

## Review on Medicinal Value and other Application of Neem Tree: Senior Seminar on Animal Health

Abebe Tibebe, Geremew Haile\*, Abriham Kebede

School of Veterinary Medicine, Wollega University, Nekemte, Ethiopia

**\*Corresponding Author:** Geremew Haile, School of Veterinary Medicine, Wollega University, Nekemte, Ethiopia, Email: geremewlov@gmail.com

**Abstract:** *Neem, commonly known as Azadirachta indica is an evergreen, temperature tolerant, flowering plant native to India but now it distributed to other continents of the world. It is among medicinal plants those have a wide range of medicinal values which every part of the tree is used as medicine both locally and after preparation in pharmaceutical industries. It is effective against microorganism and ectoparasites including bacteria, fungi, viruses, ticks and mites. In addition it has antimalarial, anticancer, antioxidant, antidiabetic, hepatoprotective, neuroprotective, and Wound healing effects. It also used in agriculture as pesticides and fertilizer to increase crop production. Nowadays drug resistance is the main problem in both animals and humans due to use of synthetic products for long period of time which makes this plant to be preferable as alternative to overcome the situation. The tree is also source of feed for animals which is providing a number of nutrients like protein, minerals, fatty acids, vitamins. This implies that they are acquiring the medicine indirectly and become resistance toward diseases. Regardless of its benefit, different researches and reviews those introduce neem to the world have not been done well particularly in Ethiopia when compared to other medicinal plant. An extensive research and development activities should be undertaken by the help of government which allocate budget to study regarding to the tree.*

**Keywords:** Anticancer, Azadirachta indica, Medicinal plant, and Microorganisms

### 1. INTRODUCTION

*Neem (Azadirachta indica)*, is native of India and growing in most of tropical and subtropical countries. The tree has adaptability to a wide range of climatic, topographic and edaphic factors. It thrives well in dry, stony shallow soils and even on soils having hard calcareous or clay pan, at a shallow depth. So that it requires little water and plenty of sunlight to survive in the environment [1]. The plant is distributed widely in the world providing a source of inspiration for novel drug compounds, as plant derived medicines which have made large contributions to human health and well-being. Presently it can be seen growing successfully in about 72 countries worldwide, in Asia, Africa, Australia, North, Central and South America. The tree was introduced into West Africa at the beginning of this century [2].

Neem is a member of the Mahogany family. Order Rutales, Suborder Rutinae, Family Meliaceae, Subfamily Melioideae, Tribe Melieae, Genus *Azadirachta*, Species *indica*. Two species of *Azadirachta* have been reported, *A. indica* A. Juss native to Indian subcontinent and

*Azadirachta excels Kack*, confined to Philippines and Indonesia [3].

Every part of the tree has been used as traditional medicine for household remedy against various diseases [4]. It elaborates a vast array of biologically active compounds that are chemically diverse and structurally variable with different ingredients isolate from different parts of the tree [5]. The active ingredients include alkaloids, flavonoids, phenolic compounds, carotenoids, steroid and ketones, which have antihelminthic, antimicrobial, antiulcer, antifertility, antidiabetic, anti-inflammatory and antitumor properties and the plant is used in combination with oil for more effectiveness to reduce toxicity [6, 7].

The neem seed oil has toxicity effect against ectoparasites like ticks and mites which are common on cattle, equines, sheep, goats, wild ungulates and dogs [8]. Alcohol and aqueous extracts of flowers of the tree also effect against cattle filarial parasite [9]. The plant debris (after oil extraction) are potential source of organic manure and leaves could be used as a source for the preparation of compost having both fertilizer

and pesticidal potential [10]. Instead of killing the pests, it affects their life cycle. Antifeedant properties found in neem compounds helps to protect the plants when applied on them and also it is being used to manufacture bioinsecticide that is environmental friendly and do not have any side effect effects on plants and soil [11].

Generally, there are a wide range of medicinal plants in Ethiopia including neem tree, which are used for healing purpose both traditionally and in preparation form. Regardless of its medicinal values only few researches and reviews have been done on neem tree and nowadays microorganisms have been developed resistance to most of existing synthetic antimicrobials used for long period of time which needs alternative sources of drugs to solve the problem. Therefore, the objective of this paper is to review medicinal values and other applications of neem tree.

## 2. MEDICINAL VALUES AND OTHER APPLICATION OF NEEM TREE

### 2.1. Neem Tree Parts Used as Medicines and Its Biological Components

All parts of the tree including leaves, bark, roots, seed and twigs contain active ingredients and used as medicine. Neem leaves are useful for increase immunity of the body, reduce fever, treating various foot fungi, useful against termites, used in curing neuromuscular pains and Anticlotting agent, Antihelminthic, Antituberculosis, Antitumour, Antiseptic, Antiviral, Contraceptive, Cosmetics, Fertilizers, Insecticides and Insect repellents [12]. Neem bark and roots can control fleas and ticks on pets, relieve skin infections such as acne, psoriasis, scabies and eczema. In addition used for treatment of diabetes, aids, cancer, heart disease, herpes, allergies and ulcers [13]. Neem oil acts as Analgesic, Antihelminthic, Antihistaminic, Antiprotozoal, Antipyretic, Antiviral, Bactericidal, Contraceptives, Fungicides, Insecticides, and Cosmotics. Neem twigs (small thin branches of the tree) act as Oral deodorant, Toothache reliever and Tooth cleaners [14].

**Table1.** Summarized medicinal values of neem parts

	Part	Medicinal uses
L	Leaf	Eye problem, intestinal worms, anorexia, and skin problem
	Bark	Analgesic, alternative and curative fever
	Flow er	Bile suppression and elimination of intestinal worms

	Fruit	Relieves piles, intestinal worms, urinary disorder, epistaxis, eye problem, diabetes, wounds
	Twig	Relieves cough, asthma, piles, intestinal worms, spermicidal
	Gum	Effective against skin diseases like ring worms, scabies, wounds, ulcers etc.
	Seed pulp	Intestinal worms
	Oil	Intestinal worms

Source: [15].

Neem has more unique bio-active compounds, of which More than 135 compounds have been isolated from different parts of it. These active compounds have potential applications in animal care, public health, agriculture and for even regulating human fertility [16]. In addition they have bitter principles, which are responsible for antifeedant and toxicity property that leads to starvation and finally death of insects [17, 18].

These compounds are classified into two major groups, isoprenoids and non isoprenoids. The isoprenoids include diterpenoids and triterpenoids containing protomeliacins, liminoids, azadirone and its derivatives, genudin and its derivatives and csecomeliacins such as nimbin, salannin and azadirachtin [15]. The non isoprenoids include proteins (amino acids), carbohydrates (polysaccharides), sulphurous compounds, polyphenolics such as flavonoids and their glycosides, dihydrochalcone, coumarin, tannins, aliphatic compounds and phenolic acids [19].

### 2.2. Pharmacologic Action of Neem Tree Products

The mechanism of action on microorganisms (bacteria and fungi) is not fully understood but, in viruses it inhibits multiplication and attachment to host cell [20]. The major actions of Azadirachtin on insects are to modify hemolymph ecdysteriod by inhibiting the release of morphogenetic peptide, prothoracicotropic hormone (PTTH) and allatotropins from the brain-corpus cardiacum complex. Neem products also work on juvenile hormones. The insect larva feeds and as it grows, it sheds its old skin. When the neem components, especially azadirachtin, enter the body of the larva, the activity of ecdysone is suppressed and the larva fails to moult, remains in the larval stage and also it inhibits the formation of chitin or the hard part covering of the insect as a result of applying

neem extracts on storage food which inhibits or prevents normal metamorphosis of immature stages ultimately dies [21].

Crops treated with a neem product leads to anti-peristaltic wave in the alimentary canal which produces something similar to a vomiting sensation in the insect because of the presence of azadirachtin, salanin and melandriol. Because of this sensation, the insect does not feed on the neem treated surface. Its ability to swallow is also blocked. So it can be said that Azadirachtin (AZ) and AZ-containing extracts from the neem tree show distinct antifeedant activity, primarily through chemoreception (primary antifeedancy), but also through reduction in food intake due to toxic effects after consumption [22]. The hepato protective mechanism is due to that 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 which are indicators of liver damage. Thus, this plant clearly notifies the improvement of the functional status of liver cells. Neem leaf extract has sperm atotoxic effect. It can cause immobilization and mortality of human spermatozoa at a 3 mg dose within 20 seconds [23].

### 2.3. Antimicrobial and Anti Parasitic Effect of Neem Tree

#### 2.3.1. Antibacterial effect

Neem possesses a wide spectrum of antibacterial action against Gram-negative and Gram-positive microorganisms. The antibacterial activity of neem extracts against 21 strains of foodborne pathogens was evaluated and result of the study suggested that it possess compounds containing antibacterial properties that can potentially be useful to control bacteria and spoilage organisms [24]. Another experiment was made to evaluate the antibacterial activity of the extracts of *A.indica* on bacteria isolated from adult mouth and results revealed that bark and leaf extracts showed antibacterial activity against all the test bacteria used [25].

Water extracts of neem twigs inhibits growth of dental caries organisms *Streptococcus mutans*, *S. salivarius*, *S. mitis*, and *S. sanguis* [26]. Neem has suppressed several species of pathogenic bacteria, including: *Staphylococcus aureus*, a common source of food poisoning and manypus-forming [27]. The susceptibility of the microorganisms to the extracts of neem leaves was compared with certain specific antibiotics.

Its leaves possessed good anti-bacterial activity, confirming the great potential of bioactive compounds and is useful for rationalizing the use of this plant in primary health care [28]. The methanol extract of *A. indica* exhibited pronounced activity against *Bacillus subtilis* [29].

#### 2.3.2. Antifungal effects

Nimbidin, Nimbin, Nimbidol and Neem oil are very effective against fungi like *Tinea rubrum* ring worm fungus, *Trichophyton interdigitale*, *Coccidioides immitis* and species of *Trichophyton* at very low concentration. High antimycotic activity with extracts of different parts of neem has already been reported. Extracts of leaf, oil and seed kernels are effective against certain human fungi; due to this property is given great importance in the field of science. *A.indica* leaf extract has antifungal activity against three fungal species: *Aspergillus flavus*, *Alternaria solani* and *Cladosporium*. Neem oil has been the cure for many fungal diseases caused by the above fungi which has been a lifesaver [30].

In a study done by [31] shows that the ethanolic extract of *A.indica* leaves is more effective against *Rhizopus* 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 [32]. Neem oil is used to prevent aflatoxin which is produced due to contamination of the poultry feed by fungus and the neem leave extract antagonises the production of Patulin caused by *Penicillium expansium* [33].

#### 2.3.3. Antiviral effect

Neem leaves are found to be effective against Dengue virus type -2 in which it halts the replication of the virus itself in an invitro environment and in the laboratory animals. The aqueous extract of its bark were found to be effective against Herpes simplex virus type 1 by blocking its entry into natural target cell [34]. Even though it does not cure it shows the ability to prevent smallpox, chickenpox and fowl pox [35]. In HIV/AIDS patients, a 12-week oral administration of acetone water neem leaf extract (IRAB) had a significant influence *in vivo* on CD4 cells (which HIV reduces) without any adverse effects in the patients [36]. It may be applied topically to appropriate parts of the body during an outbreak or just prior, when stress is

high and we begin to get that 'feeling' that often occurs just before an outbreak. To speed relief, one may also take the oral supplements, such as neem leaf capsules [34].

#### 2.3.4. Antihelmethic effects

Diseases caused by helminthes parasites in livestock continue to be a major productivity constraint, especially in small ruminants in the tropics and subtropics. In the Developing world, the greatest impact of parasitic diseases is in direct and potential productivity losses. The greatest losses associated with nematode parasite infections are sub-clinical, and economic assessments show that financial costs of internal parasitism are enormous. *A. indica* leaves were dispensed to animals without processing even locally [7].

#### 2.3.5. Effects against ectoparasites

The application of neem extracts to livestock is effective in the control of ticks or mites are wide spread in the developing world. The idea of cultivation of plants and low-cost extraction of active compounds as a local industry in developing countries has considerable appeal. There seems to be a prevailing view that plant extracts or botanicals are safer and cheaper to produce than synthetic products. Control of ticks with chemical acaricides has become difficult because of its diminishing efficiency due to resistance development [8].

#### 2.3.6. Neem as insect repellent

Azadirachtin is a powerful insect repellent that disrupts metamorphosis in moth larvae at extremely low concentrations. The smell of neem is enough to repel leaf eating insects (such as grasshoppers and leafhoppers). Neem oil formulation find wide usage as a biopesticide for organic farming, as it repels a wide variety of pests including, beet armyworm, aphids, the cabbage worm, white flies, mites, beetles, moth larvae, mushroom flies, leaf miners, caterpillars. Grasshoppers have been observed to starve to death rather than eat neem as the only food source [37].

### 2.4. Other Medicinal Uses of Neem Tree

#### 2.4.1. Antioxidant activity

Free radical or reactive oxygen species are one of the main factors in the genesis of various diseases. However, neutralization of free radical activity of neem is one of the important steps in the diseases prevention. Antioxidants stabilize/deactivate free radicals, often before they attack targets in biological cells [38]. Neem

plays role in the activation of anti-oxidative enzyme that plays role in the control of problem caused by free radicals/reactive oxygen species. Neem has been reported to have antioxidant activity. Plants fruits, seeds, oil, leaves, bark, and roots show an important role in diseases prevention due to the rich source of antioxidant [39].

#### 2.4.2. Anticancerous activity

*A. indica* and their active compounds play vital role in the prevention of cancer development and progression. The exact molecular mechanism is not understood fully. But, it contains flavanoids and various other ingredients that play an important role in inhibition of cancer development by activating the tumour suppressor genes and inactivate the activity of several genes involved in the cancer development and progression [40]. Presence of anti angiogenic agents to block new blood vessel growth is crucial step in the inhibition/prevention of tumour growth [41].

#### 2.4.3. Wound healing effect

Neem oil contains active ingredients that directly deal with wound healing process. Because it directly helps the skin to retain its nature as it heals. It also has high amount of essential fatty acids which plays an important role in adding moisture and soft texture to the skin during the process. In addition to its ability to restructuring of skin, neem leaf extracts and seed oil keeps the wound free from microorganism due to their antimicrobial effect which reduces the time of healing. Neem also has another important role in healing of wound, it inhibit the inflammation which prolong the duration of healing. Finally it helps the formation of granulation tissue and elastin as well as collagen [42].

#### 2.4.4. Hepatoprotective effect

Neem helps to protect liver from damage, which in turn helps to cleanse blood. The active ingredients of the tree minimize chemically induced liver damage by stabilizing level of serum enzymes and boosting level of antioxidants like those found in vitamin A, E and natural carotenoids, which neutralize free radicals and prevent liver damage [43]. The aqueous extract of neem offer protection against paracetamol induced liver necrosis. The elevated levels of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma glutamyl transpeptidase (GGT) indicative of liver damage significantly reduced on administration of this extracts [44].

#### 2.4.5. Antidiabetic, Antifertility and Antiulcer effects

Aqueous extract of neem leaves significantly decreases blood sugar level and prevents adrenaline as well as glucose-induced hyperglycaemia. When orally fed, also produces hypoglycaemia in normal rats and decreased blood glucose levels in experimentally induced diabetes in rats. Neem and seed extracts have contraceptive property when administered orally at the beginning of the post-implantation stage resulted in pregnancy termination in rodents and primates, without any permanent effects [45]. Neem bark extract reduce human gastric acid hypersecretion, and gastro-esophageal and gastroduodenal ulcers. It gives significant protection from discomfort speed healing of gastric and duodenal lesions [46].

#### 2.4.6. Neem as Animal Nutrition

The processed Neem cake poses a good appetizer characteristic together with wormicidal activity which is used as poultry feed. Furthermore, Neem leaves has a significant amount of protein, minerals (except Zinc) and digestible amounts of crude protein (CP) and total digestible proteins (TDP) which serves a better nutrition to the animals such as goat, sheep and cow [33]. Despite its bitter components, livestock consume diets containing varied percentage of neem cake. Alkali treatment of this byproduct with caustic soda (10-20g sodium hydroxide) yields palatable products by removing the toxicant triterpenoids. After treatment it is incorporated into poultry feed [47].

#### 2.4.7. Agricultural Application of Neem Tree

Approximately one third of world's agricultural food stuffs get destroyed by more than 20,000 species of field and storage pests. To prevent this loss, large amounts of synthetic pesticides are applied, out of which only 0.1% reaches the target pests and more than 99% contaminates the ecosystem. In addition, synthetic pesticide usage has resulted in development of resistant pests. Cost-effective, nontoxic, biodegradable, eco-friendly and botanical 'soft-pesticides' are the need of present day agriculture as an alternative to hazardous and recalcitrant synthetic pesticides [48].

Neem is one of soft pesticide used as a biocontrol agent to control many plant diseases [49]. The material left after oil is squeezed out from seeds and is popularly known as the seed cake. It acts as a bio fertilizer and helps in providing the required nutrients to plants. It is widely used to

ensure a high yield of crops. It is used as a fertilizer both for food crops and cash crops, particularly rice and sugarcane crop [50].

Its pesticides are generally water soluble and help in the growth of the plants. It acts as pest repellent and pest reproduction controller. This medicinal plant is being used to manufacture bioinsecticide that is environmental friendly and do not have any toxic effects on plants and soil. Insecticides from neem are used to protect both food as well as cash crops like rice, pulses, cotton, oils seeds, etc [51]. Neem is used as manure, which is any animal or plant material used to fertilize land especially animal excreta for improving the soil fertility and thus promoting plant growth. And also the compounds found in it help to increase the nitrogen and phosphorous content in the soil. It is rich in sulphur, potassium, calcium, nitrogen [52].

#### 2.4.8. Industrial Uses of Neem

Several industries including pharmaceuticals, cosmetics, disinfectants, rubber, bio-pesticide and textile industries use neem oil for preparation of different products. Such neem based commercial preparations are currently available [53]. A new shampoo, based on seed extract of neem was highly effective, more than permethrin based product, against head lice under *in vitro* conditions [54]. Its oil and powdered neem leaves are employed in various cosmetic preparations such as face creams, nail polish, nail oils, shampoos, and conditioners. Neem cake, a byproduct of neem oil industry is used as livestock feed, fertilizer and natural pesticide. Also neem oil is commonly used in soap production [55].

It is now considered as a valuable source of unique natural products for development of medicine against various diseases and also for the development of industrial products. It is a source for many oral-hygiene preparations and dental care products. Neem bark yields gum and tannins which are used in tanning, dyeing etc. Neem seed pulp is used as a rich source of carbohydrate in fermentation industries and for methane gas production. Cultivation of neem and processing of neem products provides employment and income generation opportunities [56].

#### 2.4.9. Application and Status of Neem Tree in Ethiopia

Neem is used in Ethiopia to control development and growth of African bollworm, which is pest to cotton. It is checked on the larvae of bollworm by collecting the undamaged fresh leaves of neem

and seed from middle Awash, Ethiopia. Then crashed and applied on the larvae and shows inhibitory effect [57].

In Ethiopia there are many vector control methods, most of them are too expensive, ecologically harmful and environmentally unsafe or they are practically infeasible and inaccessible to be used. Moreover, insecticide resistance is now a major problem facing malaria vector control programmes in most African countries, including Ethiopia, with most important vector species, showing resistance to one or more of the insecticide classes used in vector control. There is a need to have an intervention that better avoids such problems. This may include the uses of mosquito repellents which may be commercially available or locally produced by the community itself [58].

In Ethiopia, wogert (*Silenemacroserene*), kebericho (*Echinopskebericho*), tinjut (*OstostegiainTEGRIFOLIA*), and woira (*Oleaeuropaea*) and Neem have been shown to have repellent effects against *Anopheles arabiensis* under laboratory conditions [59]. Dry Ethiopian neem seed (*A.indica* A. Juss) were provided from Dire Dawa nursery center, 160 km east of Jijiga. To obtain neem oil, its seeds were crashed using the kornetvegetable machine [60]. On the study done in Tolay, south west Ethiopia prove that neem has larvicidal effect on *An.gambiae*. Higher concentrations of neem oil formulation caused higher mortality against *An.gambiae* larvae, while at lower concentrations the rate of mortality was very low [61].

### 2.5.Side Effects of Neem Tree

Neem leaf extracts appear to be very safe at recommended intake levels with no significant reports of problems. Also, use of neem has consistently reported no adverse effects either as anti malaria or an anti-retroviral agent. Water extracts of neem leaf have been shown to decrease blood levels of chloroquine in rabbit but this has not been investigated with acetone water extracts of neem. The use in pregnancy has also not been evaluated and thus is not yet recommended. There were also no well-known drug interactions with neem products [36]. However, neem products are not risk free. Adverse effects of neem components were noted in nontarget aquatic invertebrates fish, some

mammals, and humans (Reye's syndrome). Finally, aflatoxins were usually present in neem extracts if the fungus *Aspergillus* was present during the storage of neem products [62].

### 3. CONCLUSION AND RECOMMENDATIONS

Neem, the versatile medicinal plant is the unique source of various types of compounds having diverse chemical structure. It has a wide range of application in both humans and animals as treatment for several diseases caused by microorganism and another factors. It is used as pesticides and insecticides on agriculture and also it is used in industries for development of new drugs. Due to its content of nutrients neem can be used as animal nutrition after treating by sodium hydroxide which prevents the bitter taste of the tree. Neem also has considerable effect on ectoparasites and helminthes those developed resistance to acaricides and antihelmenthic. Very little work has been done on the biological activity and plausible medicinal applications of these compounds and hence extensive investigation is needed to exploit their therapeutic utility to combat diseases. Despite the great role of neem in the primary health care, the knowledge on this medicinal plant depth and width become declining due to its secrecy, unwillingness of young generation to gain the knowledge, influence of modern education, religious impacts, and lack of awareness.

Based on above conclusion the following recommendations are forwarded:

- A drug-development programme should be undertaken to develop modern drugs with the compounds isolated from neem.
- An extensive research and development work should be undertaken on neem and its products for their better economic and therapeutic utilization.
- The government should take attention to this tree by allocating budget to study and supporting researches regarding to neem tree.

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**Citation:** Abebe Tibebu, Geremew Haile, Abriham Kebede. *Review on Medicinal Value and other Application of Neem Tree: Senior Seminar on Animal Health. ARC Journal of Immunology and Vaccines.* 2(2): 16-24.

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