A review on chemical composition, medicinal value and other applications of *Azadirachta indica*

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It was estimated from World Health Organization (WHO) that most of the world population depends on herbal medicine for their health care. *Azadirachta indica* also known as neem plant is one of the most popular medicinal plants in Asia and Africa which was used from the anceint times for many medicinal purposes. It is used in many traditional remedies because of its richness with biological active constituents. Some of these chemical constituents are Nimbidin, Nimbin, Nimbolide, Gedunin, Azadirachtin, Mahmoodin, Cyclic trisulphide and others which are used as antipyretic, anti-inflammatory, antibacterial, antigastric ulcer, ant arthritic, spermicidal antifungal, antimalarial, hypoglycemic, immunomodulatory, diuretic and antitumor. Traditionally different parts of the plant are used by populations from many countries for the treatment of several diseases such as leprosy, epistaxis, eye problem, elimination of intestinal worms, anorexia, skin ulcers,

INTRODUCTION

ROS mediated PCD in plant

PNeem (*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 wellbeing. Presently it can be seen growing successfully in about 72 countries worldwide, in Asia, Africa, Australia, North, Central and South America [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]. Biologically active principles isolated from different parts of the plant include: Azadirachtin, meliacin, gedunin, nimbidin, nimbolides, salanin, nimbin, valassin, meliacin forms the bitter principles of Neem oil, the seed also contain tignic acid responsible for the distinctive odour of the oil [6,7]. Neem kernels contain 30-50 % of oil mainly used by the soap, pesticide and pharmaceutical industries and contain many active ingredients which are together called triterpene or limnoids [8].The four best limnoids compounds are: Azadirachtin, Salannin, Meliantriol, and Nimbin. Limonoids contain insecticidal and pesticidal activity [9].

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

biliousness, and Skin diseases like ringworms, burning sensation, wounds and itching. 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.

The present work provides comprehensive information on the medicinal use, other application, the chemical constituents and side effects of *Azadirachta indica*.

Key Words: Traditional medicine; Azadirachta indica; Pharmacological action; Neem oil

[10]. Alcohol and aqueous extracts of flowers of the tree also effect against cattle filarial parasite [11]. The plant debris (after oil extraction) is potential source of organic manure and leaves could be used as a source for the preparation of compost having both fertilizer and pesticidal potential [12]. 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 bio insecticide that is environmental friendly and do not have any side effect effects on plants and soil [13].

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 the chemical compositions, medicinal values and other applications of neem tree [14,15] (Table 1).

LITERATURE REVIEW

Traditional uses

In many parts of the world, the herbal remedies from medicinal plants are used traditionally, but their access to formal healthcare is limited. World Health Organization (WHO) has estimated that as many as 80% of world's population rely on herbal traditional medicines as their primary health care. This means that the use of natural products as medicine has been widely practiced through folklore from ancient time in world up to now [16,17]. Over 3000 years the neem tree is well known in India and its neighboring countries. It was one of the most versatile medicinal plants having a wide spectrum of biological activities and the following are the commonly used forms of the plant in more than 50 countries. The tree parts are used against various human ailments as traditional medicine for household remedy [18]. This tree was usually used as natural pesticide, planting and afforestation as shade trees and to protect against erosion, and definitely as medicinal plants [19].

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TABLE 1 Chemical constituents of different parts of neem source Chemical formula Parts of neem Chemical constituents Glucoside of quercetin C₂₁H₂₀O₁₂ Glucoside of kaemferol C21H20O11 Quercetin C15H107 Quercetin-3-C₂₁H₂₀O₁₂ galactoside(Hperin) C₂₇H₃₀O₁₆ Rutin Isorhamnetin C₁₆H₁₂O₇ Rhamnoside of quercetin C21H20O11 C₂₁H₂₀O₁₁ Quercitin Leaves Nimbolide C27H30O7 Vilasinin C26H36O5 Nimbinene C28H34O7 $C_{26}H_{32}O_{6}$ 6-deacetyl nimbinene Nimbolide Nimocinol(6a-hydroxy-C28H36O5 azadirone) β-sitosterol C29H50O β-sitosterol-β-D-glucoside $C_{35}H_{60}O_{6}$ Neem leaf glycoprotein _____ Sugiol C20H28O2 Nimbiol C₁₈H₂₄O₂ Nimbin C₃₀H₃₆O₉ Trunk Nimbinin C28H34O6 Nimbolin a C39H46O8 Nimbolin b C39H46O10 sugiol $C_{20}H_{28}O_{2}$ Nimbiol C18H24O2 Nimbin C₃₀H₃₆O₉ Nimbinin C28H34O6 DeacetyInimbin C28H34O8 Bark Nimbinene C28H34O7 6-deacetyl nimbinene C26H32O6 Nimbolide C27H3007 Sugiol $C_{20}H_{28}O_{2}$ Nimbiol C₁₈H₂₄O₂ Kaemferol C₁₅H₁₀O₆ Quercetin C₁₅H₁₀O₇ Myricetin C15H108 Melicitrin C20H18O12 Quercetin-3-Blossoms C21H20O12 galactoside(hperin) Kaemferol-3-C21H20O11 glucoside(astragalin) β-sitosterol-β-D-glucoside C35H60O6 β-sitosterol C29H50 Nimbin C₃₀H₃₆O₉ Nimbinin $C_{28}H_{34}O_{6}$ Nimbidic acid(salannic C26H34O7 acid) Oil Salannin C₂₀H₅₀O

Meliantriol

Azadirone

C29H50O

C29H50O

Fruit	5-hydroxy-methyl furfural	$C_{28}H_{34}O_{6}$
	Nomolin	$C_{28}H_{36}O_{6}$
	Nimolicin	C ₂₈ H ₃₄ O ₅
	17-Hydroxy-azadiradione	$C_{28}H_{34}O_{6}$
	17β-Hydroxy- azadiradione	$C_{28}H_{34}O_{6}$
	17-Epi-azadiradione	C ₂₈ H ₃₄ O ₅

Azadirachta indica is a very useful traditional medicinal plant in the African subcontinent. Each part of the tree has some medicinal properties which can be used to treat several of diseases [20]. The plant is widely cultivated in Nigeria as a decorative and medicinal plant. However, it is quite native to Asia, but has now naturalized in West Africa. It is used extensively in Nigeria for the traditional treatment of malaria and other associated conditions in form of consumption with unspecified quantities without due regards to its toxicological and other adverse effects. This way of consumption is termed as decortion [21].

Based on this traditional and other uses of Azadirachta indica, a lot of studies was conducted to ascertain its potentially pharmacologically active components and pharmacological activities [22,23]. Pakistan as most developing countries has a valuable heritage of herbal remedies [24]. Its rural population still depends on the indigenous system of medicine to a great extent that is because herbal medicines have the advantages of being readily available and economical. In addition, the local practitioners claim that these remedies frequently have fewer side effects. Therefore, because some of herbal drugs are commonly used by traditional practitioners, it was considered to be of interest to evaluate and determine the efficacy of for their antipyretic effects [25]. Besides its therapeutic efficacies, neem has already established its potential as a source of naturally occurring pesticide, insecticide, and agrochemicals as it showed oviposition deterrence, antifeedant effect on larvae, and toxicity to eggs and larvae of the beet armyworm [26].

In India, the Neem tree twigs are commonly used to scrub teeth. Moreover, the neem tree branches are used as one of the most effective forms of dental care in traditional medicines; even though, it seems a little bit unpleasant for the users [27]. Interestingly, the neem trees are an excellent alternative for modern tooth care products. Besides, the leaves of the neem tree are also used as natural treatment for acne sufferers [28]. Similarly, treatment of infected eyes can be carried by the use of neem leaves. A similar infusion can also be used in the treatment of sore throats.

All parts of neem trees including leaves, seeds, roots, bark and the flowers of the plant are used to cure different ailments, such as stomach ulcers, jaundice and to overcome a variety of infectious and parasitic diseases, ranging from leprosy, chicken pox, and malaria. Infusions and teas made from leaves are used to alleviate malaria attacks, intestinal complaints, treat dental, headache, stimulating the appetite, heartburn and as insects repellent, in addition to that it was also used as a diuretic and for diabetes, also other febrile illnesses as well as to treat numerous skin diseases [29]. The use of aqueous extracts from seeds to treat head lice is widely known. Neem oil showed good antiseptic properties. It is applied in the treatment of such skin complaints as furuncles and eczema, as well as to relieve intestinal worm infections. Apart from that, neem-based products from *Azadirachta indica* are traditionally used for pest control in agriculture and gardening since long in India.

Almost all parts of the neem tree have been used as traditional Ayurvedic, unani and sidhha medicine in India. Neem oil, bark and leaf extracts have been therapeutically used as folk medicine to control leprosy, intestinal helminthiasis, respiratory disorders, constipation, and blood purifier and also as a general health tonic. It also used for the treatment of rheumatism, chronic syphilitic sores and indolent ulcer. Bark, leaf, root, flower and fruit together cure blood morbidity, biliary afflictions, itching, skin ulcers, burning sensations and pthysis. Neem contained various compounds which showed various biological activities such as anti-inflammatory; Antiarthritic; Antipyretic; Hypoglycaemic; Antigastric ulcer; Spermicidal; Antifungal; Antibacterial; Diuretic; Antimalarial; Antitumour; Immunomodulatory etc [30] (Table 2).

TABLE 2
Pharmacological activity of various parts of Neem source

Leaves bili Barks Analgesic, a Flowers Bile suppression, elim Piles intestinal worm	epistaxis, intestinal worms, anorexia, ousness, skin ulcer
Barks Analgesic, a Flowers Bile suppression, elim Piles intestinal worm	
Flowers Bile suppression, elim	
Piles intestinal worm	Iternative and curative fever
– Piles, intestinal worm	nation of intestinal worms and phlegm
	s, urinary disorder, epistaxis, phlegm,
Fruits eye problem,	diabetes, wounds and leprosy
Twings Cough, asthma, pile	s, phantom tumor, intestinal worms,
spermatorrhoea, c	bstinate urinary disorder, diabetes
Gum Scabies, wo	ounds, ulcers, skin diseases
Seeds Lepros	y and intestinal worms
Oil Lepros	

Beneficial effects of neem oil

Insecticidal activity: The insecticidal activity of phytochemical against mosquito larvae has been well documented although no commercial products based on phytochemical are currently being used in mosquito control programmes to our knowledge. One of the most extensively used "natural" plant derived insecticides is neem, extracted from the plant *Azadirachta indica* [31]. The neem oil extract had a toxic effect against Anopheles stephensi. aegypti larvae with median lethal concentrations (LC50) of 1.6, 1.8 and 1.7 ppm respectively. Recently, entomopathogenic fungi have been formulated in neem oil and tested against larval and adult. The results showed that the formulation of fungusand neem was more effective than neem alone for adults and larvae [32]. The "formulation" of fungus in water was not as effective as fungus formulated in neem oil against adults, although larvae were not exposed to formulations of fungus without neem.

Antibacterial activity: This study has proven that the neem oil at lower concentrations can be used as an effective antibacterial agent for the treatment of pathogenic bacteria infections without any toxicity to the human system. The *in vitro* toxicity study on the immune cells is essential to assess the effects of the nanomaterial at the cellular level [33]. The lymphocytes are immune cells that protect the humans against infections by humoral and cellmediated immunity. The human lymphocytes are the most commonly used system to study the cytotoxicity and genotoxicity of the neem extracts prepared for therapeutic applications.

Anti-fungal activity: Like antibacterial and antimalarial properties of neem, the antifungal properties are also given great importance in the field of science. *Azadirachta indica* (Neem) leaf extract was taken to test its 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. It has been a lifesaver [34].

Reproductive effects of neem oil: Male anti fertility activity of neem leaf extract was studied in mice, rats, rabbits and guinea pigs by daily oral feeding of a cold-water extract of fresh green neem leaves. There was no inhibition of spermatogenesis. During this period there was no decrease in body weight and no other manifestation of toxicity observed. There was a marked decrease in the mortality of spermatozoa. The infertility in rats was not associated with loss of libido or with impotence and the animals' maintained normal mating behavior. The male anti fertility activity was reversible in 4 to 6 weeks. Neem oil also shows reversible male anti fertility activity in mice without inhibition of spermatogenesis. Thus it does not have any harmful effects on reproductive system [35,36].

Mosquito repellent activity: Neem Seed oil extracted from *Azadirachta indica* plant and formulated in Vanishing cream base was evaluated for repellent action against Anopheles gambiae. *Azadirachta indica* belongs to family meliaceae [37]. Many mosquito-borne diseases, such as malaria, dengue fever (DF), dengue hemorrahagic fever (DHF) and filariasis is some of the serious problems all over the tropical regions. Although the most common mosquito repellent currently available on the market, deet (N,N-diethyl-3-methylbenzamide) has shown excellent protection from mosquito bites and other biting insects there were reports of toxicity problems after application of deet, range from mild effects such as in skin diseases.

Neem oil on tumor cells: Cancer cells are characterized by a number of hallmarks, including excessive cell growth, reprogramming of energy metabolism that supports the uncontrolled proliferation, immortality, resistance to cell death, induction of angiogenesis, the ability to invade and metastasize to distant sites, and suppression of immune response against tumor cells. Preclinical studies have shown compelling evidence suggesting that the anticancer effects of neem are mediated through modulation of multiple cellular processes. Neem components inhibit proliferation, induce apoptosis and other forms of cell death, and reduce cellular oxidative stress. Tumor microenvironment plays an essential role in angiogenesis and metastasis. Tumor cells possess the ability to modulate their surrounding environment (or microenvironment), which stimulates inflammation, facilitates cell invasion, and induces angiogenesis. Neem extracts are prepared using a variety of different solvents including ether, petrol ether, ethyl acetate, and diluted alcohol. Therefore, the spectrum of bioactive components and the percentage of individual components in the extract vary depending on the process of extraction.

Neem and cancer: Currently, studies on effect of administration of neem solutions on cancer, diabetes, heart disease and AIDS are being carried out. Anticarcinogenic activity of neem leaf extract was observed in murine system [38]. Injection of neem leaf preparation to tumor in mice reduced tumour growth, exhibiting anticarcinogenic activity [39]. Induction of apoptosis in rat oocytes was seen when treated with neem leaf extract [40]. Buccal pouch carcinogenesis in hamsters was inhibited by ethanolic leaf extract of neem [41]. The ethanolic leaf extract of neem also caused cell death of prostate cancer cells (PC-3) by inducing apoptosis [42].

Wound healing activity: 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 [43].

DISCUSSION

Other uses of neem tree

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 [44]. 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 [45].

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 [46]. 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 [47].

Neem as animal nutrition: The processed Neem cake poses a good appetizer characteristic together with wormicidal activity which is used as poultry feed. Futhermore, Neem leaves has a significant amount of protein, minerals (except Zinc) and digestable amounts of crude protein(CP) and total digestible proteins(TDP) which serves a better nutrition to the animals such as goat, sheep and cow. Despite its bitter components, livestock consume diets containing varied percentage of neem cake. Alkali treatment of this byproduct with caustic soda (10-20 g sodium hydroxide) yields palatable products by removing the toxicant triterpenoids. After treatment it is incorporated into poultry feed [48].

Neem in agriculture: 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

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the ecosystem. In addition, synthetic pesticide usage has resulted in development of resistant pests. Cost-effective, nontoxic, biodegradable, ecofriendly and botanical 'soft-pesticides' are the need of present day agriculture as an alternative to hazardous and recalcitrant synthetic pesticides [49].

Neem is one of soft pesticide used as a bio control agent to control many plant diseases [50]. 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 [51]. 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 bio insecticide 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 [52]. 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 [53].

Neem in industry: 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 [54]. A new shampoo, based on seed extract of neem was highly effective, more than permethrin based product, against head lice under in vitro conditions [55]. 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 [56]. 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 [57].

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 [58]. 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 [59].

In Ethiopia, wogert (Silenemacroserene), kebericho (Echinopsk ebericho), tinjut (Ostostegiaintegrifolia), and woira (Oleaeuropaea) and Neem have been shown to have repellent effects against Anopheles arabiensis under laboratory conditions [60]. Dry Ethiopian neem seed (A.indica A. Juss) were provided from Dire Dawa nursery center, 160 km east of Jigjiga. To obtain neem oil, its seeds were crashed using the kornetvegetable machine [61]. 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 [62].

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 asanti 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. However, neem products are not risk free. Adverse effects of neem components were noted in non-target 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 [63].

CONCLUSION

It is heartening to see that a traditional Indian plant medicine has now led to several therapeutically and industrially useful preparations and compounds, which generates enough encouragement among the scientists in exploring more information about this medicinal plant. As the global scenario is now changing towards the use of nontoxic plant products having traditional medicinal use, development of modem drugs from neem should be emphasized for the control of various diseases. In fact, time has come to make good use of centuries-old knowledge on neem through modern approaches of drug development. For the last few years, there has been an increasing trend and awareness in neem research. Quite a significant amount of research has already been carried out during the past few decades in exploring the chemistry of different parts of neem. An extensive research and development work should be undertaken on neem and its products for their better economic and therapeutic utilization.

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