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(REVIEW ARTICLE)

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Study the phytochemical, Biological and pharmacological aspects of *Azadirachta indica*: A review

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Abstract

Neem (*Azadirachta indica*) is a fast-growing tropical evergreen plant that belongs to the Meliaceae family. Its compounds have been shown to be effective against illnesses and insect pests that are significant economic concerns. The plant's whole body has biopesticidal properties, especially in the form of extracts from the leaves, bark, and roots. Every part of the plant has been utilized medicinally and is now considered a treasure in contemporary medicine. Salannin, quercetin, nimbolinin, nimbin, nimbidin, nimbidol, and azadirachtin are among the beneficial active compounds that have been isolated from several plant sections. This review article's primary goal is to provide information on a range of pharmacological activities, including anti-inflammatory, anti-cancer, anti-bacterial, antiviral, antifungal, antihelmethic, antidiabetic, wound-healing, and ulcer-preventing properties. activity hepatoprotective, Effects on Immunomodulation and Antinephrotoxicity.

Keywords: *Azadirachta indica*; Neem; Diabetes; Anti-bacterial; Obesity.

1. Introduction

Azadirachta indica is also referred to as the margosa tree or Indian neem. Since ancient times, it has been widely utilized in homoeopathic, unani, and ayurvedic treatment. A state of "good health" is denoted in Sanskrit as "Nimba" [1], which eventually led to the word "Neem." The tree is also known as "Sarvaroga nivarini," which means "cure all ailments." Neem is referred to as "Arishtha" in Ayurveda, which means "reliever of sickness." Due to its therapeutic qualities, the tree is still referred to as a "Divine tree" or "village pharmacy" [2]. It is estimated that over 80% of people in poor nations rely on medicinal plants to treat a variety of illnesses or ailments [3]. One of the native medicinal plants of India, neem has therapeutic qualities in all parts of the plant, including the bark, leaves, fruit pulp, roots, seeds, and flowers [4]. One example of supplementary medicine using phytotherapy is neem [5]. Every part of the plant has been utilized medicinally and is now considered a treasure in contemporary medicine. Neem is widely recognized for its therapeutic benefits, including its cool, bitter, astringent, and caustic bark. Furthermore, it is utilized to treat worm infestation, fatigue, fever, coughing, and loss of appetite. In addition, it cures wounds and vitiated ailments such as diabetes, emesis, skin disorders, and excessive thirst. Chemicals found in leaves along the bark have been shown to be beneficial for treating eye conditions and insect poison. It functions as an anti-leprotic and cures Vatik disease. Its fruits are anthelminthic, bitter, purgative, and antihemorrhoidal. This paper highlights the neem tree's numerous therapeutic applications, pharmacological actions, biological activities, and the chemistry of its constituents in light of its enormous usefulness.

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2. Taxonomy

Currently, neem trees are successfully flourishing in over 72 countries across the globe, including North, Central, and South America, Asia, Africa, and Australia [6]. Neem belongs to the family Meliaceae. Taxonomic position of neem is as under:

Order: Rutales

Suborder: Rutinae

Family: Meliaceae

Subfamily: Melioideae

Tribe: Melieae

Genus: Azadirachta

Species: indica [7-8]

2.1. Botanical description

Aziuliruchla indica belongs to the Meliaceae family. With a trunk girth of 2.5 meters and a height of /U) meters, this broad-leaved evergreen tree has a lifespan of more than two centuries. Although its deep root system is highly sensitive to water logging, it is well adapted to extracting nutrients and water from the soil profile. Neem trees grow best in hot, dry regions with annual rainfall ranging from 400 to 1.200 mm and shade temperatures that frequently approach 5°C. The tree is resistant to numerous environmental stresses, including as drought and soils that are infertile, rocky, shallow, or acidic. Neem develops ellipsoidal drupes on axillary clusters that measure approximately two centimeters in length. High amounts of secondary metabolites are seen in the kernels of these fruits [9]. Its many flowering panicles are mostly found in the axils of the leaves. The selel have ovoid, about centimeter-long petals that smell deliciously of white oblanceolate. It produces golden, ellipsoid, glabrous drupes that are 12–20 mm long. The green fruits eventually turn yellow as they ripen and have a strong, garlic-like smell. In March and April, flowers and new foliage appear. Fruits ripen between April and August, depending on the location [10].

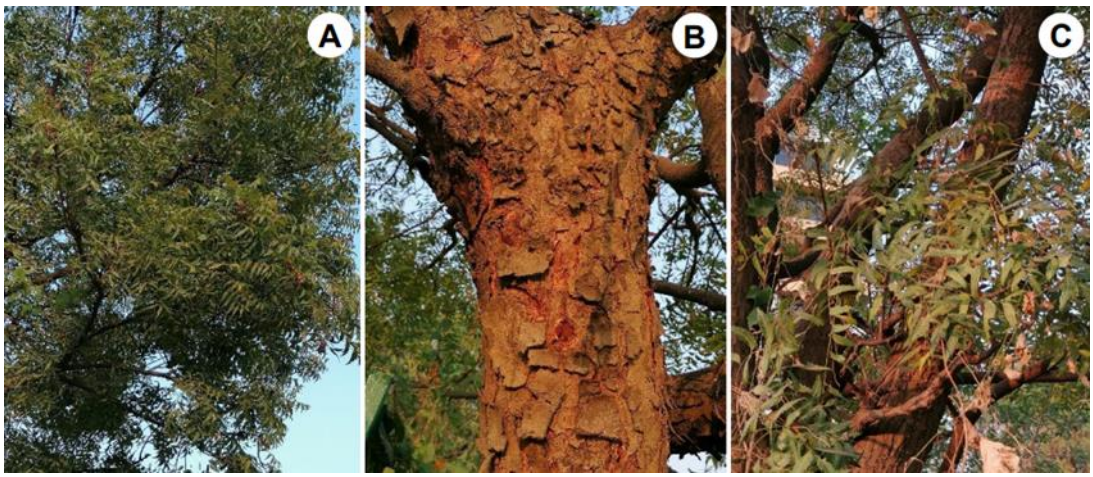

Figure 1 *Azadirachta indica A*. Juss: A, Habit; B, Bark; C, Leaves [8].

3. Neem chemistry

Neem seed kernels are the most effective source of the compounds with pesticidal activity. Neem trees don't reach complete reproductive maturity until they are ten years old, although they do start the reproductive process at three or five years of age. After this, the tree produces up to 50 kilos of fruit year, with an average of 20.5 kilograms produced annually. The seed kernels account for just around ten percent of the fruit output, and the desired physiologically active

chemicals are only ten grams per kilogram of kernel weight. Accordingly, a mature neem tree's seasonal production of pesticidal chemicals is limited to around 20 grams [11–13].

4. Secondary metabolites

Neem leaves include a variety of biologically active chemicals, such as triterpenoids, phenolic compounds, carotenoids, steroids, and ketones. Due to its biological action against a variety of insects and relative abundance in neem kernels, the tetranortriterpenoid azadirachtin has drawn the greatest attention as a pesticide. In reality, azadirachtin is a blend of seven isomeric compounds, designated as azadirachtin-A through azadirachtin-G, with azadirachtin-A being the most abundant and azadirachtin-E being thought to be the most potent regulator of insect growth [14–16]. Numerous additional chemicals have been identified and have been shown to exhibit both growth-regulating and antecedent activity in insects. About 24 molecules with at least some biological activity are obtained from polar and non-polar extractions, aside from azadirachtin. The likelihood of tolerance or resistance emerging in any of the impacted species is greatly decreased by this concoction of substances. Nevertheless, research has demonstrated that just four neem compounds—azadirachtin, salannin, melianlriol, and nimbin—are extremely efficient as insecticides [17–19]. Higher quantities of azadirachtin (fig. 1) may be present owing to genetic or environmental factors, fruit developmental stage, or even seed storage duration [20]. These concentrations might range from 10 to 25 percent. Following the isolation of Nimbin (fig. 2) as the first bitter compound from neem oil, over 135 compounds have been isolated from various neem parts. Several articles have also been published on the chemical composition and diversity of structure of these compounds, which are classified into two main classes. [21].

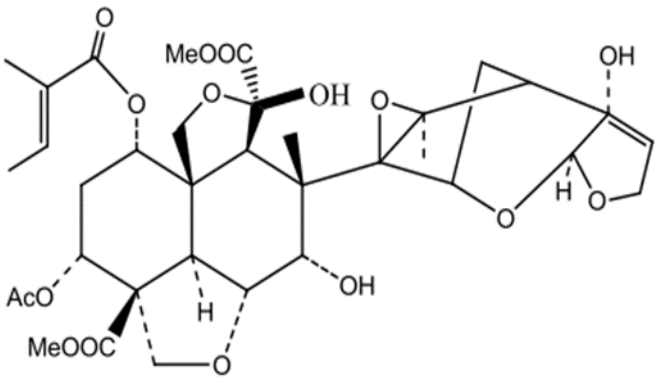

Figure 2 the structure of azadirachtin compound [20].

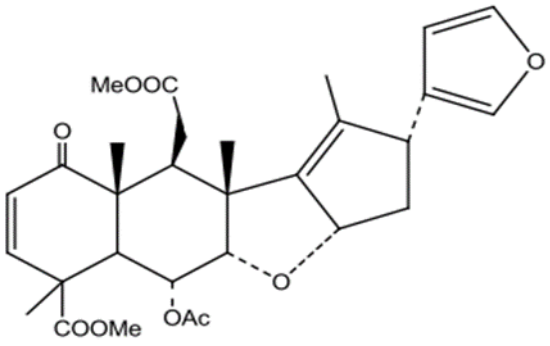

Figure 3 the structure of nimbin compound [20].

5. Medical and pharmaceutical activities

The neem plant has many medical and pharmaceutical uses in developing and developed countries because of its various biological active substances.

5.1. High blood pressure

An important component of MetS is elevated blood pressure (BP). Effects of many herbs, including Capsicum annuum L. [23] and Aloe vera [22], were studied in relation to blood pressure Elevated blood pressure raises the risk of Cardiovascular diseases (CVDs). High blood pressure is caused by a number of methods, such as: (1) Calcium (Ca) channels, which are mediated by Ca2+ ion inflow via L-type channel, release calcium to cause vascular smooth muscle contraction. Two major factors that contribute to the production of high blood pressure are (1) calcium channels and (2) extracellular signal-regulated kinases. In order to control the contraction of vascular smooth muscle, extracellular signal-regulated kinases are crucial. Vasoconstriction and the development of vascular smooth muscle cells are both decreased when ERK 1 and 2 genes are down-regulated. Nitric oxide (NO) is a vasodilator that is created by the enzymes nitric oxide synthase (NOS). As a result, extracellular signal-regulated kinases are a target for the induction of high blood pressure [25]. (4) Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that regulates the expression of several antioxidant genes. NO levels are candidates for participation in high blood pressure [26]. Nrf2 regulates signaling pathway activity to reduce the production of reactive oxygen radicals (ROS). High blood pressure is generated by ROS production, which is driven by decreasing Nrf2 expression. Smooth muscle contraction and NO depletion are the processes by which ROS-induced increased blood pressure occurs [27]. Figure 4 presents the mechanisms that underlie neem's preventive action against high blood pressure.

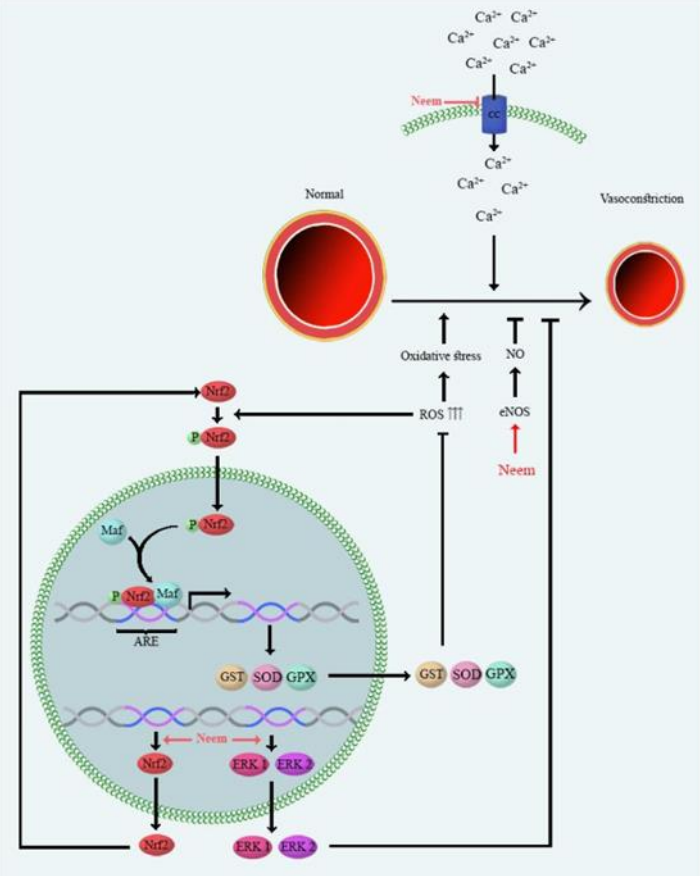

Figure 4 Neem mechanism effect on blood pressure [28].

5.2. Hyperlipidemia and neem

Hyperlipidemia is one of the most common elements of MetS. Numerous therapeutic plants, including rosemary (Rosmarinus officinalis) [30] and barberry (Berberis vulgaris) [29], have been shown to have beneficial effects on hyperlipidemia. Individuals with diabetes and obesity have elevated plasma lipid levels [31]. Due to the increased

oxidative stress caused by hyperlipidemia, endothelial dysfunction, atherosclerosis, and coronary heart disease (CHD) are all facilitated [32]. Plasma lipoproteins are shielded from oxidative stress by the antioxidant defense system, which includes SOD and GPx [33]. Oxidative damage to plasma lipoproteins is brought on by the increased production of reactive oxygen species (ROS) in stressful situations such as obesity and diabetes [34–35]. The levels of TG, low-density lipoprotein (LDL), and very-low-density lipoprotein (VLDL) in plasma rise as a result of lipoprotein oxidation [34]. The reference approach for determining the lipid profile is the measurement of serum triglyceride, total cholesterol, LDL, HDL, and cholesterol [36]. Numerous research works have demonstrated the benefits of neem in the treatment of hyperlipidemia. In streptozotocin (STZ)-diabetic mice, neem at different doses reduced blood lipid profile parameters levels while increasing serum HDL levels [37–42]. Additionally, the lipid profile of STZ-diabetic mice was corrected by two distinct dosages of neem [43–44]. In rats treated with alloxan (120 mg/kg, i.p.), neem decreased lipid profile parameters [45–47].

5.3. Diabetes and neem

In North America, neem is sold as a herbal combination supplement. Patients with type 2 diabetes (ages 18 to 70) who obtained therapy using this dietary supplement for three months saw improvements in their HbA1c levels and glucose management [48]. In the Kochhar study, 90 diabetic men between the ages of 40 and 60 had their neem's antidiabetic activity examined. For three months, subjects were given two grams of neem leaf powder every day. According to the study's findings, neem helps diabetic people with their sweating, headaches, and itching [49].

5.4. Obesity and neem

Overweight and obesity are major health issues that are spreading around the globe. Obesity is linked to a considerable rise in mortality and a decline in life expectancy [50]. A poor diet, age, genetics, stress, lack of sleep, alcohol use, inactivity, and inactivity are some of the risk factors for obesity [51]. Obesity-related consequences include diabetes, heart disease, hypertension, hyperlipidemia, and atherosclerosis [52]. The best treatment for controlling obesity can involve the use of inhibitors for two different types of obesity agents: lipase and α-glucosidase [53–54]. In an in vitro system, 520 µg/ml of an aqueous and methanolic extract of neem stem bark and roots inhibited pancreatic lipase and α-glucosidase [53]. However, rats given 500 mg/kg of neem leaf extract orally did not experience a decrease in body weight after 28 days of treatment [54].

5.5. Anti-cancer activity

The development and spread of cancer are influenced by changes in molecular and genetic pathways. An oncogene, sometimes referred to as a cancer-causing gene, is a mutant gene that is crucial to the development and spread of cancers. A study using 4T1 breast cancer BALB/c mice to examine the effect of leaf extract on the expression of the c-Myc oncogene revealed that the 500 mg kg-1 neem leaf extract (C500) group significantly inhibited c-Myc oncogene expression compared to the cancer control group [55]. Ascorbic acid, limonoids, flavonoids, terpenoids, and carotenes are just a few of the powerful antioxidants and anticarcinogens found in neem leaves. Because of their capacity to scavenge free radicals, the beta-carotene and vitamin C found in neem leaves have a major protective effect against the development of tumors. Neem contains a limonoid called limonin 17b-D-glucopyranoside, which has been shown to inhibit the development of oral carcinogenesis produced by DMBA. It has been demonstrated that the limonoid component of A. indica, azadirone 1, exhibits cytotoxic activity against cell lines of prostate, melanoma, and breast cancer. Researchers have examined azadirachtin A's cytotoxicity in human glioblastoma cell lines. Neem leaf cytotoxic components have been identified as nimbolide and 28-deoxonimbolide. Because of their ability to scavenge radicals, the flavonoids quercetin and kaemferol, which are found in neem leaves, have been shown to suppress carcinogenesis both at the initiation and promotion stages of the process. The most research attention has been focused on quercetin, a neem bioflavonoid, as an anticancer medication. It is established that quercetin inhibits the growth of tumor cells in various malignant cell lines. Both in humans and in experimental animal models, quercetin has demonstrated antiproliferative effects. Additionally, quercetin has been demonstrated to increase the therapeutic efficacy of chemotherapeutic medications and radiation. 56].

5.6. Anti-inflammatory activity

According to a study, neem leaf extract significantly reduces inflammation, but not as much as dexamethasone. A well-known and highly potent anti-inflammatory steroid is dexamethasone [57]. Nimbidin inhibits the inflammatory responses of neutrophils and macrophages, according to the results of one investigation. Nimbidin administered orally suppressed phagocytosis and respiratory burst in macrophages in response to thioglycollate, as well as chemotaxis [58]. Many researchers came to the same conclusions. In a cotton pellet granuloma test, the water-soluble component of an alcoholic neem leaf extract at a dose of 200 mg kg-1 orally demonstrated a substantial anti-inflammatory impact and

significantly inhibited the biochemical mode of action on inflammation. Neem leaf extract's anti-inflammatory properties may be related to its capacity to stabilize lysosomal membranes and its anti-proliferative properties [59].

5.7. Anti-bacterial activity

The antibacterial activity of extracts from the bark, leaves, seeds, and fruit of *Azadirachta indica* was examined in a different study against bacteria isolated from adult mouths. The outcomes showed that all of the test microorganisms were susceptible to the bactericidal effects of bark and leaf extracts. Moreover, fruit and seed extracts showed bactericidal activity only at higher dosages [60]. In a study using sodium hypochlorite as the standard irrigant, the antibacterial efficiency of herbal alternatives as endodontic irrigant was assessed. The findings showed that leaf extracts showed zones of inhibition, indicating antimicrobial characteristics. In addition, compared to 3% sodium hypochlorite, leaf extracts blocked a lot more zones [61]. Neem leaf, seed, and bark extracts exhibit antibacterial action against a variety of Gram-positive and Gram-negative pathogens, such as Vibrio cholera, Mycobacterium, and Klebsiella pneumoniae [62].

5.8. Antiviral activity

Neem bark extract (NBE), at concentrations between 50 and 100 g ml -1, significantly reduced HSV-1 entry into cells. Furthermore, the inhibitory activity of the NBE extract when preincubated with the virus instead of the target cells was shown to have a direct anti-HSV-1 effect, indicating that neem bark has this potential [63]. In addition to interfering at an early stage in the coxsackievirus virus B-4's reproductive cycle, neem leaf extract has shown virucidal action against the virus, as evidenced by virus inactivation and yield reduction experiments [64].

5.9. Antifungal activity

Studies were conducted to assess the effectiveness of several neem leaf extracts on the seed-borne fungi Aspergillus and Rhizopus. The findings showed that the development of both fungal species was considerably suppressed and regulated by the alcoholic and water extracts. Moreover, alcoholic neem leaf extract was more effective than aqueous extract in suppressing the growth of both fungal species. Neem cake aqueous extracts were discovered in another investigation to exhibit antibacterial activity against three sporulating fungus, namely Colletotrichum gloeosporioides f. sp. Mangiferae, Curvularia lunata, and Helminthosporium pennisetti [65]. The investigation's findings demonstrated that Cladosporium sp., Alternaria solani, and Aspergillus flavus were reduced in growth by methanol and ethanol extracts of *Azadirachta indica* [66]. In a study against Alternaria solani Sorauer, the antifungal activity of *Azadirachta indica* L. was examined. It was found that the ethyl acetate fraction, with a MIC of 0.19 mg, was the most effective in preventing fungal growth. Additionally, it outperformed the fungicide (metalaxyl + mancozeb), which has a MIC of 0.78 mg [67].

6. Conclusion

The traditional, pharmacological, and commercial significance of *Azadirachta indica* is highlighted in this article. Native to India, neem trees are members of the Meliaceae family. Neem is a multipurpose medicinal plant that has several uses. Antioxidant activity, anti-inflammatory, anti-bacterial, anti-cancer, antiviral, antifungal, antidiabetic, wound-healing, ulcer-preventing, and oral protection Among the documented actions are those that are contraceptive, hepatoprotective, immune-modulatory and growth-promoting, antinephrotoxic, and have an effect on snake venom.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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