DOI: 10.1002/cbic.200300749 ChemBioChem **2004**, 5, 408 – 421

Neem—An Omnipotent Plant: A Retrospection

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*Neem (*Azadirachta indica *A. Juss.) has universally been accepted as a wonder tree because of its diverse utility. Multidirectional therapeutic uses of neem have been known in India since the Vedic times. Besides its therapeutic efficacies, neem has already established its potential as a source of naturally occurring insecticide, pesticide and agrochemicals. Safe and economically cheaper uses of different parts of neem in the treatment of various diseases and in agriculture are discussed in this article. It further deals with the active chemical constituents of various neem formulations. Commercially available neem products are also mentioned along with their respective applications. Furthermore, evaluation of safety aspects of different parts of neem and neem compounds along with commercial formulations are also taken into consideration. Systematic scientific knowledge on neem reported so far is thus very useful for the wider interests of the world community.*

Lead-In

Since the dawn of human civilisation man has depended upon nature's blessings. Nature provides him with the essentials for his survival like food, clothes, shelter and medicines. Medicinal plants appear to be part and parcel of human society's fight against a wide range of diseases. For thousands of years the beneficial properties of the neem tree (*Azadirachta indica* A. Juss.) have been recognised in India, and it is perhaps the country's most useful traditional plant. Neem has been universally accepted as a wonder tree because of its diverse utility. In addition to its therapeutic efficacies, neem has already established its potential as a source of naturally occurring insecticides, pesticides and agrochemicals. Due to the adverse effects of synthetic insecticides on the environment, the need for ecologically safe alternative pest controls for agriculture has led pest-control experts to turn their attention back to the plant kingdom as a source of pesticides. Neem leads the list of plants with the highest potential for this purpose. Worldwide attention and a realisation of the long-term benefits that neem promises, both in agriculture and healthcare, have resulted in a surge of commercial interest. Neem-based materials are compatible with integrated pest management (IPM); neem products do not persist in the environment and are degraded by ultraviolet rays and rainfall. Many neem-based products tend to have low mammalian toxicity and also less effect on nontarget beneficial organisms than some of the more traditional pesticides. Safe and economically cheaper uses of different parts of neem have been reported in the treatment of various diseases and also in agriculture over recent years and these are discussed in this article. Furthermore, the active chemical constituents of various neem formulations are discussed. Commercially available neem products are also mentioned along with their respective applications. Evaluation of the safety aspects of different parts of neem and neem compounds along with commercial formulations are also taken into consideration in order to collate the systematic scientific knowledge on neem, which is very useful for the larger interests of the world community.

Introduction

The neem tree is native to the Indian subcontinent and Southeast Asia. There are two closely related species, *A. indica and A. azedarch*. The former is popularly known as Indian neem (margosa tree) or Indian lilac, and the latter as the Persian lilac. The taxonomic position of neem tree is as follows:

Order	Rutales
Suborder	Rutinae
Family	Meliaceae
Subfamily	Melioideae
Tribe	Melieae
Genus	*Azadirachta*
Species	*indica*

The genus *Azadirachta* A. Juss., which comprises three species of Indo-Malayan origin,[1] has also been characterised in detail.[1]

The tree was considered so valuable and miraculous that it became a major component of the Indian ecosystem. Multidirectional therapeutic uses of neem have been known in India since the Vedic times. Almost all parts of the tree—stem, bark, roots, leaves, gum, seeds, fruits, flowers, etc.—have been in use as traditional medicine for house-hold remedies against various human ailments from antiquity.[2] One of the Sanskrit names of neem tree is "Arishtha" meaning "reliever of sickness"; in India the tree is considered as "Sarbaroganibarini", which means "reliever of all diseases", and it is regarded as the "village dispensary". Over 700 herbal preparations based on neem are found in Ayurveda, Siddha, Unani, Amchi and other local health traditions; over 160 local practices are known in different parts of the country in which neem forms an important or sole ingredient in curing human ailments or disorders.[3]

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 DOI: 10.1002/cbic.200300749

Besides its therapeutic efficacies, neem has established its potential as a source of naturally occurring insecticide, pesticide, antimalarial agent and agrochemical. For thousands of years, Indian farmers have been aware of the insecticidal properties of neem tree. Its branches were hung in granaries to protect stored grain from pest attack. Historically, neem has also been used in India for cosmetic and medicinal purposes. For example, neem oil extracted from the seeds is used in soap, wax and lubricants, and its twigs have been traditionally used as toothbrushes. These spectacular properties of neem have attracted the scientific communities, particularly the organic chemists, biologists, clinicians and agriculturalists, around the world to undertake systematic research on this unique plant in various directions. Since the 1970s, scientists in Europe and the United States have been interested in neem because of its insecticidal properties and its low toxicity to mammals. In this connection, it would be appropriate to recall the report entitled "Neem—A Tree for Solving Global Problems" published in 1992 by the US National Academy of Sciences.[4f] A number of review articles on neem have appeared, thereby reflecting the importance and applicability of this versatile medicinal plant.[4] The aim of the present article is mainly to focus on the medicinal efficacies of various parts of neem tree used directly or through commercially available products along with their aspiring uses as cheap and eco-friendly agrochemicals, insecticides, pesticides and parasiticides reported in recent years. A brief account of the evaluation of safety aspects of different parts of neem tree and neem compounds along with commercially available formulations is also included.

Uses of Neem as Traditional Medicine

Various parts of the neem tree have been used as traditional Ayurvedic medicine in India.[5] Neem oil and the bark and leaf extracts have been therapeutically used as folk medicine in the treatment and control of leprosy, intestinal helminthiasis, respiratory disorders, constipation, blood morbidity, rheumatism, biliary infections, itching, skin ulcers and many more along with a general health promoter.[6] A few medicinal applications of various parts of neem are summarised in Table 1.[7]

Table 1. *Some medicinal uses of neem as mentioned in Ayurveda.*

Part	Medicinal uses
leaf	leprosy, eye problems, intestinal worms, anorexia, biliousness, skin ulcers
flower	bile suppression, elimination of intestinal worms and phlegm
twig	relieves cough, asthma, piles, spermatorrhoea, obstinate urinary disorder, diabetes
bark	analgesic, antipyretic
fruit	relieves piles, intestinal worms, urinary disorder, eye problem, diabetes, wounds and leprosy
gum	effective against skin diseases like ringworms, scabies, wounds and ulcers
seed pulp	leprosy and intestinal worms
oil	leprosy and intestinal worms
root, bark, leaf, flower and fruit together	blood morbidity, biliary afflictions, itching, skin ulcer, burning sensation and leprosy

However, apart from the Ayurveda records, there are several reports on the biological activity and pharmacological actions of neem based on modern scientific investigation.

Phytochemical Studies and Biologically Active Chemical Constituents

Since the report on the isolation of nimbin from neem seed oil by Siddique in 1942, more than 140 compounds have been isolated so far from different parts of neem tree;[8] indeed, organic chemists, especially natural product chemists, are still carrying out research on the active principles of *A. indic*a. The compounds may be divided into two major classes: isoprenoids (like diterpenoids and triterpenoids containing protomeliacins, limonoids, azadirone (**27**) and its derivatives, gedunin (**2**) and its derivatives, vilasinin-type compounds and *C*-secomeliacins such as nimbin, salanin (**16**) and azadirachtin (**1**)) and non-isoprenoids, which include proteins, amino acids, carbohydrates, sulfur compounds, polyphenolics such as flavonoids and their glycosides, dihydrochalcone, coumarin and tannins, aliphatic compounds, etc. Although a large number of compounds have been isolated from various parts of neem, very few of them have been studied so far for biological activity.[9] Several reviews have already dealt with the chemistry and structural diversity of the chemical constituents of neem and also the biological activities of some of these constituents.[10] Hence, these have been excluded from this review. Only a few significant chemical constituents of neem are mentioned in Scheme 1; biological activities of some of these are summarised in Table 2.

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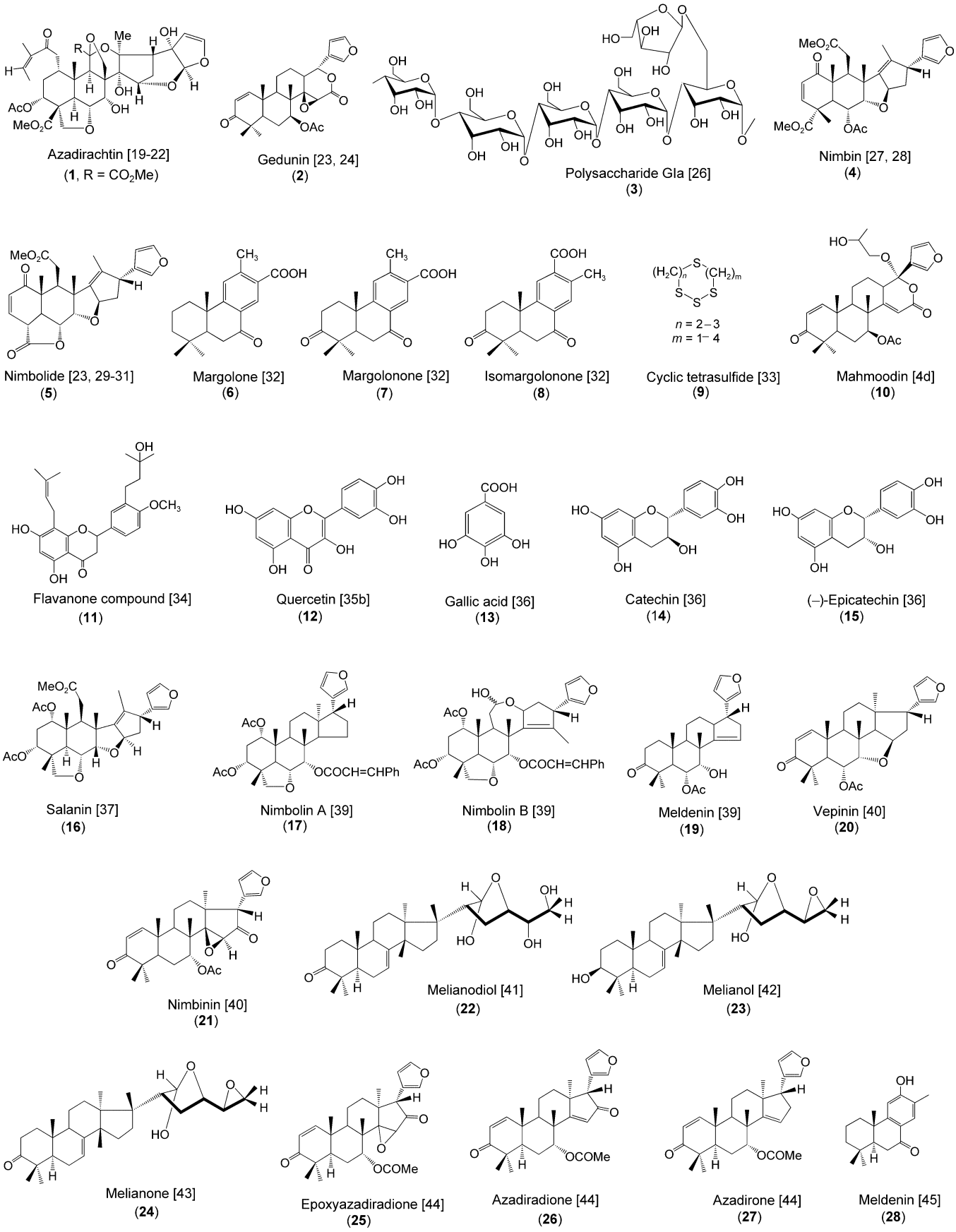

Scheme 1. *Structure of some useful neem compounds. Numbers in square brackets indicate reference numbers.*

Table 2. Biological activities of some active principles of neem.

Neem compounds	Source	Biological activity
nimbidin (a major crude bitter principle extracted from seed oil)	seed oil	anti-inflammatory [11] antiarthritic [12] antipyretic [13] hypoglycaemic [14] diuretic [15] spermicidal [16] antifungal [17] antibacterial [17] antigastric ulcer [18] antiviral [19] antipsoriasis [19]
sodium nimbidinate		anti-inflammatory [11,12,19] diuretic [19] anticardiac failure [19]
azadirachtin (**1**)	seed	antimalarial [20] locust antifeedant; very active insect phagorepellent and systemic growth disruptor [19,21,22]
gedunin (**2**)	seed oil	antifungal [23] antimalarial [24]
polysaccharides		anti-inflammatory [25]
polysaccharide Gla (**3**)		antitumour [26]
nimbin (**4**)	seed oil	spermicidal [27]
nimbolide (**5**)	seed oil	antibacterial [23,29] antimalarial [30,31]
margolone (**6**), margalonone (**7**) and isomargalonone (**8**)	bark	antibacterial [32]
cyclic tetrasulfide (**9**)	leaf	antifungal [33]
mahmoodin (**10**)	seed oil	antibacterial [4a]
flavanone compound (**11**)	gum	antifungal [34]
quercetin (**12**)	leaf	hypoglycaemic [35]
gallic acid (**13**), catechin (**14**) and (−)-epicatechin (**15**)	bark	anti-inflammatory and immunomodulatory [36]
salanin (**16**)	fruit pulp	spermicidal [37]
22,23-dihydronimocinol and des-furano-6α-hydroxazadiradione	leaf	insecticidal [38]

For structures see Scheme 1.

Plausible Medicinal Applications: An Overview of Pharmacological and Clinical Studies

Different parts of the neem tree have been used traditionally in the treatment of a number of diseases. Nowadays, various neem formulations available on the market are being used against ailments. A vast number of clinical and pharmacological studies on the different parts of neem and also on the commercially available neem formulations have been carried out. The results in almost all cases have been found to be highly satisfactory.

Hypoglycaemic effect

A. indica is used for the treatment of diabetes in Indian folklore. Aqueous extracts of neem leaves significantly decrease blood sugar levels and prevent adrenaline- and glucose-induced hyperglycaemia.[35a] Aqueous leaf extracts also reduce hyperglycaemia in streptozotocin-induced diabetes, and the effect is possibly due to the presence of a flavonoid, quercetin (**12**).[35b] The leaf extract of *A. indica* has been reported to block the effects of epinephrine on glucose metabolism and reduce peripheral glucose utilisation in diabetic rats, and to some extent in normal rats; this indicates the antihyperglycaemic potential of the plant.[46] Khosala et al. and Gosain et al. studied the hypoglycaemic effects of neem-leaf extract and seed oil in normal and alloxan-induced diabetic rabbits.[47a,b] The effect, however, was more pronounced in diabetic animals for whom administration for four weeks after alloxan-induced diabetes significantly reduced blood glucose levels. The hypoglycaemic effect was found to be comparable to that of glibenclamide. Pretreatment with *A. indica* leaf extract or seed oil administration started two weeks prior to alloxan partially prevented the rise in blood glucose levels relative to control diabetic animals. The results suggest that *A. indica* could be of benefit in diabetes mellitus for controlling the blood sugar or may also be helpful in preventing or delaying the onset of the disease. The potent blood-sugar-lowering activity of *A. indica* leaf extract was reported by Chattopadhyay on the basis of the experimental results obtained from normal and streptozotocin-induced diabetic rat models.[48] The antidiabetic effect of an alcoholic extract of neem was also examined in experimentally induced diabetes mellitus in rabbits.[49] "Pancreas Tonic" (M/S Botanical Indian Laboratories Private Ltd., New Delhi) is a commercially available herbal drug on the market as a dietary supplement for diabetes mellitus.[50] The drug is composed of extracts of a number of plants including neem, and clinical studies of this herbal composition have revealed a good response in human beings. "Armycard capsules", which contain neem as one of the components, are effective against all types of diabetes and tend to enhance insulin secretion from the pancreas.[51]

Antiulcer effect

Neem-leaf extract has significant antiulcer and antisecretory effects in rats.[52] It has been found to reduce ulcer index, free and total acidity and the volume of gastric secretion significantly at 80 and 160 mg kg^{-1} doses. A clinical study with nimbidin, a bitter principle of neem, revealed its high effectiveness in healing ulcers in the duodenum and also in relieving pain in the epigastric region.[18,53] The nimbidin fraction of neem oil (from seeds) contains stearic acid and palmitic acid, and these two fatty acids are supposed to play a vital role in the ulcer-healing properties of nimbidin.[54] An aqueous extract of neem barks has been found to possess highly potent antiacid secretary and antiulcer activity, and the bioactive compound has been attributed to a glycoside.[55]

The drug "Bhunimbadi Ghanasar", which contains neem as one of its constituents, is very effective in relieving common symptoms of "amlapitta" (acid dyspeptic disease) without any side effects.[56]

"Nimbatiktam" is the crude extract isolated from the seed kernels or oil of neem. The active principle of this crude extract

has been identified as nimbidin (1.2% *w/w*). The drug showed significant ulcer-healing capability without any notable side effect.[57]

Salanin, a limnoid bitter principle of neem seed oil, also has ulcer-healing activity. Salanin had protective activity against aspirin-induced gastric lesions at oral doses of 10, 20 and 50 mg kg^{-1} in experimental animals.[37] Recently, Bandyopadhyay et al. studied the efficacy of a neem bark extract as a potential therapeutic agent for the control of gastric hyperacidity and ulcer along with its mechanism of action, standardisation and safety evaluation.[58] The extracts dose-dependently inhibit pylorus-ligation- and drug (mercaptomethylimidazole)-induced acid secretion with ED_{50} values of 2.7 and 2 mg per kg body weight, respectively. The extract is highly potent in the dose-dependent blocking of gastric ulcer induced by restraint cold stress and indomethacin with ED_{50} values of 1.5 and 1.25 mg per kg body weight, respectively. Bark extract has been found to be equipotent to the well-known drug ranitidine but more potent than omeprazole in inhibiting pylorus-ligation-induced acid secretion; however, in a stress ulcer model, bark extract is more effective than ranitidine but almost equipotent to omeprazole. The investigators suggested that the bark extract inhibits H^+-K^+-ATPase activity in vitro in a concentration-dependent manner similar to omeprazole. The bark extract also prevents oxidative damage of the gastric mucosa by significantly blocking lipid peroxidation and by scavenging the endogenous hydroxyl radical, which is the major causative factor for ulcer. The hydroxyl-radical-mediated oxidative damage of human gastric mucosal DNA is also protected by the extract in vitro. The pharmacological effects of the bark extract are attributed to a phenolic glycoside.[58] A single raw extract dose of 1 g per kg body weight (mice) given in one day and application of 0.6 g per kg body weight per day given orally over 15 days to a cumulative dose of 9 g per kg was well tolerated and below the observed LD_{50}. It is also well tolerated by rats with no significant adverse effect.

Antimalarial activity

Neem has been found to possess antimalarial activity.[59] Extracts of neem seeds were studied for their effect on in vitro and in vivo growth and development of the human malarial parasite *Plasmodium falciparum* and found to have highly appreciable results.[60] Interestingly, the antiplasmodium effect of neem components was observed on parasites previously shown to be resistant to other antimalarial drugs (chloroquine, pyrimethamine); this suggested a different mode of action.[60] Neem seed fractions are thus active not only against the parasite stages that cause the clinical manifestation, but also against the stages responsible for continued malaria transmission. The limnoids (meldenin, isomeldnin, nimocinol and nimbandio) isolated from the ethanolic extract of fresh neem leaves have been found to demonstrate antimalarial activity against chloroquine-resistant *P. falciparum* strain K_1.[61]

Antioxidant and anticarcinogenic activity

The antioxidant activity of neem seed extract has been demonstrated in vivo during horse grain germination, which is associated with low levels of lipooxygenase activity and lipid peroxides.[62] Arivazhagen et al. evaluated the effects of garlic and neem-leaf extracts on lipid peroxidation and antioxidant status during administration of *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG), a carcinogenic nitrosamine, in male Wistar rats.[63] Extracts of garlic and neem leaf were administered orally for five consecutive days before intraperitoneal injection of MNNG. Enhanced lipid peroxidation in the stomach, liver and circulation of MNNG-treated rats was accompanied by a significant decrease in glutathione (GSH) and the activities of glutathione peroxidase (GPx), glutathione-*S*-transferase (GST) and gamma-glutamyl transpeptidase (GGT). Administration of garlic and neem-leaf extracts significantly decreased the formation of lipid peroxides and enhanced the levels of antioxidants and detoxifying enzymes in the stomach, which is the primary target organ for MNNG, liver and circulation. The results of their study suggest that garlic and neem may exert their protective effects by modulating lipid peroxidation and enhancing the levels of GSH and GSH-dependent enzymes.Reports are available regarding the use of neem to treat patients suffering from various forms of cancer.[64] The chemopreventive effects of neem-leaf extract have been explored against oral carcinogenesis induced by 7,12-dimethylbenz[*a*]anthracene (DMBA) by modulation of lipid peroxidation, as revealed by reduced incidence of neoplasm.[65] One patient with parotid tumour and another with epidermal carcinoma responded successfully when treated with neem seed oil.[66] Arivazhagar et al. also speculated that garlic and neem leaves might significantly alter cancer development at extrahepatic sites by influencing hepatic 73-biotransformation enzymes and antioxidants.[67]

Dermatological applications

Neem is very effective against common skin diseases like acute and chronic eczema, ringworm and scabies. The ethanolic extract of *A. indica* leaves demonstrated much more significant antidermatophytic activity than the aqueous extract, when tested in vitro against 88 clinical isolates of dermatophytes by using the agar dilution technique. The MIC90 of the ethanolic extract was 100 μg mL^{-1}, whereas that of the aqueous extract was 500 μg mL^{-1}.[68] Nimbidin was found to be effective in various skin diseases such as furunculosis, arsenical dermatitis, ulcers due to burns, *Herpes labialis* infection, scabies and seborrhoeic dermatitis. A herbal gel formulation prepared from the extract of *A. indica*, *Centella asiatica*, *Aloe vera* and Carbopol 934P as the base was found to possess excellent pharmaceutical attributes and is very effective against the causative organism responsible for the proliferation of dandruff.[69]

Clinical studies with dried neem-leaf extract showed its effectiveness in curing ringworm, eczema and scabies. A paste prepared with neem and turmeric was found to be effective in the treatment of scabies in nearly 814 people.[70] In 97% of

these cases, the paste was found to cure scabies within 3–15 days of treatment without any adverse effect. Another clinical trial showed that local application of a lotion prepared from the 70% alcoholic extract of neem leaves by dissolving the residue in propylene glycol in a ratio of 2:3 was most effective in all cases of acute and chronic eczema, ring worm and scabies, particularly in persistent scabies.[71]

Hepatoprotective activity

Aqueous neem-leaf extract was found to offer protection against paracetamol-induced liver necrosis in rats.[72] The elevated levels of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase (GGT) indicative of liver damage were found to be significantly ($P < 0.01$) reduced on oral administration of the neem leaf aqueous extract (500 mg kg^{-1}).[72b] Paracetamol-induced liver necrosis was also found to be reduced as observed macroscopically and histologically.

Effects on central nervous system (CNS)

Fractions of acetone extract of leaf showed significant CNS-depressant activity.[73] Leaf extract up to a dose of 200 mg per kg body weight produces significant anxiolytic activity in rats.[74] The plant showed analgesic properties in mice.[75] Pretreatment with the opioid antagonist naloxone and central noradrenaline depletor DSP-4 attenuated the analgesia, whereas the serotonin synthesis inhibitor PCPA potentiated the same; this suggests that both central and peripheral mechanisms and complex neutral pathways (opioid and non-opioid, i.e., monoaminergic) may be involved in this effect.[75]

Diuretic activity

The crude ethanolic extract of stem bark and root bark showed hypotensive, spasmolytic and diuretic activities. The chemical constituent, sodium nimbidinate, was found to be a potent diuretic agent in dogs.[76] A 20 mg dose of sodium nimbidinate was found to be more potent than 12 g of urea. The drug acted primarily upon renal tubules, retarded the excretion of phenolsulfonphthalein, and caused reabsorption of electrolytes and water. A higher dose given orally was found to be effective.[77] Shah et al. conducted a clinical trial on nine patients with congestive cardiac failure with anasarca to study the diuretic effect of sodium nimbidinate.[78] A dosage 250 mg per day of sodium nimbidinate was administered through a deep intramuscular pathway in the gluteal region. The injections were continued for 2–3 days with an average of about 5 injections per patient. Four other patients were studied as controls under identical stimulations with bed rest, low sodium diet adequate digitalisation without any diuretic. Eight of the patients showed a definite diuretic response, while the control group did not show any diuresis. No toxic reaction was noted except local discomfort or slight pain. In another study,[79] clinical trials were conducted with sodium nimbidinate for diuretic activity in 12 cases of congestive cardiac failure; results were encouraging in eight cases, and moderate response was observed in four cases. In all cases no significant toxicity symptoms could be diagnosed.

Spermicidal and contraceptive activity

Several researchers have examined the spermicidal and contraceptive action of neem. Aladakatti et al. recently reported that neem treatment for 48 days in albino rats resulted in a decrease in the total sperm count, sperm motility and forward velocity.[80] The percentage of abnormal sperm was found to increase, whereas the fructose content of caudal sperm of the epididymis decreased. Such observations suggest that these effects are probably due to an androgen deficiency caused by antiandrogenic properties of the leaves of neem, thereby affecting the physiological maturation of sperm. On the basis of another set of experimental results from a rat model treated with neem-leaf extract, Aladakatti and Ahamed suggested that a morphological change in the sperm head of the spermatozoa along with a decrease in the perforatonium or subacrosomal material, post nuclear cap and the nuclear material near the basal plate of the sperm head are probably due to androgen deficiency and a general disturbance in carbohydrates or polysaccharides located in the sperm head.[81]

Oral administration of an aqueous extract of neem leaf also shows antifertility effects in mice.[82] Neem oil proved to be a spermicidal agent against rhesus monkey and human spermatozoa in vitro, which is a novel method of contraception.[83–84] Riar et al. investigated the in vitro spermicidal activity of the volatile and odourless fraction of neem oil coded as NIM-76, which is obtained by steam distillation.[85] The results showed that the minimum concentration which inhibited spermatozoal motility was 0.25 mg mL^{-1} for rat and 25 mg mL^{-1} for human spermatozoa. The effect of the drug on spermatozoal motility was found to be dose-dependant, but the activity was not altered in the presence of vaginal or cervical mucosa. A hexane extract of neem seed has been found to completely abrogate pregnancy in rodents when given orally up to a concentration of 10%, with no apparent side effect.[86]

The leaves of *A. indica* were found to have reversible antiandrogenic properties in male rats.[87] Garg et al. studied the immunocontraception activity guided by fractionation and characterisation of active constituents of neem seed extracts.[88] An analytical HPLC method was developed for standardisation of the fraction and preparative HPLC was used to isolate individual components of the active fraction in quantities sufficient for characterisation. The active fraction was identified to be a mixture of six components comprising saturated, mono-, and diunsaturated free fatty acids and their methyl esters. The antifertility activity of the active fraction was reversible in nature and it was fully active even at 5% concentration. For the first time, this study proposed an active fraction from neem seeds which was responsible for long-term and reversible blocking of

fertility after a single intrauterine administration with high efficacy and no systemic toxic effects.[88]

Salanin, an active principle of neem, possesses spermicidal activity on human spermatozoa.[37] Spermicidal activity was also noted in sodium nimbidinate. A 2.5 mg% dose of sodium nimbidinate was found to kill all the rat sperm in 30 min in vitro.[89] The lethal concentration for human sperm was found to be 1000 mg% and 250 mg% at 5 and 30 min, respectively.[89] Another compound related to sodium nimbinate was also found to have a potent spermicidal action in rats up to 1:2000 dilution.[90] Praneem polyherbal pessary (PPP), which is a formulation of purified ingredients from neem leaves, *Sapindus mukorossi* (pericarp of fruit) and *Mentha citrata* oil, has been reported to exhibit potent spermicidal action on human sperm in vitro and in vivo.[91] When applied in the vagina before mating, PPP prevented pregnancy in rabbits. The investigators argued that a combination of the three herbal ingredients resulted in an eightfold potentiation of the spermicidal action.[91] The postcoital tests confirmed the spermicidal properties of PPP in females with high cervical mucous score around mid-oestrus. It also prevented the migration of sperm into cervical mucous in most women. The investigators also reported in the same communication that pregnancy was prevented by the intravaginal administration of PPP in 15 rabbits studied, whereas 13 of the 15 animals in the control group became pregnant. Praneem vilci, a highly purified oil of *A. indica* seed, was also found to be safe when administered as a single intrauterine instillation in 18 healthy tubectomised women.[92] No untoward effect was observed. The menstrual pattern and ovulatory status remained unaltered and the endometrial biopsy was normal. In ten of the above women who had also received the HSD-hCG vaccine, coadministration of Praneem vilci did not prevent the antibody response to the HSD-hCG vaccine.[92] To establish the efficacy of neem oil another experimental trial was carried out in 225 female volunteers (aged 18–35), and the efficacy of intravaginal application of 1 mL of the oil was highly satisfactory among 222 cases.[93] The active compounds of the oil are assumed to be absorbed through the vaginal mucosa into the circulation and exhibit antifertility effects in addition to direct spermicidal activity.[93]

Other significant effects

Highly satisfactory external or internal uses of neem against psoriasis, acne, external cuts, burns and wounds, indigestion, constipation, stomach ache, gingivitis, sleeplessness, boils, syphilis, diarrhoea, cholera, rheumatism, dental problems (viz., pyorrhorea), small pox, measles, snake bite (traditionally used among tribal people from Elakiri and Jawadhi Hills in Tamilnadu, India, against snake-bite envenomation) and other diseases have been reported by various researchers.[2a,b, 21, 94–95] Nimbidin gargle and dentifrices have been found to be effective in the treatment of bleeding gums and pyorrhea.[96] Different parts of neem plant exhibit anti-inflammatory, analgesic, antipyretic and hypolipidaemic activities.[97] The water-soluble part of the alcoholic extract of *A. indica* exerted significant anti-inflammatory activity in the cotton pellet granuloma assay in rats.[98] Levels of various biochemical parameters studied in cotton pellet exudates were also found to be decreased, namely, DNA, RNA, lipid peroxide, acid phosphatase and alkaline phosphatase, suggesting the mechanism for the anti-inflammatory effects of *A. indi*ca.[98]

Antihypertensive effects of neem have also been reported.[99] A hydroalcoholic leaf extract of the plant caused a dose-dependent hypotensive effect which did not alter the force of contraction or heart rate at low doses in isolated frog heart, but caused a temporary cardiac arrest in diastole at high doses.[100]

Recently, the effect of an aqueous extract of *A. indica* has been evaluated on perfused frog and rabbit heart, and the results are very satisfactory such that *A. indica* could be of benefit against arrhythmia associated with coronary artery disease (CAD).[101] Dose-dependent negative inotropic and chromotropic effects have been observed in both heart preparations along with an increase in coronary blood flow in isolated rabbit heart.[101]

Nimbidol, one of the phytochemicals of neem, has been found to be an antiarthritic agent.[21a] Neem flower is used as one of the constituents of the indigenous drug "Amber Mezhugu", which is useful against rheumatism.[21a] "Onan Cutar Tailam" (containing neem seed oil) is used in the Siddha system of medicine for epilepsy.[102]

The significant in vitro and in vivo (in mice) potential of aqueous extracts of neem leaves to inhibit *dengue* virus type-2, which is predominantly involved in re-emerging dengue fever and dengue hemorrhagic fever (DMF), has also been reported.[103]

Very recently, Acharya et al. reported a preliminary study on the effect of *A. indica* on bronchial smooth muscles.[104] *A. indica* leaf juice (200 mg kg^{-1}) was administered orally to guinea pigs, and its highly significant protective effect on histamine aerosol-induced bronchospasm was observed. There was a 63% delay in the onset dyspnea in *A. indica*-treated animals compared to 16% in control animals.

Use as an Agrochemical

Besides therapeutic efficacies, applications of neem products as agrochemicals are noteworthy. Addition of neem extract to garden soil over a period of 28 days at regular intervals resulted in a significant increase in the population of nitrogen fixers.[105] Plants grown in soils with 0.1% and 0.2% added neem extract showed improved performance over the control plants in terms of growth and vigour.[105] Uses of aqueous extracts of neem leaves, neem cake and Neemix (commercial formulation of neem seeds) in agriculture are found to be highly effective in promoting growth and the nitrogen-fixing capacity of organisms without adversely affecting the diazotropic cyanobacteria of rice fields.[106] A urea–neem oil adduct "Pusa neem golden urea" (PNGU) is used as a nitrification-inhibiting agent.[107] PNGU has been tested against commercial prilled urea with a high-yielding rice variety Pusa 169, and the results

indicate that PNGU at 120 bgN ha^{-1} produced 1.7 t ha^{-1} more grain than the commercial urea.[107] Neem cake blending of prilled urea (i.e., neem-coated urea, NCU40) has been shown to greatly enhance the utility of nitrogen applied as urea and found to reduce fertilizer nitrogen requirement by 30% relative to prilled urea alone, and it improves plant growth, yield and fertilizer N-efficacy.[108] Very recently, Mukherjee et al. reported that the application of neem cake at 3 Q ha^{-1}, 50% as basal and 50% in top dressing after 10–12 days of sowing, along with chemical fertilizers (30:40:40) kg NPK ha^{-1} was effective for rice variety Pusa Basmati-1.[109] The application of neem cake with urea increases the seeding vigour. Neem cake also increased the greenness and maintained it longer, which persisted even after transplanting. Nursery diseases like sheath blight, brown spot, stem borer and nutrient deficiencies were also controlled by the neem cake and urea mixture at the recommended seed land ratio (30 kg ha^{-1}).

Uses as Pesticide, Insecticide and Parasiticide Agents

Due to ever-growing awareness of the hazardous side effects of chemically synthesised pesticides and insecticides, more and more emphasis is being given to the use of biopesticides. Several countries have already banned or restricted the use of appreciable numbers of such synthetic chemicals that have been identified as highly toxic or hazardous. The World Health Organisation (WHO) has already called for an immediate ban on the use of endosulfan, a hazardous synthetic pesticide that causes serious eye, kidney and liver problems. The Government of India has already banned the use of a number of highly toxic and hazardous pesticides and imposed restriction on the use of many others to prevent environmental pollution. The multitudinal backlash against synthetic insecticides and the need for ecofriendly and safe alternative pest control for agriculture have led pest-control experts to turn their attention to plants as sources of pesticides. Botanical insecticides are relatively safe and degradable and are readily available sources of biopesticides. In this regard, neem has already emerged at the top of the list of plants with the highest potential. The following species of neem trees in the Meliaceae family have been the subject of botanical pesticide research: *Azadirachta indica* A. Juss., *A. excelsa* Jack, *A. siamens* Valeton, *Melia azedarach* L., *M. toosendan* Sicb. and Zucc. and *M. volkensii* Gurke. The Meliaceae, especially *A. indica* (Indian neem tree), contains at least 35 biologically active principles of which azadirachtin (**1**) is the most active insecticidal ingredient and is present predominantly in the seed, leaves and other parts of the neem tree.[110] Worldwide attention and a realisation of the long-term benefits that neem promises in agriculture and healthcare have resulted in a surge of commercial interest. Neem has experienced ongoing development as an insecticide over the past 30 years, particularly in the USA and many countries in Europe. At this point, it would be justified to mention a number of research teams from Germany led by Prof. H. Schmutterer (Institute of Phytopathology and Applied Zoology, University of Giessen, Germany), whose research on neem spans nearly fifty years and has contributed immensely to the understanding and development of neem as a potent alternative to synthetic pesticides in the field of agriculture. Their contribution is perhaps the most primary input for today's enormous interest in neem research. Multidirectional biological efficacies on a variety of insects of economic importance and the possibility of homemade insecticides using neem are the most significant contributions from these teams.Neem produces many limnoid allomones with known biological activities, which have been extensively studied during the past 30 years and demonstrated to have a remarkable effect against 413 species in 16 different insect orders including Homoptera and aphids.[111–112] The biological activities of the neem allelochemicals include feeding and oviposition deterrence, repellency, growth disruption, reduced fitness and sterility.[113] However, Saxena reported the growth inhibitory and disrupting effects of neem derivatives on homopterous insects to be more pronounced than either the repellent or the antifeedant effect.[114] The same results were found by Mourier et al. on cassava mealy bug (*Phenacoccus manihoti*).[115] The strategy of using low levels of neem products with the systemic mode of action has the added benefit of not harming beneficial insects.[116]

The most common commercial formulations of neem available are Neemix (W. R. Grace and Co.), which is effective against leaf miners, mealy bugs, aphids, fruit flies, caterpillars and psylla; and Align (AgriDyne), which is active against some minor leaf rollers. Very recently, Kumar et al. studied the biological efficacy of eight commercial Indian neem formulations (namely, Nimbecidine®, Econeem Plus®, Soluneem®, Limonool®, Neemgold®, Econeem®, FortuneAza® and NeemAzal®-F) in detail and argued that there is a need for a balanced approach in the development of commercial neem formulations of higher azadirachtin content, which would be of interest in exploring whether there is an optimum concentration level for azadirachtin that can be used in neem-based formulations.[117]

A herbal formulation from Dabur Ayurved Ltd., India (AV/EPP/14), containing neem as one of the components is an efficient herbal ectoparasiticide.[118] Neem Azal-F (commercial neem formulation),[119] Jawan (neem-based natural pesticide),[120] Achook,[121a] Dazomet (neem-based natural pesticide),[121b] and extracts of different parts of neem have been successfully used in controlling and causing mortality of nematodes.[122] Neem cake, neem leaves (powder or aqueous extract), neem oil and extracts of neem seed or kernels have been found to control phytopathogenic fungi on many plants such as tomatoes, rice, cotton, soya, grapes, wheat, beans, roses and cucumbers.[122b,123] An active chemical component of neem, isolated from acetone extracts of neem gum and identified as 8-prenyl-5,7-dihydroxy-3′-(3-hydroxy-3,3-dimethylbutyl)-4′-methoxyflavanone, has been proved to exhibit satisfactory antifungal activities against *Fusarium solani*, *Fusarium oxysporum*, *Aspergillus niger*, *Aspergillus fumigatus*, *Alternaria alternata* and *Phthium aphanodermafum*.[34] In addition, the neem compounds curcumin, 1-cysteine, nemicidine, nemol and vimicidin have been proved to be antifungal and strong insect repellents.[124] Ethanolic extracts of neem were found to possess

moderate toxicity against housefly and this natural product could be an alternative to the highly toxic synthetic insecticide delta-methrin.[125] Neem itself and various neem formulations are safe and ecofriendly insecticides.[126] Neem products have been found to be effective repellent and antifeedant insecticides against leaf borers, leaf folders, gall midge, grasshopper, rice hispa, pulse beetle, predatory spider, citrus blackfly, housefly and bunch and psychid caterpillars.[127]

From ancient times neem leaf has been in use in India for the storage of food grain. Recent experiments in different localities ranging from high humidity to saline coastal areas have revealed that pulses and cereals can be stored in gunny bags or in any other container along with neem leaves (20–25 leaves per gunny bag) and whole dried turmeric (10–20 fingers per gunny bag); a combination of neem leaves and whole dried turmeric has proved to be antifungal and a repellent to insects.[125,128] These neem formulations are technologically very cheap, easily available, nonhazardous and can save about 30% of a country's food grain with minimal investment.[125]

Neem products are also reported to have mosquito-repellent properties and larvicidal activity against mosquitoes. An aqueous crude extract of neem leaves has been found to exhibit a potential larvicidal capability against *Anopheles stephensi*,[129] whereas a methanolic neem seed kernel extract (at 0.02% concentration) has been found to reduce the rate of mosquito egg hatchability and to suppress larval development, population and adult emergence against *Culex pipiens*.[130] Neem oil mixed with coconut oil and formulated neem cream are effective mosquito repellents that provide protection against *Aedes albopictus*, *Aedes aegypti*, *Anopheles stephensi*, *Anopheles culicifacies* and *Culex quinquefasciatus* mosquitoes.[131] The neem products have been found to be safe alternatives to insecticide-impregnated coils for personal protection against mosquitoes; one application (2 g per person) has been reported to exert 68% efficacy for four hours.[131b]

Substances with pesticidal properties are found in all parts of the neem tree. However, the greatest concentration of these substances is found in the seeds. Azadirachtin (**1**), the most active principle of currently available neem-based insecticides and pesticides, is extracted from the seed kernels. In another extraction process, neem oil is extracted from the seed kernels. More than 60 insect pests may be affected by azadirachtin including aphids, beetles, caterpillars, lace bugs, leafhoppers, leaf miners, mealy bugs, psyllids, thrips and whiteflies. Azadirachtin shows a variety of modes of action. It has been found to be a very active insect phagorepellent and systemic growth disruptor, which induces dramatic changes in insect growth, development and reproduction.[21b] Azadirachtin reduces the level of the insect hormone ecdysone, thereby disrupting the insect's moulting process so that the immature larvae cannot develop into adults; the immature larvae and nymphs remain in an immature stage and die. Adults are not killed by the growth-regulating properties of azadirachtin, but mating and sexual communication may be disrupted which results in reduced fecundity. In addition, neem oil forms a coating on the insect's body that blocks the tracheal openings and suffocates the insect. Neem oil is also known to prevent germination and penetration of some fungal spores. As azadirachtin has a number of different modes of action, it is less likely that insects or pathogens will develop resistance to neem products compared to chemicals with a single mode of action.

Evaluation of Safety Aspects

A number of reports are available on the safety evaluation of different parts of neem and its various biologically active products.[132] The details of these studies are beyond the scope of this review; hence, only the major findings are presented here.

Safety evaluation of different parts of neem

Neem leaves: Neem-leaf extract was found in mice and guinea pigs. Mice administered orally with methanolic extract of neem leaves were affected by gastrointestinal spasms, apathy, hypothermia and terminal convulsions resulting in death.[133] Intravenously administered aqueous leaf extract at a dose greater than 40 mg per kg body weight produces toxic manifestations leading to death in guinea pigs.[133] Panda and Kar evaluated the safety of neem-leaf extract with respect to thyroid function in male mice;[134] they studied the effect at two different dosages (40 and 100 mg kg^{-1} day^{-1}) for 20 days. While the higher dosage decreased serum triiodothyronine (T_3) and increased serum thyroxine (T_4) concentrations, no significant alteration in levels was observed in the lower-dosage group, indicating that the high concentrations of neem extract can be inhibitory to thyroid function, particularly in the conversion of T_4 to T_3, which is the major source of T_3 generation. A concomitant increase in hepatic lipid peroxidation (LPO) and a decrease in glucose-6-phosphatase (G-6-Pase) activity in the higher-dosage group also indicated the adverse effect of neem extract despite an enhancement in the activities of two defensive enzymes, superoxide dismutase (SOD) and catalase (CAT). Crude neem-leaf extract has been found to show genotoxic effects in mice. Awasthy et al. reported that oral administration of the crude ethanolic extract to adult Swiss albino mice for 7 days at 5–20 mg/10 g body weight per day significantly increased the incidence of structural and mitotic disruptive changes in metaphase chromosomes of bone marrow cells on days 8, 15 and 35 of observation.[135] It is also reported that crude neem-leaf extract causes genotoxicity in male mice germ cell at a dose of 0.5–2 g per kg body weight when administered for 6 weeks. Some structural change in meiotic chromosomes along with chromosome strand breakage or spindle disturbances and abnormal regulation of genes controlling sperm shape were observed.[136] Brown Hisex chicks fed with a diet containing 2% and 5% neem leaf from their 7th to 35th day of age developed hepatonephropathy and significant changes in blood parameters like erythrocyte count, haemoglobin concentration, packed cell volume and mean corpuscular volume,[136] resulting in a depression in body weight gain and efficiency of feed utilisation.[137]

Neem bark: A methanolic extract of neem bark showed oral LD_{50} at about 13 g kg^{-1} in acute toxicity studies on mice.[133] Stem bark extract shows lethal effect in three common snail species, namely, *Biomphalaria pfeifferi*, *Bulinus truncatus* and *Lymnaea natalensis* and also against fish, namely, *Aphyosemon giardneri*.[138] Aqueous bark extract shows effective antiacid secretory and antiulcer activity in rats; detailed toxicity studies have also recently been conducted in rats with the neem bark aqueous extract.[139] As mentioned earlier, such extracts have been found to be safe in rat models. A single dose of 1 g of raw extract per kg body weight (mice) given in one day and application of 0.6 g raw extract per kg body weight per day by oral route over 15 days to a cumulative dose of 9 g kg^{-1} was demonstrated to be well tolerated with no significant adverse effect and was below the LD_{50}.[58]

Neem seed: Aqueous neem seed kernel extract exhibited toxicity to *Oreochromis niloticus* (tilapia) and *Cyprinus carpio* (carp).[140] About 60% mortality was noticed in white leghorn chicks within a day of feeding powdered ripe neem berry aqueous extract.[140,141] An aqueous extract of neem seed kernel (1 mL/100 g body weight daily of a 50 g L^{-1} solution) produces trypsin inhibitory activity as observed in weanling rats.[140–142]

Neem oil: Neem seed oil exhibited acute toxicity in rats and rabbits with LD_{50} values of 14 mL kg^{-1} and 24 mL kg^{-1}, respectively; the possible target organs for toxic effects were the CNS and the lungs.[125] Neem oil produces toxic effects in humans in a number of isolated cases.[133,139,140,143,144,145] The oil causes toxic encephalopathy, particularly in infants and young children. The usual features are vomiting, drowsiness, tachypnea and recurrent generalised seizures. Leucocytosis and metabolic acidosis are significant laboratory findings.[146] Management is aimed primarily towards the control of convulsions, although supportive management is equally important. However, use of neem oil (1%) in kerosene lamps for mosquito repellency was found to be safe.[147] The safety aspects of this personal protection method developed by the Malaria Research Centre were evaluated by animal studies and clinical examination of population before and after exposure. Single application of neem oil (1%) did not produce skin irritation in rabbits or an adverse effect on guinea pigs after exposure to aerosol. Clinical examination of 156 adults and 110 children did not reveal any major adverse effects after one year of exposure to 1% neem oil.

Neem compounds and commercial formulations

Nimbidin produces sub-acute toxicity in adult rats after daily administration of 25, 50 or 100 mg kg^{-1} for six weeks.[133] Nimbidol was also found to be more potent than nimbidin at a dose of 25 mg per 100 g body weight, given orally twice a day for 4 days, in suppressing the injection of *Ploasmodium gellinaecum* in chicks.[148] The LD_{50} value of sodium nimbidinate when administered by intraperitoneal route in mice was found to 700 mg kg^{-1}. The dogs tolerated up to 200 mg per kg body weight by oral, intramuscular and intravenous routes. With a large single dose (100 mg per kg body weight), proliferation of endothelial cells in the glomerular apparatus was noticed, and the renal tubules revealed cloudy swelling, fatty infiltration and necrosis in the convoluted segment.[148] Nimbolide (**5**), a major chemical component of neem seed oil, and nimbic acid were found to be toxic to mice when administered intravenously or intraperitoneally.[140,149,150] Lethal doses of nimbolide and nimbic acid cause death in most animals by dysfunction of the kidneys, small intestine and liver as well as by marked and sudden drop of arterial blood pressure. Nimbolide shows potent cytotoxic effect on NIE-115 neuroblastoma (mouse), 143B.TK-osteosarcoma (human) and Sf9 (insect) cultured cell lines with an IC_{50} value of 4–10 μM.[151] Other limnoids like epoxyazadiradione and salanin have cytotoxic effects at IC_{50} values of 27 and 112 μM, respectively. Azadirachtin is relatively short-lived and easily degradable. Its mammalian toxicity is low and it can be used up to and including the day of harvest without protective clothing after the spray is dried. It is, however, toxic to fish and aquatic invertebrates. Raizada et al. performed sub-chronic toxicological testing with azadirachtin to document its safety for use as a pesticide.[152] Technical azadirachtin (12%) orally administered to male and female rats at dosages of 500, 1000 and 1500 mg kg^{-1} day for 90 days did not produce any signs of toxicity, mortality, changes in tissue weight, pathology and serum and blood parameters. It can be suggested that azadirachtin at the highest dose tested is well tolerated by rats of both sexes. The highest dosage, 1500 mg per kg body weight, can be used as a basal dose for the determination of the no observed effect level (NOEL) of azadirachtin to calculate its safety margin. Rahman et al. studied the long-term effects of Vepacide, a neem-based pesticide, on biochemical profiles.[153] Vepacide caused increase in aspartate and alanine aminotransferase in serum, kidney and lung, and these enzymes decreased in liver in both male and female albino Wistar rats when measured after 45 and 90 days of treatment. The enzyme profiles elucidate that they increased in serum and simultaneously decreased in liver; this indicates necrosis of the liver. In other tissues, the level of enzymes increased, indicating an adaptive mechanism due to chemical stress. As a result of Vepacide treatment, the lung was more affected followed by liver and then the kidney.Several studies were performed with Margosan-O, a botanical insecticide derived from neem seeds. However, no apparent toxic effects were observed in rats or mice.[140] The LC_{50} value of Margosan-O is more than 2 mL kg^{-1} in albino rabbits when tested for acute dermal toxicity.[133] Scott and Kaushik conducted microcosm trials with Margosan-O to assess the potential hazards of the product to aquatic organisms. Residue analyses of the active ingredient, azadirachtin, determined that it had a half life of 36–48 h in water exposed to natural sunlight.[154] Two applications of Margosan-O at the recommended application rate for pests did not harm aquatic invertebrates categorised as planktonic and filter feeding (*Culex* sp. and *Daphnia* sp.). However, the benthic invertebrate (*Chironomus riparius*) was affected by multiple applications of neem. These results show that the use of Margo-

san-O and possibly other neem extracts in or near aquatic environments could lead to disturbances in benthic populations and may cause decreases in numbers of organisms that are important in food web and nutrient cycling processes.

Summary and Outlook

The neem tree appears to be an omnipotent plant. It is a versatile medicinal plant and the unique source of a vast number of phytochemicals with diverse chemical skeletons. Work on the biological activity and plausible medicinal applications of these compounds is still insufficient and further extensive investigation is needed to exploit their therapeutic utilities against various diseases. There is currently a global search for nontoxic, safe and highly effective plant products with traditional medicinal use; hence, for prevention and treatment of various diseases, the development of modern drugs from neem should be pursued. In addition, different parts of neem and their extracts have been found to be safe, cheap and ecofriendly pesticides, insecticides, parasiticides and agrochemicals. Neem-based materials are compatible with integrated pest management (IPM); neem products do not persist in the environment and are degraded by ultraviolet rays and rainfall. In recent years, there has been an increasing trend and awareness in neem research. In fact, the time has come to make good use of centuries-old knowledge of neem through modern scientific approaches and techniques, so that such a unique gift of nature can be utilised to a greater extent. It is of no doubt that the neem tree would be commercially exploitable with great use and this requires more and more commercial formulations. The neem tree may be regarded as an "industrial plant" and it promotes a lot of small-scale industries in India and other countries of the world. For this reason, further extensive research and development on neem and its products is needed. From the above discussion, it is thus evident that owing to its unique properties and applications in various areas of social need, this "Divine tree" demands special attention and interest from the world community. More systematic scientific investigation into neem directed towards the larger interests of society would ultimately be a blessing for mankind.

Acknowledgements

I thank Prof. K. S. Mukherjee, Chemistry Department and Prof. Shelley Bhattacharya, Faculty of Zoology and Dean of Science, Visva-Bharati University, Santiniketan, India, for their constant encouragement and constructive help during the preparation of this manuscript.

Keywords: agrochemicals · drugs · natural products · neem · pesticides · phytochemistry

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Received: August 22, 2003 [A 749]

