Research Journal of Medicinal Plant

ISSN 1819-3455

Academic Journals Inc.

www.academicjournals.com

Research Journal of Medicinal Plant 5 (3): 230-245, 2011
ISSN 1819-3455 / DOI: 10.3923/rjmp.2011.230.245

The Growing Importance of Neem (*Azadirachta indica* A. Juss) in Agriculture, Industry, Medicine and Environment: A Review

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ABSTRACT

There has been astronomical increase in the costs of chemical fertilizers, agrochemicals, animal feeds and synthetic drugs in the developing countries, with an increasing indebtedness and acute poverty. This situation exerts enormous pressure to explore local resources, handy to combat these deficits and improve quality of life of the people. One of such available resources with great potentials in the 21st century is the neem (*Azadirachta indica* A. Juss) tree. Neem belongs to the family Meliaceae. It is the most versatile, multifarious trees of tropics, with immense potentials. It possesses maximum useful non-wood products such as leaves, bark, flowers, fruits, seeds, gum, oil and neem cake than any other tree species. Biologically neem has numerous bioactive ingredients with diverse applications. These bioactive ingredients are known to have antiallergenic, antidermatic, antifeedent, antiviral, antifungal, anti-inflammatory, antipyorrhoeic, antiscabic, insecticidal, larvicidal, anti-implantation, nematicidal, spermatocidal and other biological activities. This review is an attempt to assemble all the major research findings in neem which is of direct relevance to environment, industry, medicine and agriculture.

Key words: Neem, industry, agriculture, medicine, environment

INTRODUCTION

The neem is a tropical evergreen tree native to Indian sub-continent (Roxburgh, 1874). It has been used in Ayurvedic medicine for more than 4000 years due to its medicinal properties. Most of the plant parts such as fruits, seeds, leaves, bark and roots contain compounds with proven antiseptic, antiviral, antipyretic, anti-inflammatory, antiulcer and antifungal uses. It has great potential in the fields of pest management, environment protection and medicine. Neem is a natural source of eco-friendly insecticides, pesticides and agrochemicals (Brahmachari, 2004). Neem is considered to be a part of India's genetic diversity (Sateesh, 1998). It is the most researched tree in the world and is said to be the most promising tree of 21st century. The tree has adaptability to a wide range of climatic, topographic and edaphic factors. It thrives well in dry, stony shallow soils and even on soils having hard clay pan, at a shallow depth. Neem tree requires little water and plenty of sunlight (Sateesh, 1998). The tree grows naturally in areas where the rainfall is in the range of 450 to 1200 mm. However, it has been introduced successfully even in areas where the rainfall is as low as 150 to 250 mm. Neem grows on altitudes up to 1500 m (Jattan *et al*., 1995;

Chari, 1996). It can grow well in wide temperature range of 0 to 49°C (Hegde, 1995). It cannot withstand water-logged areas and poorly drained soils. The pH range for the growth of neem tree lies in between 4 to 10. Neem trees have the ability to neutralize acidic soils by a unique property of calcium mining (Hegde, 1995).

Biologically active principles isolated from different parts of the plant include: azadirachtin, meliacin, gedunin, salanin, nimbin, valassin and many other derivatives of these principles. Meliacin forms the bitter principles of neem seed oil; the seed also contain tignic acid (5-methyl-2-butanic acid) responsible for the distincitive odour of the oil (Schmutterer, 1990; Uko and Kamalu, 2001; Lale, 2002). These compounds belong to natural products called triterpenoids (Limonoids). The active principles are slightly hydrophilic, but freely lipophilic and highly soluble in organic solvents like, hydrocarbon, alcohols, ketones and esters (Schmutterer and Singh, 1995). Therefore, this review will focus on the relevance of neem and its products in agriculture, industry, biomedicine and environment.

ORIGIN AND DISTRIBUTION OF NEEM

Two species of *Azadirachta* have been reported, *Azadirachta indica* A. Juss-native to Indian subcontinent and *Azadirachta excelsa* Kack. confined to Philippines and Indonesia (Jattan *et al*., 1995; Hegde, 1995). The former grows as a wild tree in India, Bangladesh, Burma, Pakistan, Sri Lanka, Malaysia, Thailand and Indonesia. Presently neem trees can be seen growing successfully in about 72 countries worldwide, in Asia, Africa, Australia, North, Central and South America (Ahmed *et al*., 1989; Sidhu, 1995; Sateesh, 1998; Fathima, 2004).

There are an estimated 25 million trees growing all over India (Rembold, 1996), of which 5.5% are found in Karnataka and it is in the third place next to Uttar Pradesh (55.7%) and Tamilnadu (17.8%) occupying the first two places respectively. The other states of India where neem tree is found growing includes Andhra Pradesh, Assam, Bihar, Delhi, Gujarat, Haryana, Himachal Pradesh, Kerala, Madhya Pradesh, Maharashtra, Meghalaya, Orissa, Punjab, Rajasthan, West Bengal along with Andaman and Nicobar Islands, the Union territory (Sindhuveerendra, 1995; Chakraborthy and Konger, 1995; Bahuguna, 1997; Fathima, 2004). India stands first in neem seed production and about 442,300 tons of seeds are produced annually yielding 88,400 tons of neem oil and 353,800 tons of neem cake.

TAXONOMICAL CLASSIFICATION OF NEEM

Neem is a member of the Mahogany family. It has similar properties to its close relative, *Melia azederach*. The word *Azadirachta* is derived from the Persian azaddhirakt (meaning 'noble tree'). The taxonomic positions of neem are as follows:

Order: Rutales
Suborder: Rutinae
Family: Meliaceae
Subfamily: Melioideae
Tribe - Melieae
Genus: *Azadirachta*
Specie: *Indica*
Latin: *Azadirachta indica*

Indian: Holy tree, Indian lilac tree
Hindi: Neem, Nim
Sanskrit: Nimba
Hausa: Dogon yaro
Igbo: Ogwu akuma

BOTANICAL DESCRIPTION OF NEEM

It is a hardy, fast-growing evergreen tree with a straight trunk, long spreading branches and moderately thick, rough, longitudinally fissured bark. Mature trees attain a height of 7-15 m (23-50 feet) (Ogbuewu, 2008). The tree starts producing the yellowish ellipsoidal drupes (fruits) in about 4 years, becomes fully productive in 10 years and may live for more than 200 years. The leaves are compound, imparipinnate, comprising up to 15 leaflets arranged in alternate pairs with terminal leaflets (Ogbuewu, 2008). The leaflets are narrow, lanceolate, up to 6 cm long. The flowers are abundant, sweet-smelling white panicles in the leaf axils. Seed propagation in nurseries followed by direct planting in the field is the accepted method to produce plantation stands (Ogbuewu, 2008). The one seed neem fruit is yellow when ripe and is about one inch long (Ogbuewu, 2008). Neem flowers mature from May to August (Koul *et al*., 2006) in India.

CHEMISTRY OF NEEM

Major chemical constituents of neem are Terpenes and Limonoids. The major active components in the Limonoids are azadirachtin, 3-deacetyl-3- cinnamoylazadirachtin, I-tigloyl-3-acetyl-II-methoxyazadirachtin, 22, 23-dihydro-23β-methoxyazadirachtin, nimbanal, 3-tigloylazadirachtol, 3-acetyl-salannoV nimbidioV margocin, margocinin, margocilin and others (Ogbuewu, 2008). Terpenoids are isoazadirolide, 6 nimbocinolide, nimbonone, nibonolone, methylgrevillate and Margosinone. Neem increases the production of Glutathione-s-transferase, thus improving the ability of the liver to detoxify itself of chemical contamination.

NEEM AND ENVIRONMENTAL PROTECTION

Afforestation: The large scale plantation of neem trees help to combat desertification, deforestation, soil erosion and to reduce excessive global warming (Sateesh, 1998). Neem has high rate of photosynthesis and liberates more oxygen than many other tree species, thus purifying the atmosphere (Nigam *et al*., 1994). Neem products have water purifying activity. Neem leaf powder could be used as biosorbent for the removal of dyes like Congo red from water (Bhattacharyya and Sharma, 2004). The temperature under the neem has been found to be ~10°C less than the surrounding temperature, during hot summer months in the northern parts of India. In agro-forestry, neem product benefits extended to providing shade, firewood, timber, wind breaks, shelter belt and check against desertification in the semi-arid zone of northern Nigeria.

Neem has the ability to re-sprout after cutting and to re-grow its canopy after pollarding. Thus it is highly suited for pole production. In Saudi Arabia neem plantation when full grown is expected to provide shade to about two million pilgrims (Ahmed *et al*., 1989). In Nigeria, neem forms about 90% of the trees in the forestry plantations established in the 12 states within the savanna zone under the afforestation programme, Nigeria inclusive (Nwokeabia, 1994). In Chad, neem constitutes about 17% of the tree cover (Ohabuike, 1995). Neem plantations have been used for halting the spread of Sahara desert in the countries from Somalia to Mauritania.

PEST MANAGEMENT PROSPECTS

The dependency on synthetic chemicals during early and middle twentieth century has prompted the large scale synthesis of newer chemicals (pesticides). Many a times, the side effects of the synthetic pesticides are more serious than problems themselves. They are also known to cause health problems in farmers of both developed and developing countries. According to World Health Organization estimation, annually 220,000 deaths occur due to acute poisoning caused by synthetic pesticides (Sateesh, 1998).

Neem based pesticides are found to be much safer in this regard. Today, neem has gained importance internationally as all communities have inclined towards green technology. Neem products have no ill effects on humans and animals and have no residual effect on agricultural produce. This makes neem the best, reliable substitute to hazardous pesticides. The demand for chemical pesticides will be reduced by large scale use of neem based pesticides that will in turn reduce the load of synthetic chemicals in environment.

Today, modern societies, finding themselves confounded in the web of their creation, are willing to revert to nature for remedies and neem tree provides a promising means in this matter. Neem wood is durable and termite resistant and thus used as mulch materials. The pesticidal activity of neem span a wide spectrum, having repellent, phagodeterrent (antifeedant), insect growth regulatory (IGR), anti-ovipositional, fecundity and fitness reducing properties on insects. Schmutterer and Singh (1995) listed 413 insect pest species sensitive to neem products. These principles act as ecdysteroid analogues, which affect corpus cardiacum and block reproductive and growth processes in most insects causing sterility in females and degenerative changes in male testis due to disturbance in insect metabolism. Formulations like: Margosan O(R), Neemix (TM), Azatin(R), NIM-20 and NIM-76, gave negative result with respect to toxicity effect on mammals (Schmutterer, 1990; Govindachari *et al*., 2000). Hence, Neemix (TM), was registered for use on vegetables in US for its inherent safety. In most tests, neem products performed equally or sometimes better than synthetics like Pirimiphos-methyl (Actellic 25 EC), Permethrin and Lindane (γBHC) (Ogunwolu and Oddunlami, 1996; Lale and Mustapha, 2000). Furthermore, the oriental yellow scale insects *Aonidiela orientalis* threatens survival of this Jewel in the savanna (Mahmood, 1995), through necrosis, chlorosis and scorching of the whole foliage, as they inject toxic metabolites into the foliage.

Neem based pesticides are easy to prepare, cheap and highly effective and thus constitute an important source of pesticide for economically poor third world country farmers (Brahmachari, 2004). Neem bio-pesticides are systemic in nature and provide long term protection to plants against pests. Pollinator insects, bees and other useful organisms are not affected by neem based pesticides (Tanzubil, 1996).

Organic fertilizer prospects: Neem cake is a cheap and useful fertilizer. The plant debris is potential source of organic manure (Brahmachari, 2004). Neem cake coated with urea has been produced, which when used increases nitrogen assimilation compared to untreated urea. Neem leaves could be used as a source for the preparation of vermi-compost having both fertilizer and pesticidal potential (Gajalakshmi and Abbasi, 2004).

Biological Nitrogen Fixation (BNF) maintains soil nitrogen (N) fertility. Non-symbiotic micro organisms like photosynthetic bacteria and Blue Green Algae (BGA) enhance this process. It is also known to increase soil fertility and water holding capacity. In field experiments neem cake stimulate algal growth by suppressing the grazers particularly Ostracods (class: Crustacea). BGA

biomass tripled and N-fixation activity increases by 10 fold (Grant *et al.,* 1983). The underlying mechanism is acute toxic effect rather than anti-feedant on the Ostracods. Admixing neem cake with urea fertilizer improves efficiency of fertilizer utilization in crop production by gradual release of nitrogen to crops (Ketkar, 1983). In tomato fields, neem cake significantly reduce root-knot nematode index to zero, with improved growth of tomatoes. The cake inhibited larval emergence and egg hatching. Finally these effects of neem enable exploitation by Nigerian, Indians and other Asians.

NEEM AND AGRICULTURE

Animal feeds: The livestock industry in developing countries has been plagued by numerous problems, which include scarce feed ingredients that are in strict competition with man's dietary need. The high cost of conventional feedstuff has already sent a lot of livestock farmers out of business, thus leading to reduction in overall animal protein production and availability for humans dietary's need. The provision of feed alone has been reported to account for 60-80% of total cost of livestock production in developing countries alone (Igboeli, 2000; Esonu, 2006). In view of this, there is increased interest by livestock farmers on the search for non conventional feed ingredients of comparable quality that are believed to be cheaper such as leaf and seed meals of ethnomedicinal plants (Okoli *et al*., 2001, 2002).

In an effort to develop new feedstuff for animal rearing, a number of researchers in recent times has investigated the proximate composition of neem seed cake (Bawa *et al*., 2006; Uko and Kamalu, 2001) and leaf meal (Oforjindu, 2006; Esonu *et al*., 2005, 2006; Ogbuewu *et al*., 2010a, b) and its use as feedstuff in poultry (Esonu *et al*., 2005; Oforjindu, 2006; Uko and Kamalu, 2007) and rabbits (Sokunbi and Egbunike, 2000a; Ogbuewu, 2008). Result of proximate analysis of neem showed that neem leaf meal had of 92.42% dry matter, 7.58% moisture, 20.68% crude protein, 16.60% crude fibre, 4.13% ether extract, 7.10% ash and 43.91% nitrogen free extract (Esonu *et al*., 2005; Oforjindu, 2006; Ogbuewu, 2008).

Neem cake has also been very widely used as animal feed (Bawa *et al*., 2006;Uko and Kamalu, 2007). Despite the bitter components, livestock consume diets containing varied percentage of neem cake. Alkali treatment of neem cake with caustic soda yields palatable product, by removing the toxicant triterpenoids (Devakumar and Dev, 1993). Nagalakshmi *et al*. (1996) and Verma *et al*. (1998) reported beneficial effect of alkali treated (10-20 g NaOH) neem kernel cake incorporated into poultry feeds. It resulted to an increased feeding value and protein utilization with spectacular growth. However, no significant difference was observed among the different dietary groups in feed intake, egg production, egg quality, fertility, hatchability and chick weight (Nagalakshmi *et al*., 1996; Verma *et al*. 1998).

Neem oil and de-oiled neem seed cake are used as animal feed. Neem oil which is rich in long chain fatty acids is used in poultry feed. Deoiled neem seed cake is rich in essential amino acids, crude proteins, fiber contents, sulphur and nitrogen (Uko and Kamalu, 2007).

Eco-friendly agrochemicals: Approximately one third of world's agricultural food stuffs get destroyed by more than 20,000 species of field and storage pests and diseases (McEwen, 1978). To prevent this loss, large amounts of synthetic pesticides are applied, out of which only 0.1% reaches the target pests and more than 99% contaminates the ecosystem (Sateesh, 1998). In addition, synthetic agrochemical usage has resulted in development of resistant pests and pathogens. Cost-effective, non toxic, biodegradable, eco-friendly and botanical soft-agro chemicals are the need

of present day agriculture as an alternative to hazardous and recalcitrant synthetic chemicals (Sateesh, 1998). Neem tops the list of 2,400 plant species that are reported to have antimicrobial properties and is regarded as the most reliable source of eco-friendly agrochemical property. Neem is also used as a bio-control agent to control many plant diseases (Kak, 2000). The insecticides from neem are non-phytotoxic with good shelf life and effective against a wide range of insects and pests.

Neem products are effective against more than 350 species of arthropods, 12 species of nematodes, 15 species of fungi, 4 strains of viruses, 2 species of snails and 1 crustacean species (Saxena *et al*., 1989; Nigam *et al*., 1994; Singh and Raheja, 1996; Mehta, 1997). Two tetracyclic triterpenoids - meliantetyraolenone and odoratone isolated from neem exhibited insecticidal activity against *Anopheles stephensi* (Siddiqui *et al*., 2003). Over 195 species of insects are affected by neem extracts and insects that have become resistant to synthetic pesticides are also controlled with these extracts. The apprehension that large-scale use of neem based insecticides may lead to resistance among pests, as being observed with synthetic pesticides, has not been proved correct. This is because the neem based insecticides have relatively weak contact effect in insects and also they have unique mode of action on insect's life cycle and physiology.

Today, many neem bio-pesticides are now in market world over (Khanna, 1992; Brahmachari, 2004). Commercially available neem formulations like Achook (0.15% E.C.), Bioneem (0.03% E.C.), Nimbicidine (0.03% E.C.) and Neemark (0.03% E.C.) showed antifungal activity against pathogenic fungi *viz*., *Fusarium oxysporum, Alternaria solani, Curvularia lunata, Helminthosporium* sp. and *Sclerotium rolfsii* (Bhonde *et al*., 1999).

NEEM AND BIO-MEDICINE

Ethnoveterinary usage: In third world countries, neem has been used for centuries to provide health cover to human and livestock in various forms. In poultry, the bark is used to treat wounds, diarrhoea, ticks and lice (Ogbuewu, 2008). In the poultry industry, aflatoxicosis caused by *Aspergillus flavus* which originates from contaminated poultry feed is prevented using neem leaves. Neem leaf extract inhibits the production of aflatoxin by *Aspergillus parasiticus* (Allameh *et al*., 2002) and Patulin production by *Penicillium expansum* (Mossini *et al*., 2004). The processed neem cake has wormicidal activity and can be used as an excellent poultry feed. The leaves are used to treat abscesses and also applied after castration (Ogbuewu, 2008). They are also effective against bleeding, udder infections, fever, foot rot and lice in ruminants. Neem leaf has anti-hyperglycaemic and hypocholesmic effects in rabbits (Sokunbi and Egbunike, 2000b; Ogbuewu *et al*., 2010a, b) and poultry (Oforjindu, 2006; Esonu *et al*., 2006).The seeds are used for the treatment of ticks in ruminants and the bark, seeds, leaves and roots are used as an insect repellent.

All parts of the plant, as well as the gum and oil, are effective against worms, wounds in the mouth, glossitis, *E. coli, bacillosis*, swelling of the liver, jaundice, bloody dysentery and intestinal wounds (Ketkar and Ketkar, 1995). They are also used for constipation, indigestion, respiratory and throat disorders, asthma, pleuropneumonia and swelling of the mucous membranes in the respiratory tract and lungs. They are also used in skin disorders including ringworm, alopecia, eczema, urticaria, scabies, ticks and lice. Other minor indications include metritis, orchitis and tetanus, rinderpest, rheumatism, stoppage of urination, swelling of the kidney, mastitis, otitis and abscess in the ear (Ogbuewu, 2008). Alcohol and aqueous extracts of flowers of neem exhibits lethal effect against cattle filarial parasite *Setaria cervi* (Mishra *et al*., 2005). Livestock insects such as maggots, horn flies, blow flies and biting flies are controlled traditionally using neem.

Neem and ethnomedicinal uses: In West Africa, India, Burma, etc., both aqueous and alcohol extracts of bark and leaves of neem are effective anti malaria agents, particularly on chloroquine resistant strains (Badam *et al.*, 1987; Udeinya *et al.*, 2008). One active component, gedunin gave significant control as effective as quinine on malaria (Khalid *et al.*, 1989; Subapriya and Nagini, 2005). The mechanism is possibly redox status of red blood cells (RBC) on parasite. The plasmodial parasite generates oxidant, while neem extracts reduced the oxidized cells to destroy the malaria parasite.

Furthermore, neem barks and leaves posses strong antiseptic property warranting use as active ingredient in tooth paste in India and Germany. While aqueous extract of leaves exhibit laxative potentials by increased bowel movement (Uko *et al.*, 1995), over dose could however produce severe abdominal cramps or rectal prolapse. Kloos and McCullough (1987) reported potency of neem seed oil on snail fever (*Schistosomiasis*) with the active principle being mulluscicidal, ovicidal and cercariacidal. Several herbalists opined that neem products have broad spectral chemotherapeutic effect on the Flat, Tape and Round worms (Devakumar *et al.*, 1985). Dental gel containing neem leaf extract reduces the oral plaque index and bacterial count (Pai *et al.*, 2004).

Neem is used to treat malarial fever in ayurvedic medicine system. Neem oil treated mosquito nets and mosquito-repellent tablets are now available in the North-east India. Gedunin (a Limonoids) obtained from neem has activity similar to quinine against malarial pathogen. The neem liminoids (Azadirachtin, salannin, deacetylgedunin) exhibited high larvicidal, pupicidal and anti-ovipositional bioactivity against malaria vector - *Anopheles stephensi*. Tablet suspension of the bark and leaf of neem showed moderate effect against malarial pathogen, *Plasmodium* sp. (Isah *et al.*, 2003). Methanolic extract fraction of neem leaves when tried against Coxsackie B group viruses, produced *in vitro* antiviral and virucidal effect (Badam *et al.*, 1999). Anticarcinogenic activity of neem leaf extract was observed in murine system (Dasgupta *et al.*, 2004).

Injection of neem leaf preparation to tumor in mice reduced tumour growth, exhibiting anti-carcinogenic activity (Baral and Chattopadhyay, 2004). Induction of apoptosis in rat oocytes was seen when treated with neem leaf extract (Chaube *et al.*, 2006). Buccal pouch carcinogenesis in hamsters was inhibited by ethanolic leaf extract of neem (Subapriya *et al.*, 2005). Good antioxidant activity was observed with neem leaf aqueous extract; flower and stem bark ethanolic extracts. Neem bark extract had potential of controlling gastric hyper-secretion and gastro-esophageal and gastro-duodenal ulcers (Bandyopadhyayk *et al.*, 2004). Acetone-water neem leaf extract showed antiretroviral activity through inhibition of cytoadhesion. The extract increased haemoglobin concentration, mean CD4+ cell count and erythrocyte sedimentation rate in HIV/AIDS patients (Udeinya *et al.*, 2004). Enhancement of antibody production and cellular mediated response by neem components helps in the treatment of AIDS.

NEEM AND REPRODUCTION

The neem seed oil, leaf extracts and NIM-76 act as powerful spermicide and significantly inhibited spermatogenesis, decreased sperm motility, count and cessation of fertility. These conditions were reversed by the withdrawal of neem products 4-6 weeks later (Sadre *et al.*, 1983). Ogbuewu *et al.* (2009) reported no significant reduction in libido of rabbit bucks fed graded levels of neem leaf meal based diets. Furthermore, neem seed oil possesses anti-implantation and abortifacient properties. Sinha *et al.* (1984) found spermatozoa of human and Rhesus monkey were immotile and die within 30 min of contact with NSO in an intravaginal dose of 1.0 mL. Vaginal biopsy revealed no side effect, while radio-isotope studies indicate non-absorption in the vagina and

non anti-ovulatory (Sinha *et al.*, 1984). These findings enabled neem oil formulation 'sensal' use in India as powerful contraceptive.

Ogbuewu *et al.* (2009) and Mohan *et al.* (1997) reported significant reduction in semen volume, sperm count, higher incidence of morphological abnormalities of spermatozoa, fertilizing ability of rabbit bucks fed neem leaf meal based diets and hatchability of eggs on birds fed neem kernel cakes. The contraceptive property of neem oil has been reported (Upadhyay *et al.*, 1994). Neem leaf extract has spermatotoxic effect (Ogbuewu *et al.*, 2009). The leaf extracts of neem showed 100% immobilization and mortality of human spermatozoa at a 3 mg dose within 20 seconds (Khan and Awasthy, 2003; Khillare and Shrivastav, 2003). A new vaginal contraceptive, NIM- 76 was developed from neem oil having antimicrobial activity against *Escherichia coli, Klebsiella pneumoniae* and *Candida albicans* (Ram *et al.*, 2002). Treatment of mice with neem leaf extract (aqueous) caused adverse effects on sperm motility, acrosomal morphology and number of spermatozoa (Mishra and Singh, 2005). Neem seed extracts inhibited folliculogenesis in albino rats. Neem extracts could thus be used as bio-rodenticides instead of toxic synthetic rodenticides that are pollutants (Roop *et al.*, 2005).

NEEM AND SERUM METABOLITES

Administration of 5 g of aqueous leaf extract or an equivalent amount of dried leaf significantly reduced the insulin dosage by 30 - 50%, without a significant effect on the blood glucose levels (Khosla *et al.*, 2000; Gupta *et al.*, 2008). Aqueous extract of neem root and leaves reduced blood sugar level in rats exhibiting antidiabetic activity (Halim, 2003). In a study with rabbits and guinea pigs, it was reported that administration of the leaf extract of *Azadirachta indica* induced a potent and dose-dependent hypotension in rabbits (5-200 mg kg^{-1}, IP) and guinea pigs (5-40 mg kg^{-1}). The extract also exhibited anti-carrhythmic activity (40 mg kg^{-1} IV) against ouabain-induced dysrhythmia in rabbits. The mechanism of action may be explained an effect on vascular smooth muscle, giving rise to vasodilatation.

The neem leaf extract provided a hepatoprotective effect against paracetamol-induced hepatic cell damage in rats, findings supported by histopathological studies (Gupta *et al.*, 2008). Both the neem leaf extract and seed oil produced a hypoglycaemic effect in normal as well as diabetic rabbits, comparable to that of glibenclamide. The effect was more pronounced in the diabetic animals. Pretreatment with *Indica* leaf extract or seed oil, given two weeks prior to alloxan, partially prevented the rise in blood glucose levels as compared to control diabetic animals (Gupta *et al.*, 2008).

Administration of aqueous extract of neem along with DOCA salt prevented the development of hypertension in rats (Obiefuna and Young, 2005). Administration of the mature leaf extract decreased serum cholesterol significantly without changing serum protein, blood urea and uric acid levels in rats (Chattopadhyay *et al.*, 2000; Ogbuewu *et al.*, 2010a, b).

Neem and anti-microbial activity: Several active principles from neem have demonstrated high efficacy, against most pathogens. As fungicides, over 14 common fungi species are sensitive to neem preparations (Khan and Wassilew, 1987) they include the genera *Trichophyton* (athletes foot), *Epidermophyton* (ringworm of skin and nails), *Microsporum* (ringworm of skin and hair) and *Candida* (thrush). SaiRam *et al.* (1997) reported protection against systemic candidiasis (*Candida albican*) by NIM-76. The mechanism is simply antifungal and immunomodulatory. In *Aspergillus flavus,* neem leaf extract fail to inhibit growth, but reduce formation of aflatoxin by blocking

polyketides production, which is commonly converted to toxins. Several diseases including Cercospora, Anthracnose, Downy mildew and Sigatoka are under investigation to establish efficacy of neem products as plant fungicides. As antibiotics, pathogenic bacteria like *Staphylococcus aureus, Salmonella typhi* are significantly suppressed by NSO. Trials with NIM-76 significantly suppressed *E. coli* and *K. pneumoniea*, which hitherto were insensitive to whole NSO (Ram *et al*., 2002). As antiviral agents, experiment with Small pox, Chicken pox and Fowl pox viruses show biological efficacy of neem extracts. Crude neem extracts adsorbed the viruses by blocking entry into uninfected cells. NIM-76 suppressed Polio virus replications and inhibited DNA polymerase of Herpes virus with no potency once infection is established *in vivo* (Rao *et al*., 1989). Therefore neem can be used against phytopathogenic fungi as a means of biological control (Jatav and Mathur, 2005).

Neem leaf and seed extracts exhibited antidermatophytic activity against dermatophytes viz., *Trichophyton ruberum, Mentagrophytes, Trichophyton violaceum, Microsporum nanum* and *Epidermophyton flocosum* under *in vitro* conditions (Natarajan *et al*., 2002). Neem seed oil showed bactericidal activity against 14 strains of pathogenic bacteria (Baswa *et al*., 2001). Crude aqueous and solvent extracts of neem were tried against 20 strains of pathogenic bacteria wherein crude extract produced better results (Srinivasan *et al*., 2001). Neem leaf extracts are antimutagenic. The ethanolic extract of neem leaves exhibited strong antimutagenic activity in *Channa punctatus*, a fresh water fish model (Farah *et al*., 2006).

INDUSTRIAL USES

In 2002, at the World neem conference, idea of promoting neem as an "Industrial Plant" was put forward (Kumar, 2003). Several industries including pharmaceuticals, cosmetics and textile industries use neem oil (Jattan *et al*., 1995). Many such neem-based commercial preparations are currently available (Khanna, 1992). In India neem is highly exploited by many Ayurvedic drug industries. Neem oil and powdered neem leaves are employed in various cosmetic preparations such as face creams, nail polish, nail oils, shampoos, conditioners (Jattan *et al*., 1995). A new shampoo, based on seed extract of neem was highly effective, more than permethrin-based product, against head lice under *in vitro* conditions (Heukelbach *et al*., 2006). Neem cake a by-product of neem oil industry is used as livestock feed, fertilizer and natural pesticide. Neem oil is commonly used in soap production. Medicated neem soaps are gaining popularity.

Neem based toothpaste is widely used in India and European countries. Neem is a source for many oral-hygiene preparations and dental care products. Neem bark yields gum and tannins which are used in tanning, dyeing etc. Neem seed pulp is used as a rich source of carbohydrate in fermentation industries and for methane gas production. Cultivation of neem and processing of neem products provides employment and income generation opportunities. Collection of neem seeds to be supplied to the industries provides important means of supplementary employment and income for the poor households, especially the rural women. India stands first in neem production and about 540,000 tons of seeds are produced annually yielding 107,000 tons of neem oil and 425,000 tons of neem cake. The amount of azadirachtin available is estimated to be about 1600 tons per annum, providing enormous amount of raw material for pesticide industry. In the product sector, annual estimated turnover is about Rs. 1000-1200 crores. Small scale industries have a major role to play in harnessing the potential. Therefore, in India it is the time to take right steps in promoting neem, both for the benefit of farmers and industries (Kumar, 2003).

NEEM AND PATENCY

During the past five decades intensive investigations on the diverse properties of neem have been carried out. As a result large numbers of research publications and books have been published. Many conferences have been conducted at national and international level. Hundreds of active compounds that are isolated from various parts of neem find their applications in pesticide, medicine, health care and cosmetic industry all over the world. World over the neem tree has been recognized as a commercial opportunity.

Many neem related processes and products have been patented in Japan, USA and European countries, since 1980s. In 1983, Temuro Corporation obtained the first US patent for its therapeutic preparation from neem bark. USA with 54 patents on neem and neem based products stands first followed by Japan (McEwen, 1978), Australia (Chakraborthy and Konger, 1995) and India (Fathima, 2004). Since 1995, more than 53 patent applications are pending in India for either gazette notification or opposition. Hopefully, if all these patents are granted India will have the largest number of patents in neem. Majority of patents that have been granted are for crop protection application (63%) followed by health care (13%), industrial (5%), veterinary care (5%), cosmetics (6%) and others (8%). Organization wise, largest number of patents are owned by Certis-W.R. Grace followed by Rohm and Haas (Kak, 2000), CSIR-India (Fathima, 2004), Trifolio (Jattan *et al*., 1995), Bayer (Chari, 1996) and EID Parry (Brahmachari, 2004).

CONCLUSION

Owing to its versatile characteristics neem is rightly called the village pharmacy. National Research Council, Washington, USA considers the neem, one of the most promising of all plants and the fact is that it may eventually benefit every person on this planet. Probably no other plant yields as many strange and varied products or has as many exploitable by-products. However, most of these findings on neem and its products are not patented, despite being potentially valuable, cost effective, reduces incidence of pests and parasite resistance with increase in agricultural production, environmental protection and health care services for humans and livestock. It is inferred from the above that neem plant is indeed a jewel globally. In line with these adequate benefits, researches on neem must be directed at identification and quantification of the active principles and patenting of findings thereby making these findings readily accessible to mankind for adoption.

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