A Comprehensive Review of the Antifertility and Pharmacological Properties of Neem (Azadirachta indica)

Moazam Ali1, Wajid Ali2, Muneeb Aslam3, Zeeshan Ahmad Bhutta4** and Muhammad Fakhar-e-Alam Kulyar5

1Department of Clinical Medicine and Surgery, University of Agriculture, Faisalabad, Pakistan
2Department of Animal Production and Technology, Nigde Omer Halisdemir University, Turkey
3Department of Pathology, University of Agriculture, Faisalabad, Pakistan
4Royal (Dick) School of Veterinary Studies, The University of Edinburgh, United Kingdom
5College of Veterinary Science, Huazhong Agricultural University, Wuhan, China

*Corresponding Author: Zeeshan Ahmad Bhutta, Royal (Dick) School of Veterinary Studies, The University of Edinburgh, United Kingdom.

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Abstract

The astounding properties of Neem have made it a charismatic plant and deliberated as a primeval cure for the modern world. Azadirachta indica (Neem) is an evergreen plant native to Sub-continent region, Africa and America. The extensive use of Azadirachta indica (Neem) in Homeopathic and Ayurveda medicine is offering solutions to the major issues facing mankind. This review article elaborates on the contraceptive as well as other pharmacological chattels like anti-inflammatory, anti-bacterial, anti-fungal, anti-ulcer, insecticidal, larvicidal and additional medicinal uses of Neem. The tremendous rise of the human population in contrast to the natural resources has alarmed the scientists to ponder how to abate this escalating ratio besides the control of unwanted pregnancies in the animals to avoid the zoonotic threat. Thus, the use of Neem helps govern the population pressure and promote its therapeutic potential in the fields of medicine and agriculture.

Keywords: Azadirachta indica; Neem History; Medicinal Uses; Anti-fertility; Taxonomy

Introduction

Medicinal plants provide the novel ingredients used in modern medicine, nutraceuticals, traditional and folk medicine. The WHO report clarifies this statement as more than 80% of the world population is dependent on plants to encounter the basic health care needs [1]. Azadirachta indica is an evergreen plant native to Sub-continent, Africa, America and other tropical regions [2]. Neem (Azadirachta indica) locally called 'Indian Lilac 'or 'Margosa' is a member of the Meliaceae family, in Persian it is termed as ‘Azad- Darakht- E- Hind’ meaning the free Indian tree. Keeping in view the therapeutic potential, several biological components present in Neem has been used as medicine by humans [3]. The US National academy of sciences in 1992 declared Neem- a plant for global issues by determining its majestic properties [4]. The US Environmental Protection Agency has approved the use of neem products in crops as it is safer for humans, animals, insects, and earthworms [5]. In general, Azadirachta indica has a complex composition as its components include Nimbin, nimbidin, nimboide and limonoids responsible to overcome the disease problems by modulating the different genetic mechanisms and other activities

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(Table 1). The purification of quercetin and B-sitosterol poly-phenolic flavonoids from neem leaves have proved to exhibit antifungal and antibacterial properties [6]. Earlier studies have affirmed the role of these components as anti-inflammatory, anti-arthritic, antipyretic, hypoglycemic, anti-tumorous and anti-bacterial chattels of neem [7-10].

<table>
<thead>
<tr>
<th>Sr. no</th>
<th>Compound name</th>
<th>Source</th>
<th>Activity</th>
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<tbody>
<tr>
<td>1</td>
<td>Nimbidin</td>
<td>Seed oil</td>
<td>Anti-inflammatory</td>
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<td>Anti-arthritic</td>
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<td>Spermicidal</td>
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<td>Anti-fungal</td>
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<td>2</td>
<td>Azadirachtin</td>
<td>Seed oil</td>
<td>Anti-malarial</td>
</tr>
<tr>
<td>3</td>
<td>Nimbin</td>
<td>Seed oil</td>
<td>Spermicidal</td>
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<td>4</td>
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<td>Anti-fungal</td>
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<td>Mahmoodin</td>
<td>Seed oil</td>
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<td>Bark</td>
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<td></td>
<td>Immunomodulatory</td>
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<tr>
<td>8</td>
<td>Margolone, margolonone and isomargolonone</td>
<td>Bark</td>
<td>Anti-bacterial</td>
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<tr>
<td>9</td>
<td>Cyclic trisulphide and cyclic tetrasulfide</td>
<td>Leaf</td>
<td>Anti-fungal</td>
</tr>
<tr>
<td>10</td>
<td>Polysaccharides G1A, G1B</td>
<td>Bark</td>
<td>Antitumor</td>
</tr>
<tr>
<td>11</td>
<td>Polysaccharides G2A, G3A</td>
<td>Bark</td>
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<tr>
<td>12</td>
<td>Phytosterols</td>
<td>Fruit</td>
<td>Anti-ulcer</td>
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Table 1: List of Isolated ingredients and their pharmacological role.

Taxonomy and general description

- Order: Rutales
- Family: Meliaceae
- Subfamily: Melioidae
- Genus: *Azadirachta*
- Species: *indica*.

*Azadirachta indica* is a tropical plant with a swift growing speed up to 20ft within 3 years. However, the neem plant also grows in the areas where the rainfall is minimum as 18 inches per annum and flourishes itself in the temperate regions of up to 120ºF. Their reported

Anti-fertility effects of neem

Auta and Hassan [11] reported the reproductive toxicity by aqueous wood ash extract of *Azadirachta indica* (neem) in male albino mice by orally administering the dose rate of 0, 5, 50 and 100 mg/kg body weight to 20 male mice for 7 days divided into four groups. Gonadal somatic index along with sperm morphology, count and motility were evaluated. The biochemistry profile includes the serum FSH levels, LH level, and Testosterone assay. Testicular histopathology also carried out to assure the anatomical changes. Results have shown that reproductive toxicity was dose-dependent as no significant effect was observed on testes weight and FSH, LH and testosterone levels (P > 0.05). Sperm motility decreased while live-dead sperm ratio and abnormal sperms increased (P < 0.05). The aqueous ash wood extract of neem causes reproductive toxicity by impairing the reproduction process by giving significant damage to testicular tissues. Lisanti, et al. [12] stated about the testicular histo-morphological changes produced by aqueous neem seed extract in five competitive groups of DDY male mice strain. Findings showed the decline in spermatogenic cells (p < 0.05) indicating infertility in male mice. Histopathology revealed the toxic effect of aqueous neem seed extract on testes as there were necrosis and vacuolation of late extended spermatids, several apoptotic cells and the creation of multinucleated giant cells in seminiferous tubules resulting in aspermatogenesis up to 36 days and thereafter. Aladakatti [13] described the Nimbolide anti-fertility effect in Wistar male rats when given a subcutaneous injection of graded doses at 0.5, 1.0 and 1.5 mg/kg in comparison to the control group for 24 days. Results exposed that nimbolide did not affect the overall bodyweight of Winstar rats while a decline in the weight of reproductive organs noted. Biochemistry profile revealed a drop-in protein content along with acid phosphatase besides an increase in total free sugar content, lactate dehydrogenase and alkaline phosphatase was recorded. A large number of irregular and atypical sperms depending upon nimbolide dose were observed during sperm analysis with a low pregnancy rate in female rats when mated with treated male Winstar rats. Santra and Manna [14] offered wild Indian rats orally the neem leaves extract in raw form at the dose rate of 200 mg/kg for 1 month to assess the anti-fertility effects. The post-treated effects were further noticed for 35 days, 40 and 45 days. Oral administration of neem leaves did not affect the general body weight and testicular weight. The results of treated groups damaged seminiferous tubules, vacuolization, untying of the strength of the germinal layer, presence of giant cells and amalgamation of the spermatids of the different phases of spermatogenesis along with the disrupted form of germ cells. The use of crude neem leaves also show a reduction in sperm production and deteriorate their morphology. About 8 weeks post-treatment all the alterations caused by neem leaves extract were returned to normal. The neem leaves extract causes the adjustable changes in testicles of rats but it can be used as a monitoring agent in the fertility mechanism of rodent pests. Khan and Awasthy [15] stated that Azadirachtin in neem leaves causes toxicity in murine germ cells at the cellular level. It causes the variations in the sperm chromosomal number, structure and effect on synaptic disorders during an early stage of cellular division metaphase I. Decline in overall sperm count and incline in sperms with the abnormal head was observed. The genotoxic effect of azadirachtin in neem extracts validates its property to cause mutations in the germ cells. Currah, et al. [16] evaluated the anatomical and functional changes in reproductive organs of rabbit bucks when nourished with a specified amount of neem leaf meal. Testicular weight, semen quality and seminiferous tubule diameter were considered. 9 rabbit bucks of age 7 - 8 months in each group were arranged in 4 groups receiving 0%, 5%, 10% and 15% NLM diets for 16 weeks. Results showed that sperm concentration, testis weight, seminiferous tubule diameter and abnormal sperm ratio in 15% NLM group were markedly low than all other dietary groups, however, sperm ejaculation was similar in all groups but was low in 15% NLM group as compared to 0% NLM control group. Thus, such drop-in production and changes in anatomical and physiological parameters were due to the anti-androgenic property of neem leaves. Neem seed tetranor-triterpenoids was evaluated by Aladakatti and Jadaramkunti [17], to halt the spermatozoa mobility just within 20 seconds along with inhibition of sperm motility and plasma membrane.
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capability and veracity in controlled dosage method. An improved technique of the sander-Cramer test was adopted in vitro to check the spermicidal effect using different concentrations. For 100% control over stoppage of sperm mobility within 20 seconds, the minimum effective concentration of azadirachtin-A was 4.50 µg/million sperm. Ultra-studies proved the loss of normal functioning of the plasma membrane by curling of tail of spermatozoa exposed to azadirachtin-A in a controlled dosage method along with presence of membrane less spermatozoa. Garg., et al. [18] prepared an herbal cream containing praneem (25%) reetha saponins (0.05%) and quinine hydrochloride (0.34%) with synergistic spermicidal effect. Monkeys demonstrated the dissolution period about 40 minutes and rabbits of about 30 minutes when applied within the vagina of individuals. A regressive trend against successful pregnancy status was noted in results over time, as the 100% results were recorded when the cream was applied half an hour before the sexual intercourse while it was at 7% after 60 minutes, 29% in 120 minutes and 75% after 12 hours in rabbits. The monkeys exhibited only up to 2.27% success rate when applied pre-coitus. The neem leaf extract, which is hydrophilic, amalgams instantly with water as well as body fluids and kills sperm within 20s, with its use, a more potent vaginal contraceptive may be developed [19]. In vitro studies approved neem a strong spermicidal agent when Rhesus monkey and human spermatozoa become immotile within 30 seconds of contact with the undiluted oil, further in vivo studies in rats [20]; rabbits [6]; rhesus monkeys [10] and human volunteers have anti-implantation or abortifacient consequence in rats and rabbits when deposited intravaginally on day 2 to day 7 of expected pregnancy with no illness in the whole reproductive tract when examined histopathologically. Radioisotope readings directed the zero absorption of neem oil from vagina thus making it an “ideal” female contraceptive, easily available, economical and non-toxic.

Anti-inflammatory

The extracts of plants and itself plants are mainly used for the treatment of inflammatory disorders. Azadirachta indica plant extract has shown anti-inflammatory properties when it is tested on rats by using cotton pellet granuloma assay with a dose rate of 200 mg/kg [21]. The mechanism which is involved in it that neem plant extract decreases the role of macrophages and neutrophils which are involved in the process of inflammation [22]. Neem oil is also effected for foot edema. For this purpose, the study was conducted on the albino rat in which paw edema was induced. Neem oil dose has been increased with a gradual increase dose rate from 0.25 ml to 2 ml per kg body weight of albino rats. It is also concluded in results that stem bark of neem extract has also decreased the ear inflammation of rats. While the bark extract was also used for the treatment of stomatitis in children. Another study has gathered the antipyretic results of methanol extracts which were extracted from neem plant leaves when it is administered to the male rabbits. These studies suggested the neem oil role as anti-inflammatory and anti-pyretic [23]. Azadirachta indica is used as medication in India for several years. It is tested in chronic and acute cases of inflammation. Moreover, it has also a low ulcer index and low cancerogenic potential [24].

Antibacterial activity

Methanolic extract of Azadirachta indica exhibited antibacterial and antihemorrhagic properties in the case of Vibrio cholera infection [25]. Instead of this, hexane and chloroform extract of Azadirachta indica plant have potential against different bacterial infections such as Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris, Micrococcus luteus, Bacillus subtilis, Enterococcus faecalis and Streptococcus faecalis. In several cases, it reduces bacterial activity [26]. Extracts of neem plant seeds are much affected against pathogenic infection of ear and eyes. Pure extracts of neem plant in acetone are the best antibacterial property among all other solvents like ethanol and methanol [27]. The seed oil of the neem plant is effective against 14 pathogens [28]. The solvent and crude aqueous extracts of Azadirachta indica (Neem) were found effective against 20 pathogenic bacterial strains, but crude extracts have shown better results [29]. Neem juice acts as an antibacterial agent and according to research, it has shown a Minimum Inhibitory Concentration (MIC) value of 3.13 against V. parahaemolyticus and 6.25% against V. alginolyticus. Same as this value was 12.5 and 25% against Vibrio parahaemolyticus and V. algino-lyticus [30].

Antifungal activity

The neem extract has also antidermatophytic results for dermatophytes. The ethanolic extract has shown better activity than aqueous
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Anti-diabetic and anti-hyperlipaemic

Anti-diabetic and anti-hyperlipaemic properties of neem have been identified by Bopanna, et al. [34] when the alloxan treated diabetic rabbits were offered neem seed kernel in powdered form. Findings explained that the alloxan treated group showed a significant increase (P < 0.001) in fasted blood sugar and urine sugar level besides a notable decrease (P < 0.001) in the overall body weight and Hb content. In contrast to this, the neem seed kernel group significantly elevated the body mass and hemoglobin level with a drastic change in the fasted blood glucose level and urine sugar contents. The same trend was noted in alloxan treated rabbits cured with insulin, glibenclamide and NP + glibenclamide. Thus, the combined NP + glibenclamide therapy (250 mg/kg and 0.25 mg/kg) respectively, not only significantly reduced the fasting blood levels it also helped out in avoiding the amelioration of body mass, hemoglobin levels besides and abridged enzymatic activity. In NP + glibenclamide group serum acid phosphatase, ALP and HMG CoA activity noticeably reduced in contrast to other antidiabetic treated groups. Satyanarayana, et al. [35] studied neem leaves aqueous extract impacts on diabetes mellitus type-2 in rat’s model, tempted by fructose and high-fat target tissues via the countenance of insulin signaling molecules and glucose oxidation. The high-fat content diet-induced diabetic rats were offered an effective oral dosage of neem leaves extract 400 mg/kg once daily for the tenure of one month. The parameters assessed in this trial were the serum lipid outline, FBG levels, glucose tolerance via the oral route, glycogen contents, gastrocnemius muscle tone, glucose oxidation and insulin indicating molecules. Results showed the impaired values for oral glucose tolerance, glycogen absorption, glucose oxidation and insulin indication glimmers like (IRS-1, phosphor-IRS-1Tyr632, phosphor-IRS-1Ser636, phosphor-AktSer473 and GLUT4 proteins) in the diabetic group in contrast to normalized values of all these parameters in neem leaves extract-treated group. Thus, Azadirachta indica leaves extract fruitfully take part in regulating the type-2 diabetes mellitus by modifying insulin molecules besides the proper utilization of glucose content in the skeletal muscles. Dholi, et al. [36] studied the hypoglycemic effects of neem in diabetic rats via a single dose of 250 mg/kg that causing a decline in glucose, cholesterol, triglycerides, urea, creatinine and lipids contents within 24 hours by 18%, 15%, 32%, 13%, 23% and 15% respectively. There is no doubt in stating that Azadirachta indica aids in managing the elevated blood glucose levels in diabetes mellitus and needs more elaborate studies regarding oral hypoglycemic remedy. Arika., et al. [37] valued the hypoglycemic effects of Azadirachta indica aqueous leaves extract in alloxan prompted white albino mice in-vivo trial. The serially diluted extract dosage was introduced intraperitoneally and orally at the rate of 25 mg/kg, 48.4 mg/kg, 93.5 mg/kg, 180.9 mg/kg and 350 mg/kg body weight. Both routes found to cause a lowering of blood glucose levels in the dosage independent way. The phytochemicals like flavonoids, tannins, saponins, alkaloids and anthraquinones present in neem were accredited to cause a decline in the blood glucose levels and assure the use of Azadirachta indica as traditional medicine for the cure of diabetes mellitus.

Anti-carcinogenic activity

The onco-static potential of neem was determined when the female Swiss albino mouse was injected intramuscularly with EAC (Ehrlich ascites carcinoma) a carcinogenic agent [38]. A neem leaf preparation (NLP) of 500 mg/kg body weight was injected intraperitoneally for 20 days. The 1st NLP shot was given 5 days post-EAC inoculation. Neem leaf preparation causes suppressing the tumor’s growth by depressing the lipid peroxidation and GSH contents. This was accomplished by neem as it improved the endogenous anti-oxidant scavenging enzyme system action, SOD (superoxide dismutase), GPx (glutathione peroxidase), and CAT - GST (catalase and glutathione S transferase) in the liver as well as in tumor cells. Conclusively, neem in general by regulating the antioxidant protection mechanism and oxidative stress demonstrated the anti-carcinogenic effects. Balasenthil., et al. [39] stated the reduction of oral squamous cell neoplasms induced by 7, 12-dimethyl Benz [a] anthracene (DMBA) by offering aqueous neem leaf extract. Neem implemented the anti-carcinogenic

efforts by regulating the glutathione and its corresponding metabolizing agents. MNNG (a carcinogenic substance) whose target organ is stomach and liver, neem implements its oncotic shielding chattels by declining the production of lipid peroxidases besides elevating the anti-oxidants concentration along with detoxification of both target organs and the blood circulation [40].

Antimalarial activity

The production of mosquito species Anopheles stephensi and Aedes aegypti was successfully halted by wood scrapings treated with 5% Azadirachta indica oil. The neem oil was further diluted with acetone and just within 6 weeks, the upbringing was controlled when the ball-shaped scrapings were placed in water tanks [41]. The development of Plasmodium falciparum was reported to be ceased by the nimboline a substance extracted from neem exhibiting anti-malarial activity [42]. Another neem isolated substance named Gedunin also testified the anti-malarial property [43]. The alcoholic, as well as the aqueous neem leaves, extract proved to be anti-malarial against the mosquito strains resistant against chloroquine [20]. Another laboratory study justified the anti-malarial chattel of neem on growing stages of cultured Plasmodium falciparum. For the culturing purpose, the RPMI 1640 was used as growth media whereas the neem extract was mixed with dimethyl sulfo-oxide and divided into 7 different (3.125; 6.25; 12.5; 25; 50; 100 and 200 μg/mL) concentration levels. After culturing both the testing and controlled groups were incubated for 72 hours under CO₂ jar. Every 8 hours the fraction of parasitemia developed over the plasmodium falciparum developing stages via extract activity. By removing the supernatant layer the thin blood smear of the erythrocyte layer was made for calculation of parasitemia and stained with 10% Giemsa stain for half an hour. By adopting the probit analysis method anti-malarial property of neem was observed by gathering 50% growth retardation. Final results of neem leaves extract revealed the abduction of plasmodium falciparum FCR-3 on the schizont stage with 50% inhibition concentration IC₅₀ at 3.86 μg/ml after 32 hours of incubation. This trial justified the anti-malarial property of neem in vitro [44].

Antiulcer activity

Bhajoni., et al. [45] assessed the anti-ulcer property of Azadirachta Indica aqueous leaves extract in Winstar rats by generating the gastric ulcers via cold stress, aspirin treatment and ligating the pyloric region. The dosage given to rats was 150, 300 and 600 mg/kg body weight per OS. For reference standard, the ranitidine was given at the rate of 20 mg/kg via IP whereas the control group was offered distilled water. Parameters evaluated were the ulcer index (UI) and percentage inhibition rate (PI). The group with pyloric ligation induced ulcer was tested with gastric stuffing, a ratio of free to total acidity and pH value. The findings suggested the dosage-dependent a marked decline (p < 0.05) in PI and UI in all tested groups in contrast to the control. The gastric stuffing value, free to total acidity ratio also reduced in the neem leaves aqueous extract group and proved that the Azadirachta indica holds the anti-ulcer activity.

Use of neem in herbal cosmetic industry

Azadirachta indica (Neem) taken as a primeval cure for the modern world while its use is as old as 4500 years ago and considered the cure of all ailments. The health refreshing advantages of neem include its efficacy against skin infections, rashes, pimples, acne as many products are available in the market. Moreover, some other issues regarding health and beauty like chubbiness, blood purification, piles, hairs, and oral problems also cured by using neem as prescribed by the physician [24].

Conclusion

Taking into account the significance of neem in different fields of life there is an utmost need to further explore its assortment in nature to initiate some effective steps to preserve this magician plant for future usage. Furthermore, researchers should also assume the collection of data regarding ethnobotanical findings to create a link between traditional and modern practice. The successful research trials assisted in exploring the photochemistry of Azadirachta indica and elaborate its anti-fertility potential, anti-inflammatory, antimalarial, antibacterial, anti-allergic, anti-ulcer, anti-fungal, insecticidal, larvicidal and other pharmacological chattels chattels, ultimately resulted in the preparation of industrial and medicinally approved products.

Conflict of Interest

No conflict of interest.

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