April 2014, Volume-5, Issue-2

Available online at www.ijppronline.in

International Journal of Pharma Professional Research

ISSN NO:0976-6723

Review Article

BIOLOGICAL AND MEDICINAL PROPERTIES OF AZADIRACHTA INDICA: A REVIEW

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Abstract

Neem has a vital role in various problems associated with human health. The chemical constituents present in the neem plant makes it a doctor tree due to its wide scope in biological activities associated with it, and has become a global context today. Neem has been extensively used in Ayurveda, Unani and Homoeopathic medicine and has become a centre of attraction of modern medicine. Hence, the article is aims to utilize the medicinal properties of whole neem plant in various disorders of mankind.

Keywords: Azadirachta indica, Anti viral, Anti fungal, Ant diabetic.

Introduction

Medicinal plants are rich source of novel drugs that forms the ingredients in traditional systems of medicine, modern medicines, nutraceuticals, food supplements, folk medicines, pharmaceutical intermediates, bioactive principles and lead compounds in synthetic drugs**.** WHO pointed out that more than 80% of world's population depends on plants to meet their primary health care needs**.** However, overexploitation of the selected medicinal plant species lead to the reduction in number of plants in the wild and inclusion of their name in the red data book [2].Neem (*Azadirachta indica*) commonly called 'Indian Lilac' or 'Margosa', belongs to the family Meliaceae, subfamily Meloideae and tribe Melieae. *Azadirachta indica* has been used medicinally throughout history by many different cultures. Many compounds have been found in the exudates of the, *Azadirachta indica* plant that have been used medically by humans.

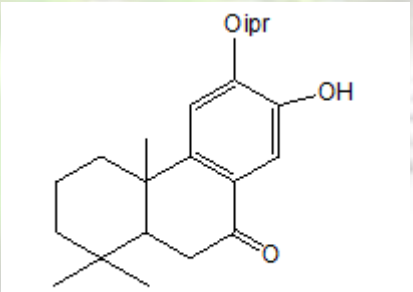
Neem is a member of the Meliaceaefamily.The only congener is *A. excelsa*. Its Sanskrit name, 'arishtha' means 'reliever of sickness' and it is considered as the 'kalpavriksh of kalyuga'. The Persian name of neem is *'Azad- Darakth- E-Hind'* which means 'Free tree of India' (Bhat et al.,, 2008). Neem can be regarded as a valuable plant source for the rationalization of its use in traditional medicine and for modren drug development.

Neem has a far wider array of uses than any other known herb. The first recorded use of neem is attributed to an ancient Indian culture over 4,500 years ago due to its medicinal properties. Neem provides shade, ornamental look, shelterbelt, fuel wood and construction material, and also helps in degraded land reclamation and soil conservation activities. *Azadirachta indica* is tropical evergreen tree, native to India and Burma; it has been transplanted to Africa, the Middle East, South America and Australia.

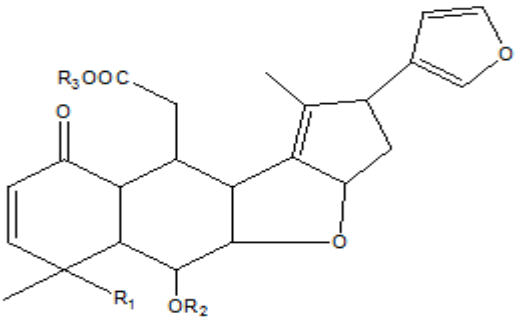
It is especially suited to semi-arid conditions and thrives even in the poorest soil with rainfalls as little as 18 inches (450 mm) per year and temperatures up to 50° C (120° F). It may grow up to 50 feet (15 m) tall and live for 200 years. The lifespan of the Neem tree is described to be anywhere between 150 to 300 years. Neem is evergreen but can shed most of its leaves under dry conditions. The compound (pinnate) leaves are alternate, 20–40 cm long, with 20–30 dark green, serrated leaflets, each about 3–8 cm long. The terminal leaflet is often absent. Young leaves are reddish to purplish in colour. Neem has a strong root system with single deep tap root and extensive lateral roots. Ripe fruit of neem are about 2 centimeters (cm) long and oval shaped. Inside the fruit there is a light coloured seed about 1.5 cm long. The neem tree with many white flowers which smell of honey appear for the first time when the tree is 2 to 3 years old, and the tree bear fruit after 3 to 5 years. Neem trees can grow in areas which have between 400 millimeters (mm) and 1500mm of rain each year. It grows best at an altitude of less than 1,500 meters. Neem trees survive very hot temperatures, up to 44°C and as low as 4°C. Some people reported neem trees surviving light frost.

2. CHEMICAL CONSTITUENT AND PROPERTIES OF NEEM

Chemical investigations of neem were undertaken by Indian pharmaceutical chemists in 1919, whereby they isolated acidic principle in neem oil, which they named as 'margosic acid". However, real chemical research originated in 1942 with isolation of three active constituents, viz, nimbin, nimbidin and nimbinene. In 1963 an Indian scientist extensively examined the chemistry of the active principles of neem. Following the discovery of neem kernel as a locust feeding deterrent, its chemistry has grown considerably. Several compounds have been isolated and characterized. The main feature is that most of them are chemically similar and biogenetically derivable from a tetracyclicterpenes. These are also called liminoids (azadirachtin, meliantrol, salanin etc.) bitter principles and occur in other botanical species as well (Rutaceae and Simaroubaceae). The unraveling of high complex structural features and biogenetic interrelationship represent classic piece of work on natural product chemistry. From the practical side these compounds also exhibit a wide variety of biological activity, for example, pesticides, antifeedants,and cytotoxic properties. Levaesmaily yield quercetin (flavonoid) and nimbosterol (ß- sitosterol) as well as number of liminoids (nimbin and its derivatives). Quercetin (a polyphenolic flavonoid) is known to have antibacterial and antifungal properties. The neem constituent belonging to chemically diverse classes have been divided into two major sections viz. I) isoprenoids, II) non-isoprinoids. The later category comprises glycerides, polysaccharides, sulphurones compounds, flavonoids and their glycosides, amino acids, aliphatic compounds etc**.** Aktar et al.,, (2008).Structure of some constitituents are given below (Fig.1).

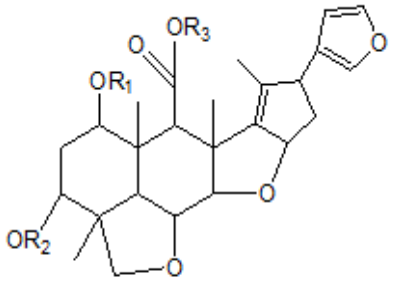


Margosone



Azadirachtin A

Where R_1=COOMeR_2=Ac R_3=Me



Salanin

Where R1=Tg (Tiglica C = 4), R2=Ac, R3 =Me

3. BIOLOGICAL ACTIVITIES OF NEEM

Nishimura et al., (1997) reported antibacterial activity of crude bark extract of neem(*Azadirachtaindica*) against *streptococcus sobrinus*. Antibacterial activity of acetonic and aqueous extracts of neem bark examined on agar plates by using strain of *streptococcus sobrinus*.

Raparla et al., (2011) evaluated *In vivo* antidiabetic activity of neem leaf extract in alloxan induced rats.The results shows that the neem (*Azardirachtaindica*)had beneficial effects on blood glucose levels in glucose-fed hyperglycemic and diabetic rats and it also protects significantly from other metabolic aberrations caused by alloxan.

Chattopadhyay et al., (2004) reported antiulcer activity of neem leaf extract. The extract of neem dose-dependently inhibits gastric lesions induced by restraint–cold stress, ethanol and indomethacin. In stress ulcer model, neem extract is more effective than ranitidine but less effective than omeprazole. Mechanism of antiulcer effect of neem (*Azadirachtaindica*) leaf extract is due to its action on H+-K+-ATPase.

Mukherjee et al., (1999) reported neem (*Azadirachtaindica*) as antibacterial agent against fish pathogenic bacteria.Aquaneem, an emulsified product prepared from kernel of the neem (*Azadirachtaindica*) was tested against four pathogenic bacteria of fish (*i.e. Aeromonashydrophila, Pseudomonas fluorescens, Escherichia coli and Myxobacteria spp.*) to test neem as antibacterial agent.Among all the bacteria tested *A. hydrophila, Myxobacteria spp.* and*P. fluorescens* exhibited maximum sensitivity to Aquaneem (*Azadirachtaindica*) in terms of percentage reduction of bacterial cell population comparison to *E. coli*.

Badam et al., (1999) evaluated *in vitro* antiviral activity of neem (*Azadirachtaindica. A. Juss*) leaf extract against group *B coxsackieviruses*. Antiviral activity of methanolic extract fraction of leaves of neem (*Azadirachtaindica A. Juss*) (NCL-11) was studied for its antiviral activity and mechanism of action against Coxsackie B group of viruses.

Mohanty et al., (2008) carried out antifungal activity of neem (*Azadirachtaindica)*against *Lagenidiumgiganteum* and *Metarhiziumanisopliae* in PYG and Emerson's YpSs agar media. The minimum inhibitory concentration of neem oil for *L. giganteum*showed higher than that for *M. anisopliae*. The minimum fungicidal concentration of neem(*Azadirachtaindica)* oil in PYG medium was lower than in YpSs for both fungi.

Asthana et al., (2006) reported antimicrobial entity from the cyanobacterium*Fischerella*sp. isolated from bark of Neem (*Azadirachtaindica*) tree. The active principle in a methanolic extract of the laboratory-grown cyanobacterium, *Fischerella*sp. isolated from neem (*Azadirachtaindica*) tree bark found to be active against *Mycobacterium tuberculosis, Enterobacteraerogenes, Staphylococcus aureus, Pseudomonas aeruginosa, Salmonella typhi, Escherichia coli* as well as three multi-drug resistant *E. coli* strains in *in vitro* assays. Antimicrobial activity was evaluated by using the slightly modified Kirby Bauer Disk Diffusion Susceptibility Method.

Ranganathan et al., (1996) evaluated *in vivo* and *in vitro* antidermatophytic activity of Azadirachtaindica. Minimum inhibitory concentration of petroleum ether extract recorded for strains of *Trichophyton rubrum, Trichophytonm entagrophytes, Trichophytonton surans, Microsporum nanum* and

Epidermophyton floccosum were above 1000 μg/ml. and those of ethanolic and ethyl acetate extract of neem leaf ranged from 500-1000μg/ml for *Trichophytonm entagrophytes, Trichophyton rubrum and Trichophytonton surans.*

Pendse et al., (1977) reported anti-Inflammatory, immunosuppressive and some related pharmacological actions of the water extract of neem in albino rats and immunosuppressive effect in albino rabbits. lt significantly inhibited acute inflammatory response evoked by carrageenin in a doss of 50 mg/100 g given orally and intraperitoneally. In chronic inflammation produced by crctcn-oil in granuloma pouch technique, 20 mg/1 00 g of the water extract significantly inhibited granulation tissue response; the reduction in exudative response and increase in the weight of adrenal glandswerenot significant. A significant inhibition of primary and secondary phases was observed Inadjuvantinduced arthritis. It significantly inhibited antibody formation by typhold "H" antigen. Mild analgesic effects of its own as well as potentiation of morphine analgesia were possessed by the extract but it was devoid of antipyretic effect.

Gupta et al., (1998) reported increasing actlon of vascular permeability by azadirachtaindica seed oil (neem oil). Neem oil produced an increase in the cutaneous capillary permeability. The capillary permeability increasing action of neem oil was discernible 1 h after its application and persisted over 4 h. Histamine action was manifested within 0.5 h and lasted upto 2 h. of its injection. Capillary permeability action was not observed at 24h of the application of tet substances. Normal saline had no effect on capillary permeability. Investigation showed that neem oil produced increase in vascular permeability. It is likely that direct injury to mast cell granules by neem oil may be responsible for increase in vascular permeability by producing chemical injury at the site of local injection.

Venugopal *et al.*, (1994) evaluated antidermatophytic activity of neem leaves in vitro. The antidermatophytic activity of the aqueous and ethanolic extracts of Neem (Azadirachtaindica) leaves was investigated against 88 clinical isolates of dermatophytes by agar dilution. The isolates included *Microsporumcanis, M.audouinii (5), Trichophytonrubrum(6),Tmentagrophytes, T.violaceum, T.simii , T.verrucosum, T.soudanense, T.erinacei and Epidermophytonfloccosum.* The results were compared with the minimal inhibitory concentrations of ketoconazole. The ethanolic extract was found to be more active inhibiting 90% (MIC 90) of the isolates at a concentration of 100 ug/ml. The MIC 50s and MIC 90s of the aqueous extract were 500 and > 500 ug/ml whereas the values for ketoconazole were 1 and 2.5 ug/ml 'respectively. Of the 88 isolates tested (55 isolates of *Microsporum*species, 31 isolates of *Trichophyton*species and 2 of E. floccosum) 82 were sensitive to the ethanolic extract at a concentration of 100 pg/ml and all at 250 t@ml. The aqueous extract inhibited 74 isolates at an MIC of 500 pg/ml and for 14, the MlCs were > 500 &ml whereas ketoconazole inhibited 71 isolates at a concentration of 1 microgram/ml and all at 5 microgram/ml.

Bopana et al., (1997) reported antidiabetic and antihyperlipaemic effects of neem seed kernel powder on alloxan diabetic rabbits. In alloxandiabeticrabbits there was a significant ($P<0.001$) increase in fasting blood glucose and urine sugar and there was a significant decrease ($P<0.001$) in body weight and total haemoglobin content. There was a significant increase in body weight and haemoglobin level, and a significant decrease in fasting blood glucose (FBG) and urine sugar in diabetic rabbits treated with NP, glibenclamide, insulin and in combination of NP and glibenclamide. Though the entire antidiabetic drugs used significantly decreased the FBG levels, combination therapy of NP (250 mg/kg) and glibenclamide (0.25 mg/kg) p to all the other groups. There was a significant ($P<0.001$) roduced greater reduction in FBG as

compared amelioration of body weight and total haemoglobin content in the diabetic phosphatase increased considerably in alloxan diabetic rabbits compared to the normal control. Treatment with various antidiabetic agents in the above experiments significantly reduced the enzyme activity. Treatment of NP with glibenclamide produced a significant (P<0.001) decrease of HMG CoA reductase, alkaline phosphatase and serum acid phosphatise activity when compared to other experimental antidiabetic agents (Table 3). Liver glucose 6-phosphatase (G6P) and serum lactate dehydrogenase (LDH) activity significantly (P<0.001) reduced in alloxan diabetic rabbits. On the contrary, Hexokinase activity significantly increased by other experimental antidiabetic agents. The most significant (P<0.001) changes were observed in the combination of NP (250 mg/kg) and glibenclamide (0.25 mg/kg). From our experiments we have found out that, though both NP and glibenclamide produced significant fall in lipid parameter and enzyme activities, the changes were more prominent when combination of NP and glibenclamide were used.

Khosla et al., (2000) reported antinociceptive activity of***Azadirachtaindica*(neem)** in rats

Tail flick reaction time was significantly increased in rats both with leaf extract and seed oil.

Naloxone pretreatment partially reversed the antinociceptive action of both leaf extract and seed oil. GAA induced writhing was reduced with both neemextact and seed oil. Neemextact was more potent than seed oil.

Lloyed et al., (2009) reported the anticandidal activity of *azadirachtaindica* .Hexane and alcoholic extact of neem seed was found to have promising anticandidal activity.

Olabinri et al., (2009) carried out experimental classification of the antioxidant capacity

of the leaf, stem and root barks of *Azadirachtaindica.* The ferric reducing antioxidant power (FRAP) and total phenolic concentration of the leaf, stem and root barks of M *Azadirachtaindica* growing in Ogbomoso, Nigeria were evaluated in vitro. Only the leaf of A. indica belonged to good FRAP. Both the stem and root bark of A. indica and all the parts of M. indica investigated belonged to high FRAP. Experimental results revealed that the antioxidant capacity ranged from 6.80 - 9.20, 12.40 - 13.00 and 10.20 -13.203 mM of reduced Fe3+ for the leaf, stem and root bark, respectively in A. indica. In M. indica, the antioxidant capacity ranged from 12.20 - 15.20, 11.00 - 11.80 and 11.20 - 12.20 mM of reduced Fe3+ for the leaf, stem and root bark, respectively. The total phenolic concentration and antioxidant capacity of M. indica stem bark showed a high significant positive correlation (r = 0.9439; p = 0.05). The total phenolic concentration of the root bark of A. indica showed a high positive significant correlation with antioxidant capacity (r= 0.9850; p= 0.05). All the plant parts examined might be exploited in clinical medicine as protective factors because of their good and high antioxidant capacities.

Prashant et al., (2009) studied the effects of neem extact on four micro-organism causing dental carries, *S. mutants, S. salivavius, S. mitis, S. sanguis.*

Kale et al., (2003) studied the effect of aqueous extract of azadirachtaindica leaves on hepatotoxicity induced by antitubercular drugs in rats. Aqueous leaf extract of neem significantly (P<0.05) prevented changes in the serum levels of bilirubin, protein, alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase. Similarly it significantly prevented the histological changes as compared to the group receiving antitubercular drugs. It also significantly reversed the biochemical and histological changes.AI aqueous leaf extract prevents as well as reverses the hepatotoxic damage caused by antitubercular drugs and the reversal of hepatotoxicity effected by the AI aqueous leaf extract is superior to that effected by withdrawal of antitubercular drugs. The hepatoprotective property of AI aqueous leaf

extract may also be because of its other properties like anti-inflammatory property which may prevent inflammatory hepatic damage, immunomodulating property and anti-oxidant property thereby reducing

the oxidative stress imposed by the drugs; this antioxidant mechanism seems to be important as AI aqueous leaf extract has been shown to reduce oxidative stress10 and oxidative stress has been found to be the most important mechanism in hepatotoxicity of anti - tubercular drugs.

Shravan et al., (2011) studied the hypoglycemic action of *Azadirachtaindica*in diabetic rats. After treatment for 24 hrs, *Azadirachtaindica* 250mg/kg (single dose study) reduced glucose level (18%), cholesterol (15%), triglycerides (32%), urea (13%), creatinine (23%), and lipids (15%). Multiple dose study for 15 days also reduced the level of creatinine, urea and lipids. In a glucose tolerance test in diabetic rats with neem extract 250 mg/kg demonstrated glucose levels were significantly less compared to the control group. *Azadirachtaindica*significantly reduce glucose levels at 15th day in diabetic rats

Sithisarn et al., (2005) reported the antioxidant activity seen by young flowers and leaves. An indicator of oxidative stress, malondialdehyde (MDA), was reduced by 46.0% and 50.6% for flower- and leaf-based extracts, respectively.

Aditi et al., (2011) studied the larvicidal properties of the extracts of *Azadirachtaindica*. Laboratory reared larvae were exposed to 1ppm concentration of *Azadirachtaindica.* Result showed that the *Azadirachtaindica*elicited 70-99% mortality to larvae. The extract of *A. indica*wasfound to be significantly effective in controlling *Culex larvae*.

Isah et al., (2003) evaluated the antimalarial activities of the tablet suspension of the bark and leaf of Azadirachtaindica on *Plasmodium yoellinigeriensis* infected mice. The suspension containing bark and leaf exhibited high prophylactic, mode-rate suppressive and a very minimal curative schizonticidal effect. The tablet suspensions from the leaf and bark at a Juss) leaf concentration of 800 mg/kg and chloroquine at a concentration of 62.5 mg/kg body weight produced average percentage (%) parasitaemia of 79.6%, 68.2% and 99.5% for leaf, bark and chloroquine, respectively, in chemosuppression.

4. CONCLUSION

By reviewing the importance of neem tree in national, regional and international perspective there is an urgent need to study its diversity and develop effect measures tostore it for current and future use. At the same time it is also essential to undertake ethnobotanical studies to link its various therapeutic uses with folklore remedies usedby tribes in different areas of its occurrence.

In recent years, ethno-botanical and traditional uses of natural compounds, especially of plant origin received much attention as they are well tested for their efficacy and generally believed to be safe for human use. It is best classical approach in the search of new molecules for management of various diseases. Thorough screening of literature available on *Azadirachtaindica* depicted the fact that it is a popular remedy among the various ethnic groups, Unani, Ayurvedic and traditional practitioners for treatment of ailments. Researchers are exploring the therapeutic potential of this plant as it has more therapeutic properties which are not known.

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