Deacetyl Ohchinolide-B, 1-Deacetylnimbolinin-A, 3-Deoxy mmelian one, 25-Diepoxy-tirucall-7-ene-21-ol, 29-Deacetylsendanin, 3-Epimelianol, 3-Epimeliantriol, Gedunin,12-a-Hydroxyamoorastatin, Meliandiol, Melianol, Melianolone, Melianone, Meliantriol, Nimbolinin-B, Meliatoxin-A1, Melianoninol, Meliatoxin-A2, Nimbolidin-A, Meliatoxin-B1, Nimbolinin-A, Ohchinal, Meliatoxin-B2, Ohchinin, Ohchinin acetate. They additionally comprise acids like octadecanoic acid and stearic acid (Sharma et al., 2013; Rishi et al., 2003; Suresh et al., 2008; Asadujjaman et al.,2013).

Stem bark

It is composed of terpenoids and limonoids such as acetoxy-14β, 15β- epoxygedunanl-ene-three-O-β-DGlucopyranoside, 12-Acetoxyamoorastatin, Amoorastatin, Fraxinellone, 12-Hydroxyamoorastatone, Hydroxy alpha-7, 24-diene-21, 16-olide, Kula tone, Kulinone, Kulolactone, Methylmalonate, a-Pinene, β-Pinene, a-Terpinene, a-A Terpineol. They additionally include flavonoids like 4',5-Dihydroxy flavone-7-O-u-L-rhamnopyranosyl-(1-4)-β-DGlucopyranoside, Anthraquinone like 5,8-Tetrahydroxy-2-methyl anthraquinone, 8-Me ether, 3-O-α-Lrhamnopyranoside. In addition, they consist of steroids such as campesterol, cholesterol, and stigmasterol, as well as linoleic acid, linolenic acid, and oleic acid (9-octadecenoic acid) (Sharma et al., 2013; Rishi et al., 2003; Suresh et al., 2008; Asadujjaman et al.,2013).

Root bark

Root bark contains terpenoids and limuloids like 12-O'Acetyl azadirachtin-A, 12-O-Acetylazedarachin-B, l-Acetyl-3-tigloyl-1, 1-methoxy meliacarpin, 12-O-Acetyl trichilin-B, 2α-Acetyl-29-deacetyl-29-isobuty rylsendanin, Azedarachin-A, Azedarach In-C, n-Cinnamoyl-3-acetyl-11-methoxy meliacarpin, l-Cinnamoyl-3-hydroxy-1, 1-methoxy meliacarpin, 1-Deoxy-3-methacrylyl-11 methoxymeliacarpinin, 1–Deacetylnimbolinin-B, 1, 12-Diacetyltrichilin-B, 7,12-Diacetyltrichilin-B, 29-lsobutyl sendanin, Meliacarpinln, E, Nimbolidin-B, Salannal, Salannin. They also incorporate steroids like 6-βHydroxy-4-canpesten-3-one, 6-β-Hydroxy-4-Stigmasten-3-one, and Azeclarachol (Sharma et al., 2013; Rishi et al., 2003; Suresh et al., 2008).

Roots

The root contains terpenoids and limonoids like 6-Acetoxy-7a-hydroxy-3-oxo-14β, 15-βepoxymeliac-l.5-diene, 6-Acetoxy-3β-hydroxy-7-oxo-14β, 15β-epoxymeliac-l,5-diene-3-0-β-D-glucopyranoside, Azecin-l, Azecin-2, Azecin-3, Azecin-4. Roots incorporate flavonoids like Apigenin-5-O-β-D-galactopyranoside; Steroids like 24- Methylenecydoartanol, 24-Methylenecydoartanone, 4-Stigmastanen-3-one, 4-Campestene-3-one β-Sitosterol, β-Sitosterol-B-D-glucoside; Acids like Trans-cinnamic acid, Vanillicacid (4-Hydroxy-3-methoxy benzoic acid) (Sharma et al., 2013; Rishi et al., 2003; Suresh et al., 2008; Asadujjaman et al.,2013).

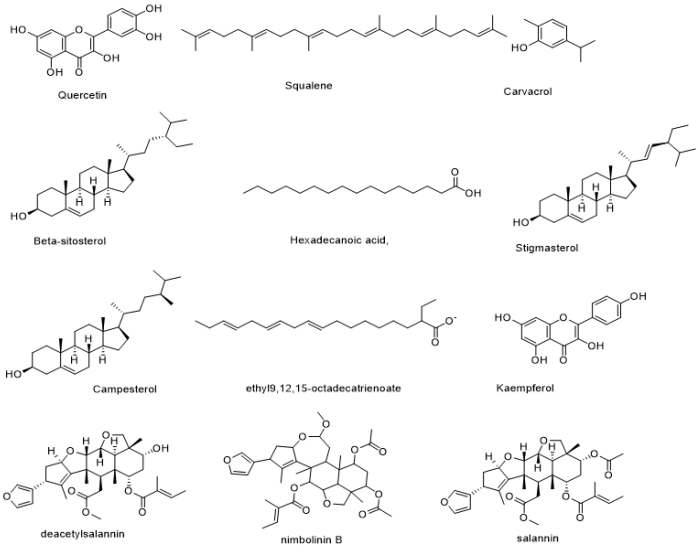

Figure 2. Different chemical structures present in the *Melia azedarach*

Table 1. Characteristics from a physicochemical standpoint, as well as the molecular structure and pharmacological activity of the phytochemicals found in *Melia azedarach*.

Sl. no	Name of compound	Molecular formula	Molecular weight	Nature of compound	Pharmacological activity	References
1	Quercetin	C15H1007	303.23	Flavonoid polyphenol	Anti-inflammatory, Anti-diabetic, anti cancer, antioxidant	Rana et al., 2019
2	Squalene	C30H50	410.7	Hydrocarbon, triterpene	Anti oxidant, anti-tumour	Zih-Rou et al., 2009
3	Car vacrol	C10H14O	105.21	Monoterpenoid phenol	Antimicrobial, antioxidant	Baser et al., 2008
4	β-Sitosterol	C29H50O	414.71	Phytosterol	Anti-fertility activity, antimicrobial, anti-cancer, anti-immflammatory activity, antioxidant	Shrishkumar et al., 2014
5	Hexadecanoic acid	C16H30O2	254.41	Palmitic acid	antioxidants, anti bacterial, antifungal, nematicide, and pesticide	Mustapha et al., 2016
6	Stigmasterol	C29H48O	412.7	Phytosterol	Antioxidant, Antimicrobial, Antifertility activity, antitumour	Kaur et al., 2011
7	campesterol	C28H48O	400.68	Phytosterol	Antimicrobial, antioxidants, anti bacterial, anti-fungal, Anti-fertility activity	Bharwdaj et al., 2014
8	9,12,15-Octadecatrienoic acid ethyl	C20H34O2	306.5	Fatty acid ester	Anti-inflammatory, Insectifuge Hypocholesterolemic, Cancer preventive, Nematicide, Hepatoprotective,	Rigoberto et al., 2017
9	Kaempferol	C15H10O6	286.23	Phytosterol	Antiinflammatory, antioxidant, antistress	Kim et al., 2020
10	Deacetylsalannin	C32H42O8	554.68	Methyl ester	Antimicrobial, antioxidants, anti bacterial, anti-fungal, Anti-fertility activity, anti-tumour	Chauhan et al., 2018
11	Nimbolinin B	C36H48O10	640.8	Triterpene	Anti-bacterial, Anti-malarial, Anti-inflammatory, immune-modulatory, Spermicidal	Shakib et al., 2020
12	Salannin	C34H44O9	596.7	Triterpenoids	Antiulcer and spermicidal activities	Srivastava et al., 2020

Pharmacological activity

Male Contraceptive Potentiality

According to the findings of Azam and colleagues (2013), the rate of sperm motility in male rats treated with (50 mg/kg *M. azedarach* of seeds and 150 mg/kg dosages) was significantly lower than that of the controls. The results also showed a significant decrease in fertility rate at the dose level of 50 and 150mg/kg doses ($p< 0.01$) compared to the controls which means M. azedarach can decrease fertility indices (Azam et al., 2013).

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Anti-fertility activity in females

The anti-implantation, estrogenic/anti-estrogenic, and progestational/anti-progestational effects of the hydro-alcoholic extract of *M. azedarach* roots were demonstrated in a study that was conducted by Vishnukanta and colleagues (2009). It was determined that the extract did not exhibit estrogenic or anti-estrogenic action, even though it displayed a significant amount of anti-implantation and anti-progestational activity. It was hypothesized that the extract contained a particular substance that impedes the biosynthesis, secretion, and properties of ovarian steroids. It also prevents the implantation process by impeding the development of oocytes and Graafian follicles. These effects were thought to be caused by the substance (Vishnukanta et al., 2008).

Folliculogenesis inhibition

Roop et al. (2005) conducted a study using fractions of *M. azedarach* seed extract at 24 mg /kg frame weight day-1 for 18 days to examine the quantitative aspects of follicular growth in cyclic female albino rats. The number of typical single-layered follicles was significantly decreased ($p<0.05$) compared to control mice. When compared to the animal control group, these extracts significantly decreased ($p<0.05$) the overall number of regular follicles in M. azedarach seed (Roop et al., 2005).

Anti-cancer activity

Jafari et al. (2013) conducted a study to evaluate *M. azedarach*'s anti-cancer activities on cancer cell lines and to evaluate their protection in humans by testing them on the normal cell line. The cytotoxic activity of M. azedarach's three major fractions in their leaf extracts was assessed in this work against the MCF-7, HT-29, A-549, HepG-2, and MDBK cell lines. Different chemically active elements found in M. azedarach may be responsible for its therapeutic anti-cancer effect (Jafari et al., 2013).

Anti-bacterial activity

The diffusion method was used by Rhaymah et al. (2006) to demonstrate the antibacterial activity of the crude leaf extract of *M. azedarach* in relation to Gram (+) and Gram (-) bacterial strains. The extract was prepared using a variety of solvents, including methanol, ethanol, dichloromethane, ethyl acetate, and water. The ethyl acetate extract and aqueous *Melia azedarach* showed significant inhibition activity in a microorganism (Rhaymah et al., 2006).

Khan et al. (2011) conducted a further experiment to test the anti-bacterial effectiveness of polar and non-polar extracts from *M. azedarach* seeds against harmful bacterial strains. The disc diffusion method has been used to assess several solvents, including Pet ether, benzene, ethyl acetate, methanol, and aqueous extracts at five different concentrations (1, 2, 5, 10, and 15 mg/ml). The seeds' various solvent extracts all showed anti-bacterial action against infections. Among all the extracts, ethyl acetate extract had the highest inhibitory activity. M. azedarach was chosen as the best conventional anti-bacterial agent (Khan et al., 2011).

In a different experiment, conducted in 2002 by Saleem and his colleagues (2002), *M. azedarach* flower extract was utilized to treat a bacterial skin illness in children. Methanol flower extract from the aforementioned plant was used to create the cream. Neomycin was a commonly prescribed medication. The outcome demonstrated that cream is an effective treatment in many circumstances (Saleem et al., 2002).

In yet another study by Saleem and colleagues (2008), it was discovered that the flower extract of *M. azedarach* possessed the power of healing rabbits suffering from a skin illness brought on by Staphlococcus aureus. Neomycin, considered the gold standard for anti-bacterial testing, was utilized in the study (Saleem et al., 2008).

Antiviral activity

It was demonstrated by Wachsman et al. (1998) that a peptide called "Meliacine" that was derived from *M. azedarach* leaves could suppress the viruses that cause foot and mouth disease (Wachsman et al., 1998). Further research by Alche and his colleagues revealed that the experiment had shown that the isolated compound "Meliacarpin," which is the purified extract of *M. azedarach* leaves, inhibits the multiplication of both vascular stomatitis and herpes simplex virus (Alche et al., 2001).

Anti-malarial activity

In a study conducted on mice, Chaturvedi et al. (2006) looked at the anti-malarial effects of a methanol extract of *M. azedarach*'s fruit, bark, and leaves against the malaria parasite Plasmodium berghei. It has been established that fruit and bark extract both significantly reduce parasitemia. The results showed that *M. azedarach* has strong anti-malarial action, however, it is less significant than chloroquine as a common medication (Charturvedi et al., 2006).

Antiprotozoal activity

According to research by Lee et al. (2007), *M. azedarach* extract has antiprotozoal efficacy against Trichomonas vaginalis by preventing cell division and interfering with protein synthesis (Lee et al., 2007).

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Anti-nephrolithiasis

Aqueous extract of *M. azedarach* was investigated by Christina et al. (2006) in a rat model of ethylene glycol-induced nephrolithiasis. The observation's overall findings supported the hypothesis that *M. azedarach* extract reduced oxalate levels, calcium, and phosphate levels in the urine. Therefore, *M. azedarach* exhibits inhibitory efficacy on induced nephrolithiasis as determined by serum and urine creatinine levels (Christina et al., 2006).

Anthelmintic activity

It was demonstrated that the ethanol extract of *M. azedarach* has anthelmintic action against the tapeworm Taenia solium and the earthworm *Pheretima posthuma* by using piperazine, which served as the experiment's reference drug. As a result of the investigation, it was discov-ered that the extract exhibited activity toward both the tapeworm and the earthworm. In addition, the results demonstrated superior effectiveness in the fight against tapeworm compared to piperazine phosphate (Szewezuk et al., 2003).

Anti-complementary activity

Kayastha BP et al. (1985) conducted a study in which they examined the effects that aqueous fruit extracts of *M. azedarach* had on the complement of rats. The extract had significant anti-complementary effects on rat serum; however, total inhibition was only achieved at higher concentrations of M. azedarach extract (Kayastha et al., 1985).

Hepatoprotective activity

Researchers from Ahmed and colleagues (2012) looked at the possibility that the chemical molecule CCl4 could harm the liver. In addition to histological examination, biochemical parameters such as SGPT, SGOT, ALP, and serum bilirubin were examined. In the group that had been exposed to CCl4, biochemical measures have improved, and histological abnormalities such as steatosis (fatty alterations in hepatocytes) and fibrosis have returned to their normal levels. Additional research is currently being conducted to identify the phytoconstituents in plants that are responsible for the hepatoprotective action (Ahmed et al., 2012).

Antiulcer activity

Moursi and colleagues (1984) conducted experiments on rats using the Gipsing-restrain stress ulcer model and looked at the effects of the lipid fraction of *M. azedarach* extracts. According to the findings, the lipid component of *M. azedarach*, in particular, the phytosterol fraction, was able to significantly lower the free and overall HCl, which was also accompanied by a reduction in overall acidity and a significant amount of antiulcer activity (Moursi et al., 1984).

Suppression of inducible nitric oxide synthase (iNOS)

According to research conducted by Lee et al. (2000), the alkaloids B-carboline, 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. This is accomplished through the inhibition of (iNOS) protein expression, which occurs (Lee et al., 2000).

Antioxidant activity

Researchers Munir et al. (2012) looked at the impact of *M. azedarach*'s antioxidant activity. The TPC (Total Phenolic Contents) and TFC (Total Flavonoid Contents) contents in dried extracts of *M. azedarach* were observed to be within side the range of 74.43-112.10 mg GAE/g DW and 13.32-28.11 mg CE/g DW, respectively. On the other hand, in ambient dried TPC (Total Phenolic Contents) and TFC (Total Flavonoid Contents) observed to according to the findings, the dried extracts of M. azedarach had a higher level of antioxidant activity than the other parts of the plant, including the stem bark, which was shown to have a higher level of antioxidant activity than the other plant parts (Munir et al., 2012).

Antipyretic activity

According to research carried out by Sultana et al. (2013), a hydro-methanolic extract of *M. azedarach* leaves revealed significant ($p<0.0001$) antipyretic effects when administered at a dose of 500 mg/kg. The leaf extract demonstrated a significant ($p<0.0001$) reduction in yeast-induced elevated body temperature compared to the standard drug paracetamol. On the other hand, the leaves extract at the dose of 250 mg/kg turned less effective when compared with a higher dose ($p<0.05$) in opposition to brewer's yeast-induced pyrexia in experimental animals. The flavonoids and/or the alkaloidal that were found in this extract were responsible for the antipyretic effect of *M. azedarach* (Sultana et al., 2013).

Wound healing activity

The wound healing potential of the leaves of *M. azedarach* was examined by Vidya et al. (2012) using an alloxan-induced diabetic rat model. The alloxan-induced diabetic rats model demonstrated that the topical treatment of methanol leaf extract of *M. azedarach* had wound healing capacity. The results revealed this to be the case. Povidone-iodine served as this study's control medication, and the trial results demonstrated that applying a

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topical extract of *M. azedarach* leaf promoted wound healing in diabetic rats. The anti-bacterial activity of the *M. azedarach* leaf extract may be responsible for the faster wound healing seen in the diabetic rats model (Vidya et al., 2012).

Immunomodulatory activity

In a study conducted by Benencia and colleagues in 1997, they found that an extract of *M. azedarach* leaves reduced phagocytosis and phorbol 12-myristate 13-acetate in human monocytes (Benencia et al., 1997).

Antifeedant activity

El-Lakwah et al. (1995) examined the effects of powdered *Melia azedarach* fruits and extracts in petroleum ether and acetone on Sitophilus oryzae F1 offspring reduction and adult repellency. The findings demonstrated that fatalities recorded after exposure to the powder were initially very low for the first week of treatment before gradually increasing to a moderate percent (El-Lakwah et al., 1995).

Conclusion

The ethnomedicinal description, phytochemistry, pharmacological action, and therapeutic use of the herb *Melia azedarach* are briefly discussed in this article. According to the review of this article, *Melia azedarach* has antiulcer, antipyretic, anti-fertility, anti-cancer, antiviral, wound healing, and hepatoprotective properties that make it useful for treating a variety of illnesses. The plant is present in different types of active substances, including terpenoids, flavonoids, steroids, acids, anthraquinones, alkaloids, saponins, and tannins. Therefore, it is possible to draw the conclusion that *M. azedarach* is a medicinal plant that has been traditionally and clinically demonstrated to be adequate for its application. In light of the numerous health advantages, research is urgently necessary to purify the *M. azedarach* components inexpensively and characterize them in respect of potential chemical make-up and mode of action at the molecular basis. These ingredients almost surely have a chance of proving to be beneficial while also being relatively less hazardous than the medications that are currently available.

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