

## Acta Traditional Medicine

Volume 01, Issue 01, 2022 (Page No. 31-40)

Journal's URL:

<http://traditionalmedicine.actabotanica.org/>



RESEARCH ARTICLE

OPEN ACCESS

### Neem (*Azadirachta Indica*): A Wonderful Gift of Nature

Radha Singh and Kusum Singh

Department of Zoology, Bundelkhand University, Jhansi U.P

Corresponding Author: Kusum Singh, Department of Zoology, Bundelkhand University, Jhansi U.P India.

E-mail: kusumsingh156@gmail.com

#### ABSTRACT

*Azadirachta indica* (Neem) tree belongs to the family Meliaceae, is an evergreen tree, native of India and widely distributed other tropical and subtropical parts of the world. It is the most beneficial and versatile traditional medicinal plant in Ayurveda, Unani and Siddha. Different parts of this plant, including, leaves, flowers, fruits, seeds, roots, bark and oil have many curative properties due to their rich source of antioxidant that have been documented in the ancient literature. Neem bark is used as an active component in a number of toothpastes and toothpowders. Neem twigs are used as oral spray, toothache reliever and for rubbing of teeth. In the modern era, it is now considered as a valuable source of unique natural products for development of medicines against various human diseases and produces a large number of phytochemicals with wide spectrum of numerous biological and pharmacological activities and also for the advancement of industrial products. Its most important bioactive constituent are Azadirachtin, Nimbidin, Nimbinin. This review gives a view mainly on the biological activities of the Neem and some of their compounds isolated, pharmacological actions of the neem extracts, clinical studies and plausible medicinal applications of neem along with their safety evaluation.

Keywords – *Azadirachta indica*, phytochemicals, biological and pharmacological activities.

#### INTRODUCTION

*Azadirachta indica* (Neem) which belongs to the family Meliaceae, originated from South Asia, but grows widely in India, Pakistan and other tropical and sub-tropical parts of the world. The number of benefits of Neem is recorded in ancient documents like 'Charak Samhita and Susruta Samhita. The people of India have well-regarded the neem tree; for centuries, millions have rubbed their teeth with neem twigs, smeared skin disorders with neem leaf juice and taken Neem tea as a tonic.<sup>1</sup> Earlier studies on Neembore that it contains numbers of biologically active compounds in almost each part of the plant (Fruit, seeds, oil, leaves, roots, bark, trunk and branches) with various medicinal properties. It is now considered as a valuable source of unique natural products for development of medicines against various diseases and also for the development of industrial products. The biologically most active compound is azadirachtin, which is essentially a mixture of seven isomeric compounds (azadirachtin A-G) and azadirachtin E which is more effective. It is a tetranortriterpenoid abundant in the seeds and present in a smaller concentration in the leaves. Neem is rich in phytoconstituents such as glycoside, alkaloids, triterpenoids, tannin, flavonoids, phenolic compounds, carotenoids, steroids and ketones etc. Other active substances are salanin, melianol, melianone, gedunin, nimbolin, nimbin, deacetylalanin, azadiractol, azadirone, vilosinin, meliacarpine, over 300 isolated and characterized components.<sup>2</sup> Its Bark is used as analgesic, substitute and curative of fever. Flower is used for removal of intestinal worms and phlegm. Fruit Relieves piles, intestinal worms, urinary disorder, epistaxis,

eye problem, diabetes, wounds and leprosy. Gum is effective against skin diseases like ringworms, scabies, wounds and ulcers.<sup>3</sup>

#### DISTRIBUTION

A native to east India and Burma, it grows in much of south East Asia and West Africa, and more recently Caribbean and south and Central America. In India it arises naturally in Siwalik Hills, dry forests of Andhra Pradesh, Tamil Nadu and Karnataka to a height of approximately 700 m. It is cultivated and usually naturalized throughout the tropical and subtropical Pakistan, Sri Lanka, Thailand and Indonesia. It is also grown in Malaysia, Singapore, Philippines, Australia, and Saudi Arabia.<sup>4</sup>

#### DESCRIPTION

It is a tall evergreen tree (40-50 feet or higher), with a straight trunk and has rough dark brown bark with wide longitudinal cracks detached by flat ridges, dark grey outside and reddish inside. Leaves are alternate, compound, light green, crowded near the end of branches, 20-40 cm long, imparipinnate, each comprising 5-15 leaflets. Leaflets are 1.2-4 cm long, ovate to lanceolate, glossy, serrate, apex acuminate, base unequal. Flowers are small and white in color. It produces yellow drupes that are ellipsoid and glabrous, 12-20 mm long, greenish, greenish yellow to yellow or purple when ripe, aromatic with garlic like odour. Seeds are ovoid or spherical with pointed apex. <sup>4,5</sup>

#### VERNACULAR NAMES <sup>4,5</sup>

Language/Country Vernacular names

Bengali Nim, Nimgachh

English Indian Lilac, Margosa tree, Neem tree, Indian cedar

Gujarati Dhanujhada, Limbado, Limba, Limdo

Hindi Nim, Nimb

Kannada Bemu, Bevinamara, Bivu, Kaybevu

Marathi Nimbay, Kadulimba

Malayalam Vembu, Ayureppu, Nimbam

Punjabi Bakam, Drekh, Nim

Sanskrit Pakvakrita, Nimba, Nimbah, Picumarda, Arista

Telgu Vepa

Tamil Veppa, Veppu, Veppam, Vembu

Arabic Nim, Neem

Burmese Thinboro, Tamarkha, Tamar, Tamaka, Tamabin

French Margousier, Margosier, Neem, Nim, Azadirac de l'Inde

Indonesian Mind, Intaran, Membha, Imba, Mempheuh, Mimba

Spanish Lila, Lilayo

Thai Sadao, Kadao, Sadao India, Khwinin, Saliam, Cha-tang

#### CLASSIFICATION 6

Kingdom - Plantae

Division - Angiospermae

Class - Dicotyledoneae

Order - Rutales

Family - Meliaceae

Genus - Azadirachta

Species - *A. indica*

#### PHYTOCHEMICAL COMPOUNDS 4, 7-9

Plant part      Compounds

Bark    Polysaccharides G1A, G1A, Polysaccharides G2A, G3A, NB-2 peptidoglycan, Margolone, Margolonone, Isomargolonone, Gallic acid, Epicatechin and Catechin.

Fruit coat      Meli tetraolone, Sesquiterpene, 2,6-Bis-(1,1)-dimethylethyl-4-methyl phenol, Azadirone, Benzopyranoids

Seed oil    Nimbidin, Salannin, Azadirachtin, Cardenolide, Mahmoodin, Nimbolides, Nimbin, Gedunin, Meliacin, Valassin.

Seed    Meliacin, Meliacinol, Azadirachtin, Propyl disulphide, Tignic acid (5-methyl-2-butanic acid), Nimbin, Deacetylnimbin, Salannin, Deacetylsalannin and Azadiradione

Neem kernels    Triterpene or limnoids, Azadirachtin, Salannin, Meliantriol, and Nimbin. Limonoids.

Leaves    Nimbin, Nimbanene, Nimbiol, Nimocinol, Nimbandiol, Nimbolide, Quercetin,  $\beta$ -sitosterol, Polyphenolic flavonoids, Amino acid, Ascorbic acid, 6-desacetylnimbinene, n-hexacosanol, 7-desacetyl-7-benzoylazadiradione, 7-desacetyl-7-benzoylgedunin, 17-hydroxyazadiradione, Cyclic trisulphide and Cyclic tetrasulphide.

#### PHARMACOLOGICAL ACTIVITIES

##### Antihyperglycemic agent

Polyherbal formulation (*Tinospora cardifolia*, *Cinnamomum zeylanicum*, *Curcuma longa*, *Trigonella foenum-graecum*, *Azadirachta indica*, and *Piper nigrum*) showed significant decrease in serum glucose. Therapeutic dose of polyherbal formulation (28.71 mg/kg) showed presence of few islets of beta cells or slight regeneration of  $\beta$  cells in pancreas but the pancreas of 2X therapeutic dose of polyherbal formulation (57.42 mg/kg) showed acinar cells that appeared to be normal. The regeneration of  $\beta$ -cells was comparatively more in 2X therapeutic dose treated pancreas.<sup>10</sup> Hypoglycaemic action of Neem leaves has observed in diabetic rats. After treatment for 24 hrs, Neem 250mg/kg (single dose study) decreased glucose level (18%), cholesterol (15%), triglycerides (32%), urea (13%), creatinine (23%), and lipids (15%).<sup>11</sup> A dose of 250

mg/kg of aqueous extract of fresh leaves of Neem was administrated orally onto streptozotocin induced and its related retinopathy in rats for 16 weeks and caused in significant fall in blood glucose level and serum lipids and there were slight increase in HDL level. The slight increase specifies the extract as positive effect in lipid metabolism of diabetic rats. Neem leaves totally inverted the unusual changes in the retina of the rats.<sup>12</sup> Moisture-resistant film-coated tablets containing the neem (*A. indica* A. Juss) leaf extract were developed and evaluated in-vitro/in-vivo for diabetes treatment. The optimal formula consists of 20% calcium silicate as adsorbent, 20% Di-tab as diluent, 1% PVP K30 as binder, 2% croscarmellose as disintegrant, and 5% PVA as film-coating agent.<sup>13</sup>

#### Antioxidant activity

The antioxidant capacity of the leaf, stem and root barks of Neem, the ferric reducing antioxidant power (FRAP) and total phenolic concentration of the leaf, stem and root barks of Neem were evaluated in vitro. Only the leaf of Neem belonged to good FRAP. Both the stem and root bark of Neem studied belonged to high FRAP. Each part of plant examined as protective factors because of their good and high antioxidant capacities.<sup>14</sup> Extracts from young flowers and leaves have strong antioxidant potential. An indicator of oxidative stress, malondialdehyde (MDA), was reduced by 46.0% and 50.6% for flower- and leaf-based extracts, respectively, prompting the suggestion to use neem as a vegetable bitter tonic to promote good health.<sup>4</sup> Azadirachtin and nimbolide showed concentration-dependent antiradical scavenging activity and reductive potential. Azadirachtin and nimbolide inhibited the development of 7,12-dimethylbenz (a) anthracene (DMBA) induced hamster buccal pouch (HBP) carcinomas through inhibition of procarcinogen activation and oxidative DNA damage and up regulation of antioxidant and carcinogen detoxification enzymes. Current finding proposed that the chloroform crude extracts of neem leaves could be used as a natural antioxidant.<sup>9</sup>

#### Anti-Inflammatory

Carbon tetrachloride extract (CCl<sub>4</sub>) of Neem fruit skin (100mg/kg) and isolated component azadiradione showed significant antinociceptive and anti-inflammatory activities.<sup>15</sup> Neem seed oil showed anti-inflammatory effect in albino rats and exposed increased inhibition of paw edema with the progressive increase in dose from 0.25ml to 2 ml/kg body weight. At the dose of 2 ml/kg body weight, Neem seed oil showed maximum (53.14%) inhibition of edema at 4th hour of carrageenan injection.<sup>16</sup> Neem leaves extract at a dose of 200mg/kg, p.o., showed significant anti-inflammatory activity in cotton pellet granuloma test. Nimbidin suppresses the functions of macrophages and neutrophils relevant to inflammation. Neem leaf extract showed significant anti-inflammatory effect but it is less effective than that of dexamethasone.<sup>9</sup>

#### Hepatoprotective activity

The aqueous Neem leaf extract has been found to provide protection against paracetamol-induced liver damage in rats.<sup>17</sup> Aqueous Neem leaves extract effect hepatotoxicity that caused by antitubercular drugs in rats and significantly prohibited changes in the serum levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin and protein.<sup>18</sup> Young stem bark extract of Neem was used to analyse the hepatoprotective activity by inducing carbon tetrachloride as acute hepatotoxic agent. After administration of Neem, it stabilizes the levels of Serum glutamate oxaloacetate transaminase (SGOT), Serum Glutamate Pyruvate Transaminase (SGPT), Alkaline Phosphatase (ALP), Serum bilirubin and elevates total protein amount.<sup>12</sup> The protective effect of active constituent of Neem such as nimbolide against carbon tetrachloride (CCl<sub>4</sub>) induced liver toxicity in rats. Hepatoprotective role of azadirachtin-A in CCl<sub>4</sub> induced hepatotoxicity in rats show that pre-treatment with azadirachtin-A at the higher dose levels reasonably repairs the rat liver to normal.<sup>9</sup>

#### Antibacterial Activity

NIM-76, a new vaginal contraceptive from neem oil showed inhibitory effect on the growth of numerous pathogens, as well as bacteria, fungi and virus. Recently, the antibacterial action of neem seed oil was evaluated in vitro against 14 strains of pathogenic bacteria.<sup>17</sup> The exposure of the microorganisms to the extracts of Neem leaves was compared with certain specific antibiotics. The methanol extract of Neem

demonstrated distinct activity against *Bacillus subtilis* (28 mm).<sup>4</sup> Neem oil also has definite antiplaque activity. Neem leaf extract can prevent the formation of biofilm in *Pseudomonas aeruginosa*.<sup>19</sup> The methanol extract of Neem leaves shows antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Proteus vulgaris*, *Salmonella typhi*, and showed low activity on *Pseudomonas aeruginosa* but it is ineffective against *Escherichia coli*. The petroleum ether and methanol extract of Neem leaves were highly effective against *Candida albicans*. Neem seeds pose an antibacterial activity against the bacteria that causes eye infection (Ophthalmic infection) such as *Staphylococcus aureus*, *Staphylococcus pyogenes*, *Escherichia coli* and *Pseudomonas aeruginosa*.<sup>12</sup>

#### Antiviral activity

Aqueous leaf extract of Neem contains antiviral activity against *Vaccinia virus*, *Chikungunya* and measles virus *in vitro*. The antiviral and virucidal properties of the methanolic extract of Neem leaves (NCL-11) have been established against group-B Coxsackie viruses. NCL-11 prevents plaque formation in different antigenic types of Coxsackie virus B at a concentration of 1 mg/ml at 96 h *in vitro*. Further studies specified that NCL-11 is most effective in Coxsackie virus B-4 as a virusidal agent, in addition to its interference at the initial phases of its replication.<sup>17</sup> Aqueous extract of Neem bark was found to be effective against Herpes simplex virus type 1 by blocking its entry into natural target cell, even though Neem does not cure but it shows the capacity to inhibit smallpox, chickenpox and fowl pox.<sup>12</sup>

#### Antifungal effects

Antifungal activity of Neem has been shown against *Lagenidium giganteum* and *Metarhizium anisopliae* in PYG and Emerson's YpSs agar media. The minimum inhibitory concentration of Neem oil for *Lagenidium giganteum* showed higher than that for *Metarhizium anisopliae*. The minimum fungicidal concentration of Neem oil in PYG medium was lower than in YpSs for both fungi.<sup>20</sup> Antifungal activity of Neem leaves against *Alternaria solani* Sorauer and results established that ethyl acetate fraction was found most effective in hindering fungal growth with Minimum inhibitory concentration (MIC) of 0.19 mg and this fraction was also effective than fungicide (metalaxyl+mancozeb) as the fungicide has MIC of 0.78mg.<sup>21</sup> The ethanolic extract of Neem leaves is more effective against *Rhizopus* and *Aspergillus* compared to aqueous leaf extract. Aqueous and ethanolic extract of Neem leaves were found effective against *Candida albicans* by which these organism shows sensitivity at the concentration of 15% and 7.5% on aqueous extract and the MIC was 7.5%.<sup>12</sup>

#### Larvicidal activity

Laboratory reared larvae were exposed to 1ppm concentration of Neem caused 70-99% mortality to larvae. The Neem extract was found to be significantly effective in controlling *Culex* larvae.<sup>4</sup> The neem oil extracted from the seeds Neem shows high mortality rate at the concentration of 32 ppm against *Anopheles gambiae* larvae and inhibits adult development by 99.3%. Third and fourth instar larvae of *Aedes aegypti* and *Culex quinquefasciatus* were exposed to various concentration of methanol and ethanol Neem leaves extract and methanol extract shows 90% of mortality against *Aedes aegypti*. Besides that, the ethanol extract against *Aedes aegypti* shows 85% of mortality rate. Methanol and ethanol Neem leaves extract shows same effect against *Culex quinquefasciatus* which show 90% of mortality.<sup>12</sup> Phytochemical compounds (coumarins, phenols, terpenes and especially triterpenes), that present in ethanolic extract of the *Azadirachta indica* leaves showed a larvicidal activity against *Aedes aegypti* larvae and potentiated the activity of conventional antibiotics against resistant bacteria.<sup>22</sup>

#### Antimalarial activity

Neem seed extract and its purified parts have been shown to prevent growth and development of asexual and sexual phases of drug sensitive and resistant strains of the human malarial parasite *Plasmodium falciparum*.<sup>17</sup> Neem extracts are effective against a variety of protozoal pathogen like *Plasmodium falciparum*. The antimalarial actions of the tablet suspension of the bark and leaf of Neem were assessed on *Plasmodium yoelli nigeriensis* infected mice. Tablet suspensions from the leaf and bark of Neem at a dose of 800 mg/kg and chloroquine at a dose of 62.5 mg/kg body weight produced average percentage parasitaemia of for leaf, bark and chloroquine is 79.6%, 68.2% and 99.5% respectively, in chemo- suppression. It showed

high prophylactic, moderate suppressive and a very minimal curative schizonticidal effect. Also in the prophylactic treatment, the tablet suspensions at 800 mg/kg and pyrimethamine at a dose of 0.35 mg/kg gave an average parasitaemia reduction of 75.3%, 65.6% and 98.3% for the leaf, bark and pyrimethamine, respectively.<sup>19</sup>

#### Anti-dental activity

Neem inhibited *Streptococcus mutans* (bacterium causing tooth decay) and inverted early carious wounds.<sup>4</sup> Dried chewing sticks of neem prevent tooth decay and periodontal disease leading to good oral health. Neem leaf extract is a potential endodontic irrigant as it has an antimicrobial effect on *Enterococcus faecalis* and *Candida albicans*.<sup>19</sup> Efficacy of neem based on mouth wash about its antigingival effect and study confirmed that Neem mouth wash is equally effective in reducing periodontal indices as chlorhexidine. The antimicrobial properties of organic extracts of neem against three bacterial strains causing dental care and petroleum ether and chloroform extract showed strong antimicrobial activity against *Streptococcus mutans*. Chloroform extract showed strong activity against *Streptococcus salivarius* and third strain *Fusobacterium nucleatum* was extremely sensitive to both ethanol and water extract.<sup>9</sup>

#### Antifertility activity

Hexane extract of Neem seed, an active part having six components has been found to totally abrogate pregnancy in rodents when given orally up to a concentration of 10%, with no apparent side effect.<sup>17</sup> Aqueous extract of Neem leaf when administered to male mice at a dose of 200 mg/kg for 28 days, smashed the seminiferous tubules, causing in the slackening of germinal epithelium, degeneration of germ cells and derangement of germ cell types.<sup>23</sup> A vaginal contraceptive has also been developed from NIM-76. It is found that 3mg of neem leaf extract immobilize and kill 100% of spermatozoa within 20 seconds. Sperm cells also totally immobilized within 20 to 30 seconds of being in contact with neem oil. Neem oil seems to be a safe and very effective contraceptive, pre and post coital.<sup>24</sup> Contraceptive effect of neem oil and leaf extract has been demonstrated in male and female rats. The total numbers of normal follicles were significantly reduced in rats orally treated with 4.6ml/kg neem seed oil for 18 days.<sup>25</sup> Aqueous extract of old and tender leaves shows 100% of mortality of the sperms without changing its morphology (head, mid-piece and tail).<sup>12</sup>

#### Anti-HIV/AIDS

In 60 HIV/AIDS patients, a 12-week oral administration of acetone water Neem leaf extract (IRAB, 1gm daily) had a significant effect in vivo on CD4 cells (reduces HIV) without any adverse effects in the patients. In 60 patients who completed treatment, 50 were completely laboratory-test compliant. The mean levels of CD4 cells increased by 159% in 50 patients, significant increases were experienced in body weight (12%), as well as hemoglobin concentration (24%), and lymphocyte differential count (24%).<sup>26</sup> National Institutes of Health update Neem extracts destroyed the AIDS virus and copyrights have been granted for these extracts as an AIDS treatment.<sup>27</sup>

#### Anticancerous Activity

Different extracts of neem leaf have been shown to produce chemopreventive effects against polycyclic aromatic hydrocarbons-induced skin and fore-stomach tumorigenesis in animals.<sup>25</sup> Nimbolide found in leaves and flowers have cytotoxic effects on human choriocarcinoma (BeWo) cells and cure with nimbolide effected in dose- and time-dependent inhibition of growth of BeWo cells. The chemopreventive potential of the limonoids, azadirachtin, and nimbolide and results showed that azadirachtin and nimbolide prevented the increase of 7,12-dimethylbenz(a)anthracene (DMBA) induced hamster buccal pouch (HBP) carcinomas through influencing many mechanisms such as inhibition of procarcinogen activation and oxidative DNA damage, up regulation of antioxidant and carcinogen detoxification enzymes, and inhibition of tumour invasion and angiogenesis. Neem hold many constituents and these constituents activate the tumour suppressor genes and deactivate the action of various genes involved in the cancer growth and progression such as VEGF, NF- $\kappa$ B, and PI3K/Akt. Neem has been stated to be a good activator of tumour suppressor gene and inhibitor of vascular endothelial growth factor (VEGF) and phosphoinositol PI3K/Akt pathways.<sup>9</sup> Alkaloid-derived limonoid, azadiramide-A, is primarily found in Neem leaf ethanolic extracts, shown to stop

cell growth and induce apoptosis in both the estrogen independent MDAMB-231 and estrogen dependent MCF-7 cell lines of breast cancer in humans.<sup>28,29</sup>

#### Immunomodulatory activity

Growth stimulating and immunomodulatory properties of Neem leaves infusion on broiler chicks and effects exposed that neem infusion successfully enhanced antibody titre, growth performance, and gross return at the level of 50 ml/liter of fresh drinking water.<sup>30</sup> Neem leaf aqueous extracts or powder, when taken orally, have been shown to enhance both the cell-mediated and humoral immune responses via different mechanisms. It produced an increase in leukocytes, lymphocyte, erythrocyte counts and synthesis of antibodies. Ovalbumin immunized mice treated with neem leaf extract (100 mg/kg) had higher IgM, IgG and anti-ovalbumin antibody. There was also increase in macrophage migration inhibition.<sup>25</sup>

#### Anti-ulcer activity

The extract of neem dose-dependently prevents gastric lesions induced by restraint cold stress, ethanol and indomethacin. In stress ulcer, neem extract is more effective than ranitidine but less effective than omeprazole. Mechanism of antiulcer effect of Neem leaf extract is due to its action on H<sup>+</sup>-K<sup>+</sup>-ATPase. Prevention of acid discharge was confirmed by inhibition of H<sup>+</sup> K<sup>+</sup> ATPase activity, whereas blockage of oxidative damage of gastric mucosa was evident from blocking of lipid peroxidation and scavenging of endogenous hydroxyl radical (OH).<sup>31</sup> Neem bark extract reduced human gastric acid hyper secretion, and gastroesophageal and gastroduodenal ulcers. After 10 weeks, the duodenal ulcers were nearly fully healed.<sup>4</sup> Oral doses of neem leaf extracts have been found to protect against peptic ulcers, duodenal ulcers and to improve the healing process of gastric lesions.<sup>25</sup>

#### Wound Healing Effect

Neem has been found to be safe and effective pro-healer for burns. Tolerability study in seven patients with 2nd degree burns revealed initial stinging sensation without any side effects on use of neem.<sup>25</sup> The wound healing activity of the extracts of leaves of *Azadirachta indica* and *Tinospora cordifolia* using excision and incision wound in Sprague Dawley rats showed significant results.<sup>32</sup> In incision wound, tensile strength of the healing tissue of both plants (*Azadirachta indica* and *Tinospora cordifolia*) treated groups was found to be significantly higher.<sup>33</sup> Leave extracts of Neem stimulate wound healing activity through increased inflammatory response and neovascularisation.<sup>34</sup>

#### Insect repellent

Neem seed extracts are effective against both asexual and sexual stages of chloroquin-resistant as well as sensitive strains of malarial parasites *Plasmodium falciparum*. Seed extract have prevented growth and development of the human malarial parasitic agent. Neem extract was found to have some neuronal protective effect in malaria positive cases. The biological activity of neem extract might be due to active compounds in Neem including phenolics, terpenoids and alkaloids which may also lead to death of mosquitoes.<sup>35</sup> Azadirachtin present in Neem can be used as a potential agent for controlling *Argulus*, a common ectoparasite of ornamental fish.<sup>36</sup> Kerosene lamps containing neem oil reduce the biting and indoor resting density of mosquitoes, with better protection against *Anopheles* than *Culex*.<sup>25</sup> Neem compounds are more effective insect repellent than the widely used synthetic chemical known as N,N,-diethyl-m-toluamide, a suspected carcinogen. Neem oil affects the efficacy of commercially available insecticides. Azadirachtin is a powerful insect antifeedant that disrupts metamorphosis in moth larvae at very low concentrations.<sup>20</sup> Recently, Incense sticks of different herbal products along with neem were made and these sticks on burning were proved to be the most effective to control mosquito.<sup>37</sup>

#### CONCLUSION

Neem and its constituents have therapeutics effect and have been traditionally used worldwide mainly in Indian Subcontinent since ancient time. Clinical based studies confirmed that Neem shows vital role in inhibition of numerous diseases due to unique source of various types of components. Modern drugs can be

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developed after extensive analysis of its bioactivity, mechanism of action, pharmacotherapeutics, and toxicity. In fact, time has come to make good use of centuries-old knowledge on neem through modern methodologies of drug improvement.

#### ACKNOWLEDGMENT

We would like to thank my guide and my seniors. This research received no particular grants from any finance activity.

CONFLICT OF INTERESTS - None

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