

Medicinal Properties of Neem Leaves: A Review

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Abstract: *Azadirachta indica*, commonly known as neem, has attracted worldwide prominence in recent years, owing to its wide range of medicinal properties. Neem has been extensively used in Ayurveda, Unani and Homoeopathic medicine and has become a cynosure of modern medicine. Neem elaborates a vast array of biologically active compounds that are chemically diverse and structurally complex. More than 140 compounds have been isolated from different parts of neem. All parts of the neem tree- leaves, flowers, seeds, fruits, roots and bark have been used traditionally for the treatment of inflammation, infections, fever, skin diseases and dental disorders. The medicinal utilities have been described especially for neem leaf. Neem leaf and its constituents have been demonstrated to exhibit immunomodulatory, anti-inflammatory, antihyperglycaemic, antiulcer, antimalarial, antifungal, antibacterial, antiviral, antioxidant, antimutagenic and anticarcinogenic properties. This review summarises the wide range of pharmacological activities of neem leaf.

Key Words: *Azadirachta indica*, neem, neem leaf, pharmacological activities, phytochemicals.

INTRODUCTION

Medicinal plants have received growing attention in the drug discovery process for various human disorders, including cancer. A medicinal plant has been defined by Park and Pezzuto [1] as “a plant that has pharmacological activity to treat disease, as compared with an edible plant that is used in daily life as a food”. *Azadirachta indica* A Juss commonly known as neem, has been well known in the Indian subcontinent for more than 2000 years, as one of the most versatile medicinal plants possessing a wide spectrum of biological activities. Its taxonomic position is as follows:

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

The latinized name of neem *Azadirachta indica* (in Persian, *Azadi* = free, *diracht* = tree) literally meaning “the free tree of India”, is an alliteration for its being intrinsically free from insect and disease problems. The neem tree is considered as a ‘*sarvaroga nivarini*’ (the panacea for all diseases) and has also been hailed as ‘*heal all*’, ‘*divine tree*’, ‘*village dispensary*’ and ‘*nature’s drugstore*’ [2].

Morphology

Neem is a large evergreen tree that may grow up to 20 m in height. The leaves are alternate and the leaflets contain

8-19 leaves that may appear in March-April. The leaves are bitter in taste [2].

Chemistry

Extensive investigations have been carried out on the chemistry of neem tree products. In particular, the leaf of neem is a ‘*storehouse*’ of organic compounds. Neem leaves contain 0.13 per cent essential oil, which is responsible for the smell of the leaves [2]. Table 1 shows the principle constituents of neem leaves identified by proximate analysis [3,4].

More than 140 active substances that are chemically diverse and structurally complex have been isolated from different parts of neem. The compounds have been divided into two major classes: isoprenoids and nonisoprenoids. The isoprenoids include diterpenoids, triterpenoids, vilasinin type of compounds, limonoids and its derivatives, C-secome-liacins. The nonisoprenoids include proteins, polysaccharides, sulphurous compounds, polyphenolics such as flavonoids and their glycosides, dihydrochalone, coumarin and tannins and aliphatic compounds [3-7]. Some of the phytochemical constituents present in neem leaf are listed in Table 2 and the chemical structures of some of the bioactive compounds presented in Fig. (1).

PHARMACOLOGICAL ACTIONS OF NEEM LEAF EXTRACT

Neem has been extensively used in Ayurveda, Unani and Homoeopathic medicine and has become a cynosure of modern medicine. All parts of the neem tree- leaves, flowers, seeds, roots and bark have been used in traditional medicine as household remedies against various human ailments. Table 3 lists the pharmacological activities of different parts of neem. However, the medicinal utilities have been described especially for neem leaf [5,6]. Neem leaves have been used extensively as ingredients in ancient medicinal preparations because of their availability throughout the year

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and the ease of extracting the compounds [3,8]. Neem leaves exhibit a wide range of pharmacological activities and medicinal applications. The ensuing discussion on pharmacological activities will be confined to neem leaves.

Table 1. Principle Constituents of Neem Leaf

	Content (on dry matter basis)
Carbohydrate*	47.46 - 51.2
Crude protein*	14.01 - 18.82
Crude fiber*	11.20 - 23.80
Fat*	2.31 - 6.93
Ash*	7.73 - 8.52
Moisture (g/100g)	59.49
Amino acids (mg/100g)	
• Glutamic acid	73.3
• Tyrosine	31.5
• Aspartic acid	15.5
• Alanine	6.4
• Proline	4.0
• Glutamine	1.0
Minerals (mg/100g)	
• Calcium	3.4
• Iron	510.0
• Phosphorus	0.13 - 0.24
• Thiamine	80.0
• Niacin	17.1
• Vitamin C	0.04
• Carotene	1.4
Calorific value (K cal/100g)	129.0

Adapted from Keher and Negi [3] and Devakumar and Dev [4].

* - per cent/100g.

Table 2. Phytochemical Constituents in Neem Leaf

• 3-Acetyl-7-tigloyl-lactone-vilasinin	• Isoazadirolide
• 3-Desacetyl-3-cinnamoyl-azadirachtin	• Nimbaflavone
• 3-Desacetyl-salanin	• Nimbandiol
• 4, 6 -dihydroxy-A-homo-azadiradione	• Nimbinene
• 6-desacetylnimbinene	• Nimbolide
• Azadirachtanin	• Quercetin
• Azadirachtanin-A	• Quercitrin
• Beta-sitosterol	• Rutin
• Hyperoside	• Vilasinin

Antiviral Activity

Aqueous neem leaf extract exerts antiviral activity against *Vaccinia* virus, *Chikungunya* and *measles* virus *in vitro* [9]. Rao *et al.* [10] found that a 10 per cent water extract of tender leaves exhibits antiviral activity against

vaccinia and *variola* viruses. Antiviral and virucidal effects of the methanolic extract of neem leaves (NCL-11) have been demonstrated against group-B-Coxsackie viruses [11]. Parida *et al.* [12] reported the inhibitory potential of neem leaves on Dengue virus type-2 replication. Aqueous neem leaf extract showed low to moderate inhibition of the viral DNA polymerase of hepatitis B virus [13].

Antifungal Activity

High antimycotic activity of the extracts of different parts of neem has been reported [6]. Extracts of neem leaf are effective against certain human fungi, including *Trichophyton*, *Epidermophyton*, *Microsporum*, *Trichosporon*, *Geotrichum* and *Candida* [14]. The antifungal activity of neem has been attributed to volatile sulfides, and the limonoid gedumin. Iyer and Williamson [15] reported inhibition of the protease activity of *Trichophyton* species by neem. Bhatnagar and McCromick [15] and Allameh *et al.* [17] have demonstrated that addition of neem leaf extract effectively inhibited aflatoxin production by *A.parasiticus*. *In vitro* antifungal activity of aqueous neem leaf extract against *Penicillium expansum* has also been documented [18].

Antibacterial Activity

The oil from the neem leaves is recognized to possess antibacterial activity against a wide spectrum of Gram-negative and Gram-positive microorganisms, including *M.tuberculosis* and Streptomycin-resistant strains [19]. Neem leaf is known to inhibit *Vibrio cholerae*, *Klebsiella pneumoniae*, *M.tuberculosis* and *M.pyogenes in vitro* [20]. Mahmoodin, a limonoid isolated from *A.indica* showed significant antibacterial activity [21].

Antimalarial Activity

Neem leaf extracts are effective against malarial parasites. Components of the alcoholic extract of leaves are found to be effective against both chloroquin-resistant and sensitive strains of malarial parasite [22]. The limonoids (meldenin, isomeldenin, nimocinol and nimbandiol) isolated from the ethanolic extract of fresh neem leaves have been found to demonstrate antimalarial activity against chloroquine-resistant *P.falciparum* strain K₁ [23].

Antifertility Activity

Administration of neem leaf powder for 24 days resulted in decrease in the weights of seminal vesicles and ventral prostate, reduction in epithelial height, nuclear diameter and the secretory material in the lumen [24]. Mateenuddin *et al.* [25] have demonstrated the anti-estrogenic activity of neem leaf extract. The ultrastructural changes induced by neem leaves in the testis of albino rats include vacuolization of Sertoli cells, diminished cytoplasmic inclusions in Leydig cells, as well as defects in the mitochondrial sheaths in late spermatids. Thus, neem leaves may affect spermatogenesis through antispermatogenic and antiandrogenic properties [26]. Aqueous extracts of old and tender neem leaves were shown to completely immobilize and kill human spermatozoa within 20 seconds [27].

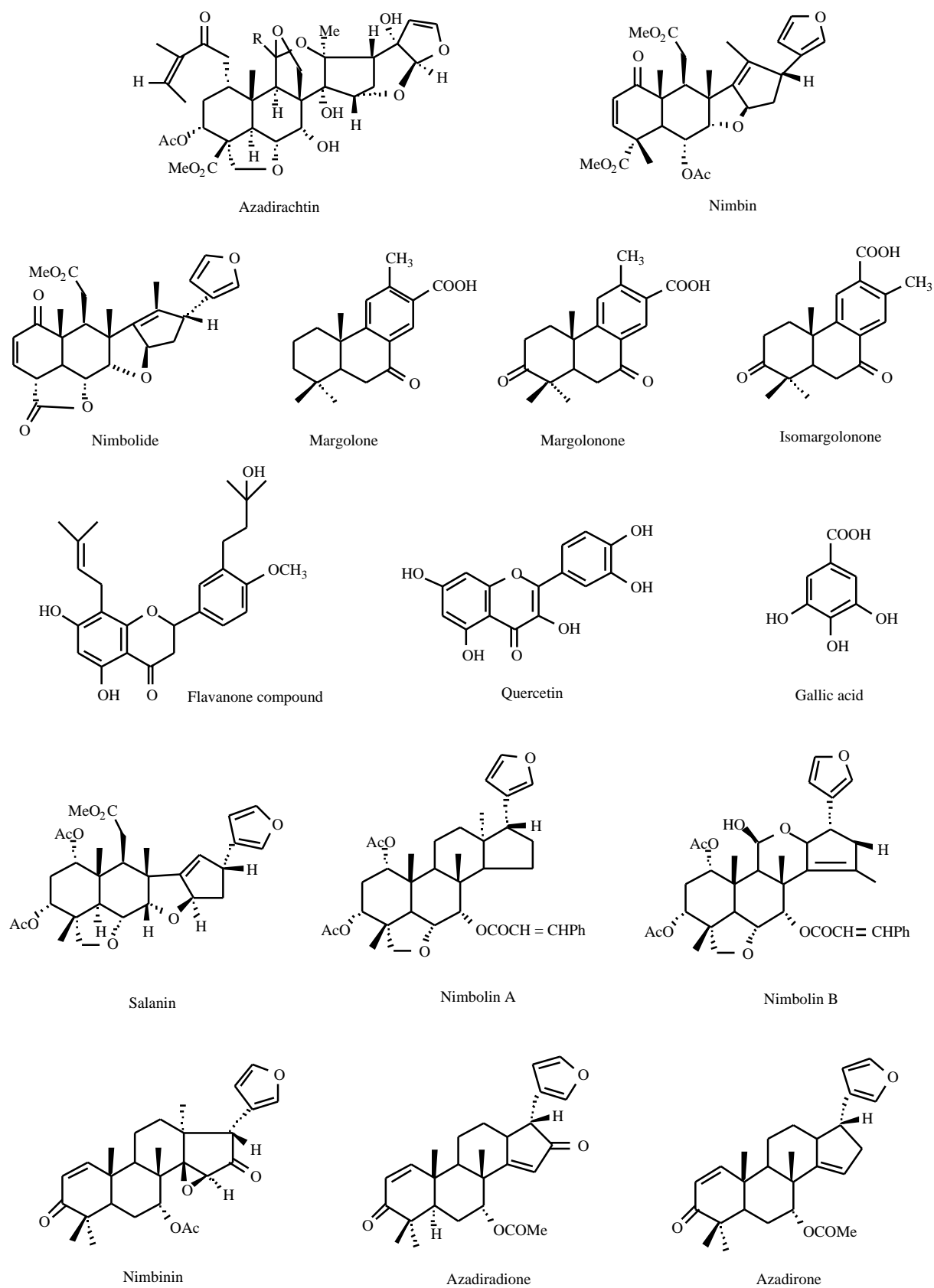


Fig. (1). Chemical structures of some of the bioactive compounds present in neem leaf.

Table 3. Pharmacological Activities of Different Parts of Neem

Part	Biological activity
Leaf	<ul style="list-style-type: none"> • Antifungal • Antibacterial • Antimalarial • Antifertility • Antipyretic • Anti-inflammatory • Analgesic • Antiulcerogenic • Antihypertensive • Antihyperglycaemic • Neuropharmacological • Antidermatophytic • Ororenal protection • Hepatoprotective • Immunostimulant • Antioxidant • Antigenotoxic • Anticancer
Bark	<ul style="list-style-type: none"> • Antibacterial • Antimalarial • Antiinflammatory • Antiulcer effect • Hepatoprotective • Immunostimulant • Anticancer
Flower	<ul style="list-style-type: none"> • Antioxidant • Anticancer
Seed	<ul style="list-style-type: none"> • Antimalarial • Antifertility • Antioxidant • Anticancer
Oil	<ul style="list-style-type: none"> • Antifungal • Antifertility • Antipyretic • Antiinflammatory • Antiulcerogenic • Antihyperglycaemic • Immunostimulant

Antipyretic, Antiinflammatory and Analgesic Activities

Neem leaf is strongly antipyretic and traditionally used for fevers. A methanol extract of the leaves has been reported to exert antipyretic effects in male rabbits [28]. Khatak *et al.* [29] obtained an antipyretic effect from various fractions of 90 per cent ethanolic leaf extract. The antipyretic effect of neem leaf extract has been attributed to nimbidine. The water-soluble portion of 70 per cent ethanolic neem leaf extract was found to possess anti-inflammatory activity in rats [30]. A 75 per cent ethanolic extract of neem leaves in doses of 400 to 800 mg/kg had pronounced anti-inflammatory effect on carrageenin-induced oedema in rats [28]. Neem also possesses analgesic activity mediated through opioid receptors in laboratory animals [29]. The ether-soluble

fraction of ethanolic neem leaf extract has been demonstrated to possess antipyretic and antianalgesic effects [29].

Antiulcerogenic Activity

Neem leaf has proven successful in treating stomach ulcers. Its antihistamine and antibacterial compounds can reduce inflammation and destroy ulcer-causing bacteria such as *Helicobacter pylori* [32]. Garg *et al.* [33] have observed antiulcer effects of neem leaves in rats exposed to restraint-cold stress or ethanol orally. Neem leaf extract was found to reduce ulcer index, free and total acidity, and the volume of gastric acid secretion [34]. Neem leaves are reported to exert antiulcer effects by preventing mucus depletion and mast cell degranulation. Recently, Chattopadhyay *et al.* [35] reported that the antiulcer effect of aqueous neem leaf extract is brought about by blocking acid secretion through inhibition of H⁺-K⁺-ATPase, and by preventing oxidative damage and apoptosis. The potent antiulcer effects exerted by nimbidin, a constituent of neem leaf, was correlated to its antihistaminic action mediated *via* H₂-receptor blockade [33].

Antihypertensive and Antihyperglycaemic Effects

An alcoholic extract of neem leaf has been reported to produce a significant and dose-related fall in blood pressure [36]. Aqueous neem leaf extract has been found to reduce blood glucose levels and prevent adrenaline and glucose-induced hyperglycaemia [37]. Oral administration of aqueous as well as alcoholic neem leaf extracts decreased blood glucose levels in experimentally induced diabetes in rats and rabbits. The antihyperglycaemic effect of neem leaf may be due to its antiserotonin activity [38, 39]. Van der Nat *et al.* [40] suggested that the antidiabetic effect of neem maybe attributed to the release of endogenous insulin by a mechanism similar to that reported for sulphonylurea.

Neuropharmacological Activity

Varying degrees of central nervous system (CNS) depressant activity in mice were observed with neem leaf extract. Singh *et al.* [41] observed a CNS-depressant activity by acetone extract of neem leaves. Leaf extract up to a dose of 200 mg/kg body weight produced significant anxiolytic activity in rats [42].

Antidermatophytic Activity

Neem has a remarkable effect on chronic skin conditions that often fail to respond to medical drugs. Local application of a lotion prepared from the 70 per cent alcoholic extract of neem leaves was found to be effective in chronic skin diseases such as eczema, scabies and ringworm infection [43]. Alcoholic neem leaf extract has been reported to control ringworm infection more effectively than salicylic acid and benzoic acid. A mixture of fresh neem leaves and turmeric powder (4:1) was found to be effective in the treatment of scabies [44]. Antidermatophytic activity of neem leaf extract has been documented against different species of dermatophytes including *Trichophyton rubrum*, *Trichophyton*, *Mentagrophytes*, *Trichophyton violaceum*, *Microsporium nanum* and *Epidermophyton floccosum* [45].

Orodonal Protection

Neem leaves have been used in the treatment of gingivitis and periodontitis. Neem has also shown greater efficacy in the treatment of oral infections and plaque growth inhibition in periodontal disorders [46,47]. Recently, Pai *et al.* [48] have demonstrated that a dental gel containing neem leaf extract (25 mg/g) reduces plaque index and bacterial count (*Streptococcus mutans* and *Lactobacilli*).

Hepatoprotective Effect

Both aqueous as well as alcoholic extracts of neem leaf were found to offer protection against paracetamol-induced liver damage [49, 50]. The levels of marker enzymes such as aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) were elevated 24 hours after paracetamol treatment, whereas rats fed with neem extract prior to paracetamol treatment showed much lower enzyme activities [49]. Kale *et al.* [51] reported the protective effects of neem leaves on hepatotoxicity induced by antitubercular drugs in rats. Aqueous neem leaf extract significantly prevented changes in serum bilirubin, protein, AST, ALT and ALP induced by antitubercular drugs such as isoniazid, rifampicin and pyrazinamide. Oomacham *et al.* [52] reported neem as one of the plants used for the treatment of jaundice.

Immunostimulant Activity

The aqueous extract of neem leaf exerts its immunostimulant activity by enhancing both humoral and cell-mediated responses [53,54]. Oral administration of leaf extract (100 mg/kg bw) induces higher levels of IgM and IgG along with increased titer of antioalbumin antibody [54]. Selective activation of the TH-1 component of lymphocyte population by neem leaf is believed to elicit and enhance cell-mediated immune response. Neem leaf extracts have been found to decrease both the classical and alternative C pathways and enhance the phagocytic activity of macrophages [55,56].

Antioxidant and Antigenotoxic Effects

Chattopadhyay [30] reported the radical scavenging properties of neem leaf. Neem leaf has been documented to decrease the extent of lipid peroxidation. Experiments from this laboratory have shown that both aqueous as well as 70 per cent ethanolic neem leaf extracts significantly reduce N-methyl-N'-nitro-N-nitrosoguanidine (MNNG)-induced lipid peroxidation, by enhancing the activities of glutathione-dependent antioxidants as well as superoxide dismutase (SOD) and catalase (CAT) [57,58]. Aqueous neem leaf extract was found to reduce the incidence of rat bone marrow micronuclei and chromosomal aberrations induced by MNNG [59]. Pretreatment with ethanolic extract of neem leaf exerted significant protective effects against the genotoxic effects of the carcinogens MNNG and 7,12-dimethylbenz[a]-anthracene (DMBA) in mice and hamsters respectively [60,61].

Anticancer Activity

Neem leaf preparations have been reported to possess anticancer properties. Yadav and Rathore [62] observed

inhibition of mitotic activity by neem leaf extract. Studies from this laboratory have demonstrated the chemopreventive potential of neem leaf extracts on MNNG-induced forestomach tumours and 4-nitroquinoline 1-oxide induced oral carcinogenesis [63-68]. Aqueous as well as alcoholic extracts of neem leaf effectively suppressed DMBA-induced HBP carcinogenesis by modulating the cellular redox status as well as carcinogen-metabolizing enzymes in the target organ, as well as in host liver and blood [61, 69-71]. Recently, Dasgupta *et al.* [72] reported the chemopreventive potential of neem leaf extract in murine carcinogenesis model systems. Administration of aqueous neem leaf extract significantly reduced tumour burden and tumour incidence in both benzo[a]pyrene-induced forestomach tumours and DMBA-induced skin papillomagenesis. The results of their study provide evidence that neem leaf extract exerts its chemopreventive effect by inducing phase-II enzyme activities associated with carcinogen detoxification, as well as by enhancing the antioxidant status in the liver. Oral administration of 5 per cent neem extract was found to offer protection against diethylnitrosamine and acetyl-amino-fluorene-induced hepatocellular carcinoma by increasing antioxidants and detoxification enzymes [73]. Baral and Chattopadhyay [74] reported a significant reduction in the growth of Ehrlich carcinoma and B16 melanoma cells by administration of neem leaf extract. The chemopreventive potential of neem leaf extracts has been attributed to inhibition of the synthesis of prostaglandins and other essential metabolites involved in tumour promotion [75].

Neem leaves contain a number of potent antioxidants and anticarcinogens including carotenes, ascorbic acid, terpenoids, limonoids and flavonoids [6]. -Carotene and vitamin C present in neem leaf play an important role in preventing tumour development by their radical scavenging properties [76,77]. Limonin 17 -D-glucopyranoside, a limonoid found in neem, has been shown to inhibit DMBA-induced oral carcinogenesis [78]. Azadirone 1, a limonoid constituent of *A. indica* has been found to possess cytotoxic activity against breast, melanoma and prostate cancer cell lines [79]. Akudugu *et al.* [80] have reported the cytotoxicity of azadirachtin A in human glioblastoma cell lines. Nimbolide and 28-deoxonimbolide have been identified as cytotoxic constituents of neem leaves [81].

Quercetin and kaemferol, the flavonoids present in neem leaf have been documented to retard carcinogenesis at initiation, as well as promotion phases of carcinogenesis by virtue of their radical scavenging properties [82-84]. Quercetin, a neem bioflavonoid has received the maximum focus of attention as an anticancer agent. Quercetin has been demonstrated to inhibit the growth of tumour cells in a number of malignant cell lines. The antiproliferative effects of quercetin have been documented in experimental animal models, as well as in humans [85-87]. Quercetin has also been found to enhance the therapeutic efficacy of radiation, as well as chemotherapeutic drugs [88,89]. A number of mechanisms have been suggested to explain the growth inhibitory effects of quercetin. Quercetin has been reported to inhibit cytochrome P-450-dependent monooxygenase system involved in the activation of chemical carcinogens [90]. Studies have shown downregulation of the expression of mutant p53 protein, as well as p21-*ras* oncogene by

quercetin [91,92]. Quercetin has also been reported to downregulate signal transduction pathways in human breast carcinoma cells [93]. In addition, quercetin is known to induce type II estrogen receptor (ER II) expression in estrogen receptor-negative human breast cancer cells, thereby inhibiting their growth [94]. Thus, the anticancer effects of quercetin may be related to its wide range of biological actions including cell cycle regulation, interaction with type II estrogen binding sites and inhibition of protein kinase C and/or tyrosine kinase activity [85].

Toxicity Studies

While the aqueous extract of neem leaf was not toxic to mice up to oral doses of 1000 mg/kg, methanolic leaf extracts showed an oral LD50 of about 13 g/kg in acute toxicity studies in mice [7,28]. Oral doses of nimbidin up to 100 mg/kg for six weeks in rats did not cause any toxicity [95].

CLINICAL TRIALS

Oral administration of aqueous neem leaf extract or equivalent amount of dried leaves in capsules was found to reduce insulin requirements by 30-50 per cent in diabetic patients [96]. Neem leaf extract has been prescribed for oral use for the treatment of malaria by Indian Ayurvedic practitioners. Clinical studies with dried neem leaf extract have demonstrated its effectiveness to cure ringworm, eczema and scabies. Topical application of a lotion derived from neem leaf has been shown to cure acute dermatological diseases within 3-4 days and chronic diseases in a fortnight [97]. A paste prepared with neem and turmeric was found to be effective in the treatment of scabies in nearly 814 people [5].

A polyherbal pessary has been developed using purified ingredients from neem leaves, *Sapindus mukerossi* and *Mencitrata oil*, which showed spermicidal action *in vitro* on human sperm and *in vivo* on postcoital tests in women. The formulation also has antimicrobial activity against a wide spectrum of microorganisms including *Candida albicans*, *C. tropicalis*, *Neisseria gonorrhoeae*, multidrug-resistant *Staphylococcus aureus* and urinary tract *E. coli*, *Herpes simplex-2* and *HIV-1*. Phase I clinical trials completed in India, Egypt and the Dominican Republic indicate the safety of this formulation, its acceptability and beneficial action in vaginosis due to infections [98,99]. A dental gel containing chlorhexidine gluconate and neem extract showed significant reduction in plaque and gingival scores [100].

CONCLUSION

Medicinal plants and phytochemicals are receiving growing consideration in recent years for the prevention and treatment of various diseases including cardiovascular disease and cancer, because of their relative safety and efficacy. The neem leaf is a treasure trove of phytochemicals with myriad health benefits. Although a number of therapeutically useful compounds have been identified, most of the pharmacological properties of neem leaf have been reported only with crude extracts. It has become increasingly important to subject neem leaf to the rigours of modern

scientific research. Extensive investigations on the metabolism, tissue distribution, pharmacokinetics, toxicity and the molecular mechanisms of chemoprotection are necessary for the development of modern drugs from neem leaf.

ACKNOWLEDGEMENTS

Financial support from the Indian Council of Medical Research, New Delhi, India in the form of a Senior Research Fellowship to Ms. R. Subapriya is gratefully acknowledged.

ABBREVIATIONS

ALT	=	Alanine transaminase
ALP	=	Alkaline phosphatase
AST	=	Aspartate transaminase
CAT	=	Catalase
DMBA	=	7,12 dimethylbenz[a]anthracene
GPx	=	Glutathione peroxidase
GST	=	Glutathione S-transferase
MNNG	=	N-methyl-N'-nitro-N-nitrosoguanidine
GSH	=	Reduced glutathione
SOD	=	Superoxide dismutase

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