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

1Ruchi Tiwari, 2Amit Kumar Verma, 3Sandip Chakraborty, 4Kuldeep Dhama and 4Shoor Vir Singh
1Department of Veterinary Microbiology and Immunology,
2Department of Veterinary Epidemiology and Preventive Medicine,
Uttar Pradesh Pandit Deen Dayal Upadhyay Pashu Chikitsa Vigyan Vishwavidyalay Evum Go-Anusandhan Sansthan (DUVASU), Mathura, 281001, India
3Department of Animal Resources Development, Pt. Nehru Complex, Agartala, Pin, 799006, India
4Division of Pathology, Indian Veterinary Research Institute, Izatnagar, Bareilly, UP, 243122, India
5Laboratory of Microbiology, Animal Health Division, Central Institute for Research on Goats (CIRG), Makhdoom, PO-Farah, Dist. Mathura, Pin, 281122, India

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 non-isoprenoids contains proteins and/or amino acids, polysaccharides, flavonoids etc. It is found beneficial in leprosy, gastro-intestinal problems, malaria, intestinal helmintiasis, 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: Azadirica 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”, dirakh 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

Corresponding Author: Amit Kumar Verma, Department of Veterinary Epidemiology and Preventive Medicine, Uttar Pradesh Pandit Deen Dayal Upadhyay Pashu Chikitsa Vigyan Vishwavidyalay Evum Go-Anusandhan Sansthan (DUVASU), Mathura, 281001, India
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 homeopathic 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; Shamma 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 Mahogany 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-isopenoids and non-isopenoids. Compounds such as diterpenoids, triterpenoids and steroids including azadirone, protomelicians, limonoids, gedunin, vilasin type of compounds, C-secomelicians such as azadirachitin, nimbin, salanin and its derivatives comprise isopenoids group while non-isopenoids 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 from, important ones are tricyclic diterpenoids, NB-II peptidoglycan, gallic acid, epigallocatechin, galliclactechin, catechin, epicatechin, margolone, margonolone and isomargolone 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; Mongkolkhajornsil et al., 2004; Bhu et al., 2009; Mukherjee and Sengupta, 2013).

APPLICATIONS OF DIVINE TREE NEEM

From several parts of Azadirachta indica more than 150 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; antulocer; antimalarial; antifungal; antibacterial; antiviral; antioxidant; antimutagenic as well as anticarcinogenic characteristics (Beeth et al., 2006; Akihiwa 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 helmintiases, 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; Dhaman et al., 2013). 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, arabinofucogalactan, dihydrochalcones, fucogalactoglucoarabinanes and others with proven immunomodulatory, antiseptic, diuretic, emmenagogue, febrifuge, antipyretic, antidiabetic, antihelmintic, anti-inflammatory, analgesics, antifeedant, antiviral, antifungal, contraceptive, in vitro spermicidal, insecticide, pediculocide, parasiticide, antimutagenic and anti-tumor 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 Serreone 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 glycosidases thus helpful in control of diabetes (Mukherjee and Sengupta, 2013).

Role in general diseases 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 (Arvahie, 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 (Bilappanavar 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 (Maisy 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, IFNγ and TNF-α 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-γ and lymphocyte proliferation (Upadhay 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) (Upadhay 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-androst-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 iroden 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 hours 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 (Udenya et al., 2004; Ghosh et al., 2006; Haque et al., 2006; Tiwari et al., 2010).

• Neem bark and oil exerts anti-leptotic 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*, *Varicella virus*, *Chikungunya*, dengue virus, picornavirus, 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; Faccini-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 Streptomyces 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 (Elavarsu 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. fumigatus, A. flavus, A. niger, M. gyipseum, M. canis, T. mentagrophytes, T. rubrum, Cladosporium sp., F. oxysporum, P. notatum and P. citrinum (SaiRam et al., 2000; Natarajan, 2002; Asif, 2012; Al-Samarni 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 (Dhayamthi 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 instance: 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, alcholic extract of neem flower led to disruption of estrous cycle leading to partial block in ovulation (Gbotororun 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 papillogenesis, 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 (Othuman et al., 2011). Nimboide, a limonoid present in leaves and flowers of the neem tree, has a 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 has shown potent antimitogenic effect suggesting the study on this aspect for well being 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 studies. 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 careinogenesis in liver (Taha et al., 2009).

Sulfonequinovosyl 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 parasite 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 importance, nearly 400 insect species including of flies, Amblyommata 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, Derastes biocular and Derastes lardarius) and nematodes (Schmutterer, 1990; Lyons et al., 1996, 1998; Wanner et al., 1997; Mulla and Su, 1999; Makeri et al., 2007; Karanamoorthi et al., 2009; Lucantoni et al., 2010; Kudom et al., 2011; Mehlhorn et al., 2011; Abdel-Ghaffar et al., 2012; Al-Quraishi 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 (Karanamoorthi 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 larvicidal 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−1 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; Garboua et al., 2006; Lucantoni et al., 2006; Hahlbroeck 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 (Quares, 1954, Chagas et al., 2008). In an experiment on rabbit, the aqueous leaf extract of neem have saccharoidal efficiency similar to ivermectin (Seddiek 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 chloroquine-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 (Farahina 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 PLA2 inhibitor (AIPLA2) 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, aloevera 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* starains (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:
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.

REFERENCES


