

## Neem (*Azadirachta indica*) and its Potential for Safeguarding Health of Animals and Humans: A Review

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**Abstract:** Since ancient era, herbal therapy remained as medicine's backbone which is economic, safer and easily available to most of people in world. Among diverse herbal treasure, *Azadirachta indica* (Neem) is a highly esteemed tree with several beneficial properties and applications especially known for its incredible therapeutic and ethnomedicinal values for humankind. Neem is regarded as "free tree of India", "wonder tree", "Nature's drug store", "Village dispensary", "Divine tree", "heal all", "Materia medica" and "Panacea of all Diseases". It is among highly exploited medicinal plant of Indian origin. It has been used in different medicinal systems: ayurveda, unani, homoeopathic medicine, therefore, considered as cynosure of modern medicine. All parts of the plant have some biological and medicinal properties hence valuable source of natural medicinal products. Compounds isolated from neem are broadly classified into two: (1) Isoprenoids (2) Non-isoprenoids. Isoprenoid compounds consists of diterpenoids, triterpenoids and steroids while while non-isoprenoids contains proteins and/or amino acids, polysaccharides, flavonoids etc. It is found beneficial in leprosy, gastro-intestinal problems, malaria, intestinal helminthiasis, tuberculosis, ringworms, skin disorders, boils, epilepsy, fever, respiratory distress, nausea, ulcers and in many other health related problems. This review gives a bird's eye view particularly on history, classification, active principles, mechanism of action and potential uses of neem in safeguarding human and animal health along with the several commercial preparations available in the market.

**Key words:** *Azadirachta indica*, neem, immunomodulation, animals, human, general health, diseases, anti-infection, anti-cancer, insecticide, pest controlling agent, anti-venom, contraceptive

### INTRODUCTION

Phytotherapy has been a backbone of medicine since long back, in which various herbs and their extracts containing active ingredient of therapeutic significance is used. In lieu of a search for some alternative therapy against infections traditional herbal remedies are again in market due to their readily availability, being cost effective and comparatively less side-effects (Mahima *et al.*, 2012, 2013a). *Azadirachta indica* (Neem), also known as sacred gift of nature is native plant of south eastern Asia and distributed in India and neighbouring countries (Kumar and Navaratnam, 2013) and known for its

incredible therapeutic and ethnomedicinal values for humankind since prehistoric era (Chopra *et al.*, 1952; Govindachari, 1992; Puri, 1999; Biswas *et al.*, 2002; Drabu *et al.*, 2012; Dhama *et al.*, 2013a). *Azadirachta indica*, is latin term which has been derived from the Persian language signifies meaning of *Azadirachta indica* where Azad stands for- "free", dirakht for- "tree" and I for-Hind which belongs to "Indian origin". Therefore, Neem tree is regarded as "the free tree of India" which is widely distributed (Kumar and Navaratnam, 2013). Now-a-days, alternative treatment regimens like bacteriophage, cytokines, panchgavya, herbal therapy and others are gaining popularity due to

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emerging drug resistance and side effects of conventional allopathic therapies (Mahima *et al.*, 2012; Dhama *et al.*, 2013b, c, d; Tiwari *et al.*, 2013a, b, c, d).

Herbal therapy is an ancient revered therapy which is again gaining the momentum in lieu of need of alternative novel therapies and with least or no side effects this therapy is rapidly speeding the steps (Mahima *et al.*, 2012; Dhama *et al.*, 2013b).

A sacred gift of nature as well as an omnipotent tree is neem. Indian subcontinent is the main region for its cultivation. The plant is a mahogany family member. Various ailments of mankind have been treated by the use of neem before any written records were available that had recorded history at its beginning (Kumar and Navaratnam, 2013).

Neem tree with the scientific name *Azadirachta indica* (*A. indica*) *A. Juss* is “the wonder tree” and “Nature’s drug store”. Neem is among the highly exploited medicinal plant of Indian origin. It has been used in different system of medicine like ayurveda, unani and homoeopathic medicine, therefore, considered as cynosure of modern medicine (Biswas *et al.*, 2002).

Every part of Neem viz., leaf, flower, fruit, seed, kernel bark, root, wood, twig, oil and their purified products possess medicinal properties and have been used in traditional remedies. Neem is also known as village dispensary’ of India. United Nations has declared Neem tree as the “Tree of the 21st century” while The US National Academy of Science has designated this incredible tree as “Neem: A tree of solving global problems” in its report published in 1992. In Indian context it is famous as “Village dispensary”, “Divine tree”, “heal all” while in European literature “Materia medica” neem has been regarded as “Panacea of all Disease”. Neem extracts have been shown to possess anti-bacterial, anti-fungal, potent antiviral and anticancerous properties (NAS, 1992; Ruskin, 1992; Udeinya *et al.*, 2004; Ghosh *et al.*, 2006; Haque *et al.*, 2006; Sharma *et al.*, 2011; UNEP, 2012; Xu *et al.*, 2012; Al-Samarrai *et al.*, 2012; Elavarasu *et al.*, 2012; Elumalai *et al.*, 2012; Dhama *et al.*, 2013a).

#### **HISTORY: LIFE STORY OF A 50,000 B.C. OLD INVINCIBLE PLANT**

History reveals the long journey of omnipotent Neem tree from old legendary time to present state defining its role in the sustainability of humankind. In the old annals of the ancient Siddha medicinal system the first medicinal plant described was neem or margosa. In ancient immemorial period Neem has been used as a

disincentive agent against highly contagious smallpox and other infectious diseases and was also regarded to defend against evil spirits from time (Kumar and Navaratnam, 2013). In old medicinal system medications and applications were compiled over palm leaves and they have been passed on from generations to generations. In the Indus civilization the use of neem tree is as old as 4500 years during the period of Harappa culture (one among the great civilization in the world). There the earliest of the documentation mentions the fruits and seeds; oils and leaves; roots and barks for the medical characters that are advantageous (<http://www.slideshare.net/imulla/neem-presentation-882503>). Writing palm leaf manuscript is among the oldest medium of conserving knowledge in India to store the history of herbal heritage. Centre for Traditional Medicine and Research (CTMR), Chennai, India revealed the medicinal uses of different parts viz., fruits, seeds, leaves, roots, bark etc., of neem trees. It explains use of neem flower against bile disorders, neem leaves to prevent and treat ulcers and neem bark to brawl against paralysis and CNS disorders (Bandyopadhyay *et al.*, 2004). Old evidences obtained from two great civilizations Harappa and Mohenjo-Daro of ancient world also witnessed that *A. indica* was the prominent herb of therapeutic importance at that time not only in Indian context but in world as well. According to epic of Mahabharata, Nakul and Sahadeva used Neem oils for treatment of wounds in horses and elephants.

#### **CLASSIFICATION: PATRONAGE OF NEEM PLANT**

**Neem:** Botanical name (*Azadirachta indica*).

**Family:** Meliaceae, neem belongs to Mahognay family.

**Synonyms/common names:** Nimba/Holy tree/Vembu/ Arishtha/Indian neem tree/Indian lilac/Margosa tree *Azadirachta indica*, is an evergreen tree which is abundantly found in most of tropical and sub-tropical countries including India and Burma. Genus *Azadirachta* has two species as per geographical distribution and *A. indica* is mostly native of Indian and Asian sub-continent. Tree has good growth rate and attains height of approximately 15-20 m and sometimes even upto 35-40 m.

#### **ACTIVE PRINCIPLE/ CONSTITUENT COMPOUNDS**

In 1942 for the first time, Nimbin, a bitter compound had been isolated from Neem (Biswas *et al.*, 2002). Above 300 compounds have been derived from diverse parts of neem. There are mainly two types of metabolites

viz., primary including protein, fatty substance or carbohydrate or sugar derivative and secondary metabolites containing various alkaloids, steroids, flavonoids, saponins etc. The compounds isolated have been broadly classified into two major groups-isoprenoids and non-isoprenoids. Compounds such as diterpenoids, triterpenoids and steroids including azadirone, protomeliacins, limonoids, gedunin, vilasinin type of compounds, C-secomeliacins such as azadirachtin, nimbin, salanin and its derivatives comprise isoprenoids group while non-isoprenoids contains proteins/amino acids, polysaccharides, sulphurous compounds, polyphenolics such as flavonoids, their glycosides, dihydrochalcone, coumarin, tannins, aliphatic compounds etc. (Biswas *et al.*, 2002). Stem bark of neem contains many tannins in condensed form, important ones are tricyclic diterpenoids, NB-II peptidoglycan, gallic acid, epigallocatechin, galocatechin, catechin, epicatechin, margolone, margolonone and isomargolonone etc. The biological activity of different active principles of Neem exert multi-facet therapeutic effects (Osman and Port, 1990; Nisbet *et al.*, 1993; Johnson *et al.*, 1996; Ragasa *et al.*, 1997; Mongkholkhajornsilp *et al.*, 2004; Biu *et al.*, 2009; Mukherjee and Sengupta, 2013).

#### APPLICATIONS OF DIVINE TREE NEEM

From several parts of *Azadirachta indica* more than 140 compounds have been isolated. They have been used in traditional practices for treating inflammation and infections; fever, skin diseases as well as dental disorders. The leaves as well as its constituents use to exhibit immunomodulatory as well as anti-inflammatory and antihyperglycaemic activities; antiulcer; antimalarial; antifungal; antibacterial; antiviral; antioxidant; antimutagenic as well as anticarcinogenic characteristics (Beuth *et al.*, 2006; Akihisa *et al.*, 2009, 2011; Rakib and Hussain, 2013). Neem plant preparations are also used by the natural healers for diverse disorders such as leprosy, gastro-intestinal problems, malaria, intestinal helminthiasis, tuberculosis, ringworms, skin disorders, boils, epilepsy, fever, respiratory distress, nausea, ulcers and in health industries also (Vanna, 1976; Biswas *et al.*, 2002; Bhowmik *et al.*, 2010; Sharma *et al.*, 2011; Dhama *et al.*, 2013a). Modern scientists are exploiting more uses of this incredible tree. Different parts of neem plant such as bark, stems, leaves, fruits, flowers and seeds possess compounds such as flavonoids, tannins, flavonoglycosides, arabinofucoglucanes, dihydrochalcones, fucogalactoglucoarabinanes and others with proven immunomodulatory, antiseptic, diuretic, emmenagogue, febrifuge, antipyretic,

antidiabetic, anthelmintic, anti-inflammatory, analgesics, antifeedant, antiviral, antifungal, contraceptive, *in vitro* spermicidal, insecticide, pediculocide, parasiticide, antimutagenic and anti-ulcer properties since antiquity (Van Der Nat *et al.*, 1987; Chattopadhyay *et al.*, 1993; Banken and Stark, 1997; Subapriya and Nagini, 2005; Farah *et al.*, 2006; Waheed *et al.*, 2006; Gbotolorun *et al.*, 2008; Xu *et al.*, 2012; Al-Samarrai *et al.*, 2012; Del Serrone and Nicoletti, 2013; Mukherjee and Sengupta, 2013). In traditional Indian system, neem leaves were used to cover the patient of chicken pox and he was suggested to sleep under neem tree. In an experimental study on rats, neem leaf extract has been reported beneficial in treatment of carbon tetrachloride led liver damage (Mujumdar *et al.*, 1998). Neem Leaf Meal (NLM) may be useful ingredient in diet of broilers due to its medicinal and nutritional importance (Bonsu *et al.*, 2012). Nimbidiol present in root and bark of neem tree can inhibit intestinal glucosidases thus helpful in control of diabetes (Mukherjee and Sengupta, 2013).

#### Role in general health and diseases:

- **AIDS:** The National Institutes of Health reports neem extracts killed the AIDS virus and patents have been awarded for these extracts as an AIDS treatment (Anyaehe, 2009)
- **Heart disease:** Neem delays the coagulation of blood, calms erratic heart beats and helps reduce elevated heart rates and high blood pressure
- **Diabetes:** Neem leaf extracts taken orally reduces the insulin requirements by 30-50% in nonketonic and insulin-sensitive diabetic patients
- **Periodontal disease:** German researchers have proven neem extracts prevent tooth decay and periodontal disease (Prashant *et al.*, 2007; Chava *et al.*, 2012) leading to good oral health (Balappanavar *et al.*, 2013). Neem leaf extract has a antimicrobial effect on *Enterococcus faecalis* and *Candida albicans*. Therefore, it can be a potential endodontic irrigant (Vinothkumar *et al.*, 2013)
- **Skin diseases:** On skin conditions that have reached chronicity neem has got a significant effect. These conditions include: Acne and psoriasis; eczema and ringworm; even stubborn warts that can be easily cleaned up with the use of organic neem oil which is of high quality. For the treatment of skin diseases in Siddha medicine both neem oil as well as leaves have been used. For clearing and beautifying as well as rejuvenating the skin as an excellent component of cosmetics neem oil can be used (Thas, 2008)

- **Ulcers:** Neem extracts give significant protection from discomfort and speed the healing of gastric and duodenal lesions (Maity *et al.*, 2009)
- **Sexually transmitted diseases:** The efficacy of neem in the treatment of sexually transmitted diseases have been highlighted by few researchers and overwhelming positive responses have been reported. The efficacy of neem extract in *Neisseria gonorrhoeae* infection is also well proven (Shokeen *et al.*, 2009)

**Immunomodulatory actions:** Neem plant extract stimulates the immune system in various ways viz., enhancing phagocytic activity and antigen presenting ability of macrophages and augmenting cytokines (Thatte and Dhanukar, 1997). Production of IL-1, IFN $\gamma$  and TNF- $\alpha$  gets stimulated indicating activation of Th1 type of responses (Mahima *et al.*, 2013b). Neem oil administered by injection has been reported to enhance phagocytic activity of macrophages MHC II expression, production of IFN- $\gamma$  and lymphocyte proliferation (Upadhyay *et al.*, 1992). Neem leaf extract given orally in mice enhanced the levels of white blood cells, IgG and IgM (Ray *et al.*, 1996). The plant extracts are effective against allergic disorders by desensitizing the host specific allergens and limiting anaphylactic reactions. It improves spleenocyte's mitogenic response to concanavalin-A (Con-A) (Upadhyay *et al.*, 1992). Anti-complement activity is envisaged in the aqueous extract of Neem. Oil of this plant specifically stimulate macrophages and lymphocytes and thereby the Cell Mediated Immunity (CMI). Neem enhances Delayed Type of Hypersensitivity (DTH) in patients with psoriasis.

Neem leaves powder when used in immunosuppressed birds increased both humoral and cell mediated immune responses thus preventing further infections with pathogens (viruses) (Sadekar *et al.*, 1998). Use of Neem leaves extracts showed adjuvant activity in augmenting immune responses of vaccines preparations with poor antigenic mass (Baral *et al.*, 2005). Antibody titres to Newcastle's disease antigen have been shown to be enhanced in broiler chickens (Renu *et al.*, 2003). Durrani *et al.* (2008) conducted a research study for investigating immunomodulatory effects of infusion of neem leaves on broiler. In this study infusion of concentrated neem leaves were provided at specific ascending concentration to various group of birds in drinking water (fresh). The study indicates improvement in the antibody titer by infusion of plant leaves (for instance against immunosuppressive disease like infectious bursal disease) along with improvement in growth performance as well as gross return. Antiviral

activity of Neem has been demonstrated against Duck Plague Virus (DPV) in poultry birds (Xu *et al.*, 2012). The survival rate of Asian seabass *Lates calcarifer* fingerlings has been observed to be increased against *Vibrio harveyi* infection (Talpur and Ikhwanuddin, 2013).

In modern days biotransformation of plant has been found as a tool for modifications of the organic substrates structurally leading to biological augmentation of products. This ultimately may be helping in curing or improving several morbidities as well as diseases. Suspension culture of *Azadirachta indica* has been used in this regard for biotransforming dianabol giving rise to two metabolites viz., 17beta-hydroxy-17alpha-methyl-5alpha-androst-1-en-3-one and 17beta-hydroxy-17alpha-methyl-5alpha-androstan-3-one. These two metabolites suppress strongly as well as differentially proliferation of T-cells that activates phytohaemagglutinin (PHA) along with inhibition of interleukin-2 (IL-2) (Khan *et al.*, 2013). Apoptosis of leukocytes mediated by cisplatin and 5-fluorouracil has been shown to be prevented by Neem in mice (Rakib and Hussain, 2013).

**Anti-infection (against infective agents as bacteria, viruses, fungi, protozoa):**

- **Malaria:** An active ingredient iroquin A isolated from Neem leaves is toxic to causative strains of malaria (WHO, 2008; Anyaehie, 2009). *In vitro* experiments have demonstrated cent-percent mortality within 72 h even in a ratio of 1:20,000
- In small pox, Neem has been found to be an effective antiseptic for the treatment. Neem extracts have been shown to possess potent antiviral properties against different viruses including herpes simplex virus type-1 infection (Udeinya *et al.*, 2004; Ghosh *et al.*, 2006; Haque *et al.*, 2006; Tiwari *et al.*, 2010)
- Neem bark and oil exerts anti-leprotic action by inhibiting *M. tuberculosis* (Subramanian and Lakshmanan, 1996; Chauhan, 2010)
- *In vitro* antiviral activity of leaf extract has been documented against *Coxsackie virus* B, *Vaccinia virus*, *Variola virus*, *Chikungunia*, dengue virus, poliovirus, measles viruses, fowl pox viruses and new castle disease viruses (Badam *et al.*, 1999; Parida *et al.*, 2002; Yanes *et al.*, 2004; Girish and Bhat, 2008; Faccin-Galhardi *et al.*, 2012)
- Neem oil preparations have been found effective against a wide spectrum of bacteria viz., *B. cerus*, *B. pumilus*, *S. aureus*, *M. tuberculosis*, *E. coli*, *P. vulgaris*, *S. typhi*, *K. pneumoniae*, *S. dysenteriae*, *Enterococcus faecalis*, *Streptococcus mutans*, *Streptococcus salivarius*, *Streptococcus mitis*,

*Streptococcus sanguis* and even *Streptomycin* resistant strains (SaiRam *et al.*, 2000; Prashant *et al.*, 2007; Mehrotra *et al.*, 2010; Sarmiento *et al.*, 2011; Maragathavalli *et al.*, 2012; Vinoth *et al.*, 2012; Chava *et al.*, 2012; Rosaline *et al.*, 2013). Few researchers have showed that *P. vulgaris* is not inhibited by Neem oil (Parekh and Chanda, 2007). Neem oil also have definite antiplaque activity (Elavarasu *et al.*, 2012). Chewing of Neem twigs are found effective in controlling dental tartar, dental caries etc (Prashant *et al.*, 2007). Neem leaf extract can inhibit the formation of biofilm in *Pseudomonas aeruginosa* (Harjai *et al.*, 2013)

- A variety of fungus has also been found sensitive to the action of neem oil. Common examples include *C. albicans*, *A. fumigates*, *A. flavus*, *A. niger*, *M. gypseum*, *M. canis*, *T. mentagrophytes*, *T. rubrum*, *Cladosporium* sp., *F. oxysporum*, *P. notatum* and *P. citrinum* (SaiRam *et al.*, 2000; Natarajan, 2002; Asif, 2012; Al-Samarrai *et al.*, 2012). Neem oil extract at concentration of 0.1% decreased the production of zearalenone, a toxin produced from *Fusarium graminearum* causing reproduction disorders in animals (Geraldo *et al.*, 2011)
- Neem leaf extract reduces the bacterial infection caused by *Streptococcus* spp., *Aeromonas hydrophila*, *Enterobacter* spp., *E. coli*, *Pseudomonas* spp., *Proteus* sp., *Vibrio* spp. and *Yersinia enterocolitica* in marine ornamental fishes (Dhayanithi *et al.*, 2010)
- As far as the potential of neem as a human as well as animal health product source is concerned vast scientific evidences are available. Oils from seed of the plant along with leaves and bark derived essential oils cause inhibition of the pathogenic intracellular bacterial growth (for instances: *Mycobacterium*) (Biswas *et al.*, 2002)
- Extracts of neem as well as limonoids are effective against a variety of protozoal pathogens viz., *Trypanosoma* and *Leishmania*, *Plasmodium*. Alcoholic extract of flowers of neem has got antifilarial activity against *Setaria cervi* which usually infects water buffalo (Tahir *et al.*, 1998; Yanes *et al.*, 2004; Mishra *et al.*, 2005; Udeinya *et al.*, 2008)
- **Psoriasis:** In conditions of psoriasis neem seed oil and leaf extracts acts as wonder cure because it not only mitigate the itching and pain produced but also reduce the scaling and redness of patchy lesions (Tiwari *et al.*, 2013d)
- Neem leaves showed anti-dermatophytic activity also (Pankajalakshmi and Taralakshmi, 1994)

**As herbal contraceptive:** Mechanism of action of neem as contraceptive is believed to be mediated through spermicidal activity and non-hormonal hence it does not have side-effects:

- **Birth control by intra-vaginal application (women):** *In vivo* studies have demonstrated that neem oil is 100% effective in preventing pregnancy when used as a vaginal lubricant prior to coitus (Jacobson, 1995). In an experimental study on rabbit, application of neem with some other herbal preparation prior to coitus prevents the pregnancy (Raghuvanshi *et al.*, 2011). In an experiment conducted on rats, alcoholic extract of neem flower led to disruption of estrous cycle leading to partial block in ovulation (Gbotolorun *et al.*, 2008)
  - In mouse model, neem oil inhibits the development and attachment of embryos and thus warrants its use as a postcoital contraceptive (Juneja *et al.*, 1994)
- **Antimicrobial:** A new vaginal contraceptive NIM-76 obtained from neem oil has shown antimicrobial activity (SaiRam *et al.*, 2000)
  - Seed oil extract controls follicular development in female mice (Dhaliwal *et al.*, 1998, 1999)
  - Within 20-30 sec of coming in contact with the oil of neem seed immobilization of sperm cells take place. Neem leaf however is not a herb specific for male neither does it possess spermicidal and antifertility effects as does oil from neem seed. Neem seed oil possesses the above two activities (i.e., spermicidal and antifertility effects while in the female vagina (<http://www.dhealthstore.com>))
  - If leaf extract of neem is administered in mice experimentally, results showed anti-fertility effects by toxic effect on sperm-egg interaction (Juneja and Williams, 1993)
- **Birth control (men):** In India and the USA, studies in monkeys have proved neem extract as first male birth control pill as it has potential to reduce fertility in male monkeys without inhibiting libido or sperm production

**Anti-cancer effects:** Active principles in form of various chemical compounds present in bark, leaves, seeds and seed oil reduces tumors and cancers very efficiently without producing side effects. Biologically active

compounds (polysaccharides, limonoids, terpenoids and steroids) have been widely used for curing of various cancers conditions. Antitumorogenic properties inclusive of immunomodulatory and apoptotic activities have been explored for the prevention, protection and suppression of various types of tumours and cancers by moderating their molecular mechanisms and mode of action. In fore-stomach and skin papillomagenesis, the function of active principles has been ascertained to noteworthy carcinogen detoxification in hepatic tissues of Swiss albino mice (Dasgupta *et al.*, 2004; Mahapatra *et al.*, 2011; Paul *et al.*, 2011). Neem extracts have been shown to possess potent anticancerous properties against oral squamous cell carcinoma (Udeinya *et al.*, 2004; Ghosh *et al.*, 2006; Haque *et al.*, 2006; Dhama *et al.*, 2013a) and induces apoptosis in 4T1 Breast Cancer BALB/c Mice (Othman *et al.*, 2011). Nimbolide, a limonoid present in leaves and flowers of the neem tree, have apoptosis-inducing property (Srivastava *et al.*, 2012; Kavitha *et al.*, 2012), thus beneficial in human breast cancer (Elumalai *et al.*, 2012). In fish model, neem extract have shown potent antimutagenic effect suggesting the study on this aspect for well beings of mankind (Farah *et al.*, 2006). In an experimental study on mice, aqueous preparation from neem leaves generated immune response that also reacted with Carcinoembryonic Antigen (CEA), so it can be used in immunotherapy of CEA positive tumors (Sarkar *et al.*, 2007). Neem Leaf Glycoprotein Matured DCs (NLGP-DCs) is found as effective candidate vaccine for antigen specific cancer immunotherapy (Chakraborty *et al.*, 2008; Goswami *et al.*, 2010). The effect of aqueous extract of *A. indica* on hepatocarcinogenesis caused in rats by Diethyl Nitrosamine (DEN) as well as 2-Acetylaminofluorene (AAF) has been studied. The extract of the plant in 5% weight/volume (w/v) has been prepared for the study. For amplification of the AAF mitochondrial ribonucleic acid (mRNA) reverse transcription polymerase chain reaction (RT-PCR) has been used along with application of Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay to detect fragmentation of de-oxy ribonucleic acid (DNA) *in situ*. By such study it is seen that *A. indica* has got a chemopreventive capability by regression of the DEN/ AAF induced carcinogenesis in liver (Taha *et al.*, 2009).

Sulfonoquinovosyl diacylglyceride identification along with cytotoxic activity as well as property of DNA binding has been shown by Chatterjee *et al.* (2010). The molecular basis of cell radiosensitization with phytochemicals from hypoxic breast cancer has been shown by Aravindan *et al.* (2013). The property of

induction of p53-independent apoptosis as well as autophagy by the limonoids of neem oil has been shown by Srivastava *et al.* (2012).

**As insecticides and pest controlling agent:** Neem has been used historically to rid the body of several forms of ectoparasites and pests and the action is rapid. Hormone mimicking activities of neem extracts causes interference with the parasitic life cycle inhibiting their ability to feed as well as prevent the hatching of eggs (Kumar and Navaratnam, 2013). Neem plant contents have been reported to be an effective bioinsecticide (Chary, 2011) and found useful in the control of many insect species of medical and veterinary and importance, nearly 400 insect species including of flies, *Amblyomma variegatum*, spruce budworm *Choristoneura fumiferana*, lice, head louse, shaft louse (*Menopon gallinae*), feather louse (*Lipeurus caponis*, or *Columbicola* sp.), spiders, mosquitoes, triatomines, cockroaches, fleas, beetles (*Alphitobius diaperinus*, *Dermestes bicolor* and *Dermestes lardarius*) and nematodes (Schmutterer, 1990; Lyons *et al.*, 1996, 1998; Wanner *et al.*, 1997; Mulla and Su, 1999; Makeri *et al.*, 2007; Karunamoorthi *et al.*, 2009; Lucantoni *et al.*, 2010; Kudom *et al.*, 2011; Mehlhorn *et al.*, 2011; Abdel-Ghaffar *et al.*, 2012; Al-Quraishy *et al.*, 2012a, b; Walldorf *et al.*, 2012). Neem extract and neem powder have been used by the urban people of African countries as mosquito repellent (Karunamoorthi *et al.*, 2009) and for the control mosquito (*Culex quinquefasciatus*) breeding in anthropogenic habitats (Kudom *et al.*, 2011). Nanoemulsion of neem oil and Tween 20 were found as potent and selective larvicide for *Culex quinquefasciatus* (Anjali *et al.*, 2012). Neem leaf slurries can also be a sustainable method to reduce the larval density of malaria vector *Anopheles gambiae* (Luong *et al.*, 2012). Applications of neem cake at 500 kg ha<sup>-1</sup> to rice-fields were found helpful in control of culicine mosquito vectors of Japanese Encephalitis Virus (JEV) and along with increase in grain yield (Rao *et al.*, 1992; Maciel *et al.*, 2010). Neem extracts have got positive effect on regulation of growth as well as repellent activity against which many arthropod ectoparasites are susceptible to. For instance for successful control of both lice as well as ticks along with several mosquito species including significant parasitic diseases vectors neem extract has been found valuable (Mulla and Su, 1999; Garbouy *et al.*, 2006; Lucantoni *et al.*, 2006; Habluetzel *et al.*, 2007).

In several population of Asia and Africa neem and its use in order to combat mosquitoes has become an integral part of the 'backpack' (a traditional knowledge). On

application to exposed parts of the skin the efficacy of neem extract as a repellent can be judged well. Neem oil moreover can expel the mosquitoes that are blood sucking in nature when used in kerosene lamps. The traditional custom involving burning of *Azadirachta* leaves helps in reduction of human biting as well as resting at indoor of mosquitoes. Validation studies of similar nature must get encouragement for provision of a rational basis for disease control in an integrated fashion by exploiting both science of modern era as well as knowledge of traditional medicine (Dua *et al.*, 1995; Ansari and Razdan, 1996; Kweka *et al.*, 2008).

The efficiency of sole treatment of head lice with an extract of neem seed has been studied by Abdel-Ghaffar *et al.* (2012). Luong *et al.* (2012) in their study has described about a sustainable slurry from neem leaf which is a natural product as well as act as a larvicide from anopheline mosquitoes.

In an experimental study on sheep of Morada Nova breed, the result of supplementation of dried neem leaves on antinematodal activities varied with the season and composition (protein content) of diet offered. Results were significantly positive in rainy season in contrast to dry season (Quarles, 1994; Chagas *et al.*, 2008). In an experiment on rabbit, the aqueous leaf extract of neem have acaricidal efficiency similar to ivermectin (Seddiq *et al.*, 2013).

US Environmental Protection Agency has approved use of neem extracts over food crops as pest control agents by considering them non-toxic to human, animals, birds, useful insects:

- **Insect repellent:** Studies have shown that one neem compound is a more effective insect repellent than the widely used synthetic chemical known as DEET (N,N,-diethyl-m-toluamide), a suspected carcinogen with long periods of use
  - Neem oil affects the efficacy of commercially available neem insecticides (Stark and Walter, 1995)
  - Neem seed extracts are effective against both asexual and sexual stages of chloroquin-resistant as well as sensitive strains of malarial parasites *P. falciparum*. Seed extract have inhibited growth and development of the human malarial parasitic agent. Neem extract was found to have some neuronal protective effect in malaria positive cases (Farahna *et al.*, 2010) thus mitigate the inflammation of central nervous system (Bedri *et al.*, 2013)

- Azadirachtin obtained from seed kernel extract of neem showed pesticidal activity against larvae of *Plutella xylostella* (Verkerk and Wright, 1993)
- Neem oil was found suitable for control of *Spodoptera frugiperda*, a pest on corn (Tavares *et al.*, 2010)
- Azadirachtin present in neem can be used as a potential agent for controlling *Argulus*, a common ectoparasites of ornamental fish (Kumar *et al.*, 2012)

**Snake anti-venom property:** *Azadirachta indica* PLA(2) inhibitor (AIPLAI) is a snake venom inhibitor which has been isolated from the leaves of *A. indica* (neem) (Mukherjee *et al.*, 2008). In *in vitro* studies it has inhibited phospholipase A2 (PLA2) of snake venom successfully (Mukherjee *et al.*, 2008).

**Healthy cloth production in textiles and clothing industry:** In textiles and clothing industry also Neem is becoming popular due to its anti-microbial potential. Now a days, consumers are very aware and particular for their health and hygiene not only while feeding, living but also in regards to what they wear. By seeing this trend, manufacturer are using herbal finishes such as using curcumin, neem, alovera instead of synthetic or chemical ones for maintaining quality and protection of fabrics (Purwar and Joshi, 2004; Nataporn *et al.*, 2006; Jothi, 2009). Researches done earlier revealed that neem chitosan nanocomposites treated cloths/fabrics demonstrated an increased antimicrobial activity as compared to other fabric treatments such as neem chitosan composite, neem alone and chitosan. Chitosan is a natural polysaccharide which is a chitin derivative and has antimicrobial, biodegradable properties. These properties are combined with nanoencapsulation, a new technique responsible for slow controlled sustained release of the active ingredient that is antimicrobial agent even after 30 washes. Neem chitosan nanocomposite treated fabrics showed bacterial reduction when studied against *E. coli* and *Staphylococcus aureus* strains (Sarkar *et al.*, 2003; Rajendran *et al.*, 2012). Studies have demonstrated the antibacterial effect of silver nanoparticles by aqueous extract of Neem leaves in cotton cloth leading them to sterilization (Tripathi *et al.*, 2009).

**Commercial preparations:** Some of neem products available in the market are:

- Neem as insect repellent-nimit
- Neem as a constituent of strain remover and of floor cleaner-nimyle
- Neem in agriculture-nimgreen
- Neem-as medicine
- Neem-skin conditioner
- Neem-vim (liquid) as dish washer
- Neem-liquid soap
- Neem-face wash, facial scrub (Himalaya)
- Neem as herbal contraceptive-NIM-76

### CONCLUSION AND FUTURE PERSPECTIVES

In present scenario, interest is renewed in herbal medicines due to its less side effects and being safer. Interest and demand is increasing to obtain more drugs from plant sources to alleviate the ailments of humankind. The use of different parts of several medicinal plants to cure specific ailments has been in vogue form. The green medicine has been popular since ancient times being safe and multiple benefits. Neem is rich source of different compounds having medicinal properties, so drug development programme should be started utilizing the biological and medicinal properties of neem. The hepatoprotective effect of *Azadirachta indica* is encouraging for the researchers to undertake further preclinical studies in details. However, there should be scientific trials for validation of different medicinal properties of neem so that this plant can better be utilized. In modern era, emphasis should be on control of diseases of human, animals and environment using non-toxic herbal products. By making quantum of research on biological and medicinal properties of neem, some of the herbal products have been prepared but still there is lot of scope in this field for better utilization of this wonder plant.

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