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Azadirachta indica (neem): An important medicinal plant: A literature review of its chemistry, biological activities, role in COVID-19 management and economic importance

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Abstract
Medicinal plants have been a crucial component in the fight against disease in human culture since the dawn of civilization. *Azadirachta Indica*, also referred to as *Melia azedarach*, A. juss, has thrived. It has been used in Ayurvedic medicine for more than 4000 years due to its medicinal properties. Numerous phytoconstituents, including nimbin, salanin, meliacin, azdirachtin, gallic acid, quercetin, gedunin, and catechin, are present in *Azadirachta Indica*. Each category of phytoconstituents offers us a unique chemical that is used to treat a variety of illnesses, including bacterial infections, malaria, cancer, intestinal worms, asthma, skin ulcers, diabetes, allergies, and much more. Recent research has also shown that it has management potential for the COVID-19 virus. *Azadirachta Indica* is commercially significant and is used in a variety of fields of agriculture, agroforestry, reforestation, post-harvest food packaging, environmental protection, and biodiesel production. This has shown its value as a medicinal plant.

Keywords: *Azadirachta indica*, phytoconstituents, biological activity, chemistry, Covid-19, economy

Introduction
Since the beginning of civilization, medicinal plants have been an integral element of human society in the fight against disease. *Melia azedarach*, also known as *Azadirachta Indica A. Juss*, is doing well [1]. Because of therapeutic values, Neem has been use for over 4000 years for Ayurvedic medicine. In Sanskrit, neem is referred to as "arista," which means "perfect, complete, and imperishable." The majority of plant components, including fruits, seeds, leaves, bark, and roots, include substances with documented usage as antiseptics, antivirals, antipyretics, anti-inflammatory agents, ulcer-healing agents, and antifungals [2]. In the middle of the twentieth century, substantial chemical research on neem tree products was conducted, since Siddiqui's initial report [3]. More than 135 compounds have been discovered since 1942, when nimbin, the first bitter chemical isolated from neem oil, was discovered and separated from various neem components, and several reviews on the chemistry have also been published considering the variety of these compounds' structural compositions [4]. The importance of Neem tree has long been acknowledged by the US National Academy of Science in 1992 in a paper titled "Neem - a tree for solving global problems". Neem research has advanced, as previously reported [5]. Alkaloids, lavonoids, triterpenoids, phenolic compounds, carotenoids, steroids, and ketones are among the chemical components of neem that can be extracted. However, the biologically most active compound is azadirachtin, which is a mixture of seven isomeric compounds known as azadirachtin A-G and azadirachtin E is more effective [6]. Other compounds which are found in Neem that have a biological activity are volatile oils, Salanin Nimbin and meliantriol [7]. The active components are soluble in organic solvents including hydrocarbons, alcohols, and other alcohols but are mostly lipophilic and only weakly hydrophilic [8]. The tree (Neem) was seen as being so valuable and wonderful that it played a significant role in the environment of the Indian people. Since the time of the Vedic civilization, neem has been used therapeutically in many different ways in India. Almost all tree parts, including the stem, bark, roots, leaves, gum, seeds, fruits, and flowers, have been used as traditional medicines for domestic cures for a variety of illnesses since ancient times [9].

In Ayurveda, Siddha, Unani, and other regional health systems, neem is used in over 700 herbal formulations. Neem is also a key ingredient in over 160 regional practices that use neem to treat human illnesses or diseases [10]. We focused on phytoconstituents of *Azadirachta indica*, its Biological activities and Chemistry. We also discussed about its benefits in the treatment of numerous ailments such are cancer, diabetes, allergy, fungal and bacterial infection, etc. and Role of *Azadirachta indica* in COVID-19 management. In Last, we focused on the role of *Azadirachta indica* in Economy. The neem tree got its name as A. indica as early as 1830 by De Jussieu [11].

Morphology of neem tree: The tree only requires a small amount of water and plenty of sunlight. It can thrive in a wide range of temperatures (0 to 49 °C). The range of pH needed by the neem tree for growth is 4 to 10 and because of its special calcium mining ability, it can also neutralize acidic soils [12]. Neem probably originates from the Indian subcontinent and arid regions of South Asia. Neem tree belong to the family Meliaceae. The word "Azadirachta" is derived from the Persian word "azaddhirakt," which means "Noble tree" [13].

Fig 1: Showing neem tree leaves, barks, stem and twigs

Traditional uses of neem tree

Neem trees and its various parts have been employed in Indian traditional Ayurvedic treatment for centuries [14]. Neem oil, bark extracts, and leaf extracts have long been used in traditional medicine to treat intestinal helminthiasis, control leprosy, respiratory disorders, constipation, blood morbidity, rheumatism, biliary infections, skin ulcers itching, and many other conditions [15]. However other than traditional uses, there is scientifically proven evidence that demonstrated the biological activities of Neem constituents.

Table 1: Medicinal benefits of its different parts

Parts	Medicinal Benefits
Gum	Effective against skin diseases like ringworms, scabies, wounds, etc.
Root, Bark, Leaves, Flowers, and Fruits together	Skin Ulcer, Burning Sensation, Itching, Blood Morbidity, Billiary Affliction and Leprosy
Twig	Relieves Asthma, Piles, Urinary Disorder, Eye Problems, Diabetes, and Analgesic
Oil	Intestinal Worms and Leprosy
Seed Pulp	Intestinal Worms and Leprosy
Leaf	Anorexia, Intestinal Worm, Skin Ulcer
Flower	Bile Suppression, Elimination of Intestinal Worm and Phlegm

Phytochemicals present in neem plant: Numerous studies have shown that the Neem tree contains several constituents that have medicinal benefits and have long been used to cure many ailments. In this section, we shall discuss some of them. The biologically active ingredients extracted from Neem include: Azadirachtin, nimbin, nimbolicin, salanin, quercetin, sisterol, vallasin, gallic acid, catechin, meliacin, gedunin meliacin forms the bitter principles of Neem oil, the seed also contains tignic acid responsible for the distinctive odour of the oil [16]. The compounds can be divided into two main categories: isoprenoids (such as diterpenoids and triterpenoids containing protomeliacins, limonoids, azadirone, and its derivatives, gedunin and its derivatives, vilasinin-type compounds, and C-seco- meliacins such as nimbin, salanin, and azadirachtin, and non-isoprenoids such as flavonioids and their glycoside, protein, amino acid, carbohydrate, a sulfur compound, polyphenolics, etc. [17]. In this section, Special emphasis is given to the chemistry/biological activities of the following phytoconstituents phytochemicals: Azadirachtin, Quercetin, and Gallic acid.

Azadirachtin

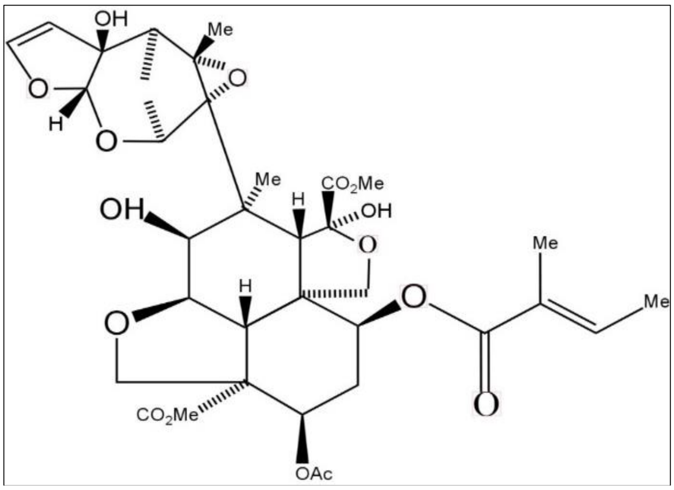

Fig 2: Structure of Azadirachtin

To obtain Azadirachtin, neem seeds are extracted utilizing a variety of fractionations and the appropriate solvents. The outcome of this process is a microcrystalline powder with a molecular weight of 720.71 g mol-1, a melting point of 154–158 °C, and a maximum UV absorption wavelength of 217 nm [18]. Although *Azadirachta Indica*'s chemical composition was first described in 1976, the suggested structure still needed to be validated. The expected chemical structure of azadirachtin was confirmed and identified using NMR and X-ray crystallographic research [19, 22]. The antifeedant action stands out as the most significant of the several qualities ascribed to this molecule, which may help to explain why it is so frequently used as an insecticide. However, this molecule has also been linked to other biological activities, such as its antimicrobial, notably antimalarial, and anticancer properties. Azadirachtin has demonstrated promising results as a chemo-preventive medication. This activity is attributed to its ability to have anti-proliferative effects on proteins involved in the cell cycle, signal transduction, and apoptosis [23, 26].

Quercetin

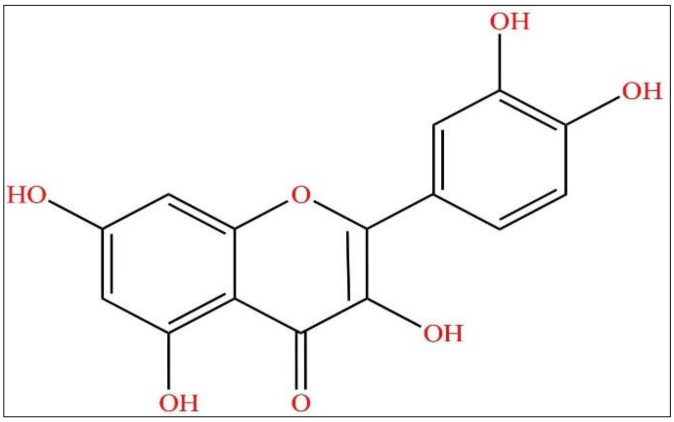

Fig 3: Molecular structure of Quercetin

Quercetin is a polyphenolic flavonoid with two benzene rings connected by a heterocyclic pyrone ring and a shared flavone nucleus. It is well-recognized to display a variety of biological functions. Flavopiridol, a medication now undergoing clinical testing, is primarily composed of its skeleton [27]. Flavonoids are among the phenolic substances found in food plants. These comprise flavonoids such as flavan-3-ols (i.e., catechins), flavan-3, 4-diols (i.e., quercetin, myricetin, and kaempferol), and condensed tannins, the procyanidins, which are catechin dimers in 4, 8 linkage. Phenolic acids are derivatives of cinnamic and benzoic acids. Glycosides are a common kind of flavonoids. For example, the aglycone quercetin is related to either rutinose (rutin) or rhamnose (quercetrin) as the 3-O-glycoside [28].
Szent-Gyorgyi first published his findings on the biological identification and separation of more than 4000 naturally occurring plant phenolics in 1936 [29]. One of these is quercetin. Regular dietary components are flavonoids [30]. Following this, it was also believed that flavonoids had additional clinically significant functions, including antihypertensive and antiarrhythmic activity, anti-inflammatory and antiallergenic properties, hypocholesterolemia activity, stabilization of platelets and mast cells, antihepatotoxic activity, and antifertility and antitumor activity [31]. Flavonoids have a lengthy evolutionary history in plant physiology. They have a history of responding to light and controlling auxin levels, which control plant development and differentiation [32]. Antifungal and bactericidal activities are two additional biological roles played by Neem plants [33, 35].

Gallic Acid

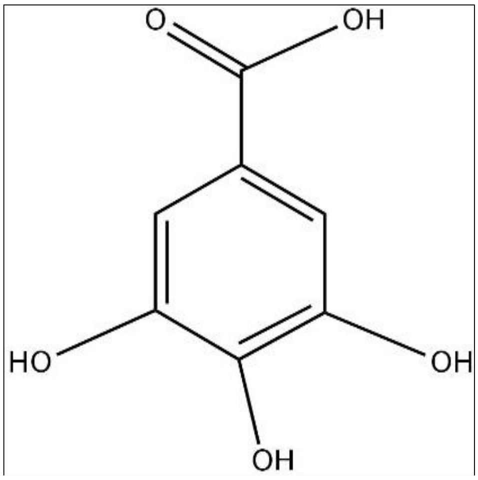

Fig 4: Structure of Gallic Acid

Carl Wilhelm Scheele first found Gallic acid (3, 4, 5-trihydroxicbenzoic acid), a well-known polyphenol as a sour-tasting, grey powder that effervesces in calcium carbonate solution, is readily soluble in ethanol, and colors litmus red. Today, it is widely accepted in many plants that a pure GA is a crystalline, colorless powder. In addition to being soluble in water, it can also be broken down by alcohol, ether, and glycerol. In petroleum ether, chloroform, and benzene, it is essentially insoluble [36]. It is selectively cytotoxic against a range of tumor cells. Endogenous plant polyphenol known as gallic acid can be found in large quantities in wine, tea, grapes, berries, and other fruits [37]. Gallic acid has strong antioxidant [38], anti-inflammatory [39], antimutagenic [40], and anticancer effects [41]. Studies also have been validated the protective effect of gallic acid in chemical induced carcinogenesis [42].

Catechin

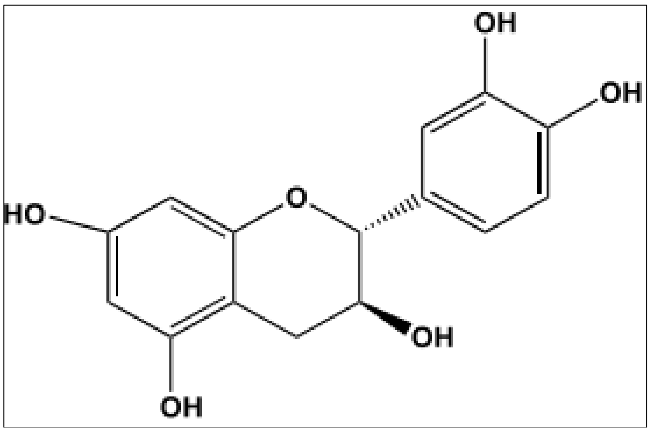

Fig 5: Molecular structure of Catechin

Catechin is a 3, 3', 4', 5, 7-pentahydroxyflavan having two steric forms of (+)-catechin and its enantiomer, its name is taken from catechu of the extract of *Acacia catechu* L. Additionally, Catechin serves as a general term for the chemical family name of the compounds that are formed from catechin. One of the richest sources of catechins is tea, which is made from the leaves and buds of the Camellia sinensis plant. Its main catechin, (-)-epigallocatechin-3-gallate (EGCG), has many positive effects on human health, including anticancer, anti-obesity, antidiabetic, cardiovascular diseases, anti-infectious, hepatoprotective, and neuroprotective effects. Although research with contradictory findings have also been reported, a number of human epidemiological and clinical investigations on tea have offered evidence for its anticancer properties. These findings have also been validated by cell-based and animal tests [43].

Recent findings on pharmacological action of neem
Neem in COVID-19 Management

The unique SARS-CoV-2 virus, also known as COVID-19, emerged in late 2019 and has since spread over the world, placing a significant load on health care systems in practically every nation on the planet [44]. The virus-caused illness COVID-19 rapidly spread from the first case that was discovered in Wuhan, China, on December 31, 2019, to the 364,191,494 confirmed cases and 5,631,457 fatalities that the World Health Organization (WHO) documented as of January 28, 2022 [45]. Seven coronavirus (CoV) strains have been identified so far, with SARS-CoV-2 being one of them [46]. It is a member of the same family as the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), known collectively as Beta-coronaviruses type Human Coronaviruses. Prior to the current outbreak, the SARS and MERS coronaviruses were the most dangerous types of CoVs, according to data from the WHO. In comparison to SARS, MERS has a fatality rate of 36% [47].

Mechanism of SARS-CoV-2 infection (COVID19)

The coronavirus is one of a large group of enclosed, non-segmented, positive (+) sense single stranded RNA viruses that are found in many different species, including camels, cats, dogs, and bats. Since the structure of these viruses closely resembles a crown or corona, they are referred to as coronaviruses. The coronaviruses cause diseases in both humans and animals. There are four known human coronavirus strains that can infect the upper respiratory tract and produce minor symptoms (OC43, NL63, HKU1, and 229E) [48]. While SARS-CoV and MERS are three human coronavirus strains that have been reported to infect the lower respiratory tract and cause pneumonia, which can be fatal, SARS-CoV-2 is a beta coronavirus with 79% genetic sequence similarity to SARS-CoV and 98% homology to RaTG13 coronaviruses found in chrysanthemum bats [49]. Furthermore, SARS-CoV and SARS-CoV-2 share a similar immunopathogenesis that results in the damage of airways [50]. The respiratory failure brought on by the ARDS syndrome, which develops in a small number of SARS-CoV-2 infections, is determined to be the main cause of death. Additionally, as immunological responses to viral infections build, the innate immune system's inflammatory cytokine production increases, resulting in the emergence of "Cytokine Storm Syndrome" (CSS) [51]. Uncontrollable inflammation brought on by this illness worsens multiple organ failure, which eventually results in death. We may thus conclude from these results that the host immune response contributes a lot in the development of disease and that viral infections are not entirely accountable for the destruction of airways. Additionally, it has been discovered that comorbidities and advanced age are connected to the disease's severity [52]. The first step in COVID-19's pathogenesis is the virus's binding to host cells in the lungs, including as airway epithelial cells, endothelial cells, alveolar macrophages, and alveolar epithelial cells. These cells are all coronavirus susceptible because they all produce the target receptor Angiotensin Converting Enzyme 2 (ACE2) [53]. After infection, there is a drop in pulmonary ACE2 expression, and ACE2 loss could be the reason for the disease's increasing severity. It is generally accepted that ACE2 controls the Renin-Angiotensin System (RAS), which controls fluid and electrolyte levels as well as blood pressure. Individuals with SARS-CoV-2 infection have shown dysfunction of the RAS system. The corona virion is composed of four proteins, spike-S, envelop-E, membrane-M, and nucleocapsid-N, as well as a single-stranded RNA genome that spans 29,900 nucleotides. The SARS-CoV-2 spike (S) protein facilitates easier virus interface with target cells that express ACE2 on their surface. It is known that the serine protease TMPRSS2 functions as a priming factor for the S protein, which helps SARS-CoV-2 enter the host cell, in addition to ACE2 [54]. SARS-CoV-2 has spread widely, although the reason why has not yet been determined. The CendR motif (Arg-Arg-Ala-Arg) in the S1 polypeptide, which aids the virus in binding to host cells via the Neuropilin-1 (NRP1) receptor, is exposed when the host protease furin cleaves the full-length S glycoprotein into the polybasic S1 and S2 polypeptides. NRP-1 is expressed in a variety of human tissues, including the blood vessels, neurons, and respiratory system. Therefore, we can conclude that NRP is a second significant host receptor involved in SARS-CoV-2 infection and may be a target for COVID-19 treatment [55].

The most recent research suggests that malicinanhydride and other chemicals obtained from neem leaves may have COVID-19 inhibitory effects. Neem leaves lower blood sugar levels and block ACE2 receptors, which are necessary for the COVID-19 virus to enter the host cell [56]. Neem includes vitamins C, E, and K, which act as a natural immunomodulator. The membrane (M) and envelope (E) proteins on the COVID-19 virus are necessary for the virus's replication, and the Nimbolin A has the highest binding free energy to these M and E proteins, according to an in silico docking research. Therefore, we can finalize that neem is a source of potentially effective antiviral medications for the future [57]. Acute lung injury, pulmonary inflammation, and alveolar damage are among conditions that neem (*Azadirachta Indica*) may help treat. Neem contains the bioactive substances azadirachtin, nimbolinin, nimbolide, quercetin, and beta-sitosterol [58]. These are known to have antiviral, antioxidant, and anti-inflammatory activities. Another finding reveals that, Neem leaf extract (NLE) treatment significantly decreased neutrophil and macrophage infiltration into BAL fluid and avoided acute lung injury in an independent investigation employing a cigarette smoke (CS)-lipopolysaccharide (LPS)-induced pulmonary inflammation in mouse model [59].

Economic importance of neem plant
Neem in agriculture

Manure is any animal or plant material used as a fertiliser, particularly animal excrement, to increase the soil's fertility and so encourage the development of plants. Due to its environmental friendliness, neem manure is becoming more popular. These compounds also help to raise the soil's levels of nitrogen and phosphorus. It contains a lot of nitrogen, potassium, calcium, and other nutrients. Neem cake, which has no adverse effects on plants, soil, or other living things, is used to make high grade organic or natural manure.

Neem as fumigant and pesticide

The neem tree has been used to combat agriculture, storage, and domestic pests. The gaseous form of neem pest fumigant functions as both a pesticide and a disinfectant. Farmers and agriculturalists use it on a business basis in a significant number of nations. This entirely natural product is being exported since it is safe for the environment and is not poisonous. In developing countries, where a lot of deaths are reported to be caused by the unintentional ingestion of synthetic pest fumigants each year, fumigant obtained from neem gains more importance. Insecticides use in agriculture is very common since they played a greater role in pest management. In general, people are becoming more informed of the harmful effects that synthetic pesticides have on living things, including plants, soil, and other living things. As a result, there has been a clear transition away from synthetic pesticides to non-synthetic ones around the world. The increased demand for natural or herbal pesticides presents a huge opportunity for makers of neem insecticides to profit [60].

Neem as a biodiesel

Neem trees begin producing seeds that can be harvested in three to five years, reach peak output in ten years, and continue to do so up to the age of 150 to 200 years. Neem trees that are ripe may yield 30 to 50 kilograms of fruit annually. In India, there are reportedly close to 20 million neem trees. Indian neem trees have the capacity to produce 1 million tonnes of fruits and 0.1 million tonnes of kernels yearly, assuming a 10% kernel yield. From 40% to 60% of neem seeds are oil [61]. Neem oil output in India may reach 30,000 tons per year, using a conservative estimate of 30% oil content. Neem oil frequently has a color ranging from light to dark brown, a bitter flavor, and a strong scent. Along with triglycerides, terpenoids, which give food its bitter taste, make up a sizeable component of its basic constituents. Among the fatty acid profiles of seed oils of 75 plant species containing 30% or more fixed oil in their seed or kernel, neem *(Azadirachta Indica)* oil is one of the oils best suitable for use as biodiesel [62].

Neem in environmental protection

Neem is said to eliminate dangerous chemicals from the air and surroundings. In addition to keeping things cool, it is believed that the neem tree's shadow prevents the growth of several harmful diseases. In the sweltering heat, the temperature beneath the neem tree is around 10 C cooler than the surrounding air. It is one among the very few trees that can offer shade in areas when dryness is a problem [63].

Neem in post-harvest food packaging

Food preservation and packaging play a crucial role in safeguarding food products from the environment, and their main objective is to meet consumer and industrial demands by assuring food safety and reducing environmental impact. Active packaging, which contains natural antimicrobials and antioxidants, is a revolutionary technology that can extend the postharvest shelf life of perishable foods while also maintaining or enhancing the quality and safety of prepared food products. Neem oil can be used as a bioactive component to create novel and environmentally friendly food packaging, such as biodegradable, recyclable, non-toxic, and active films and coatings. Biopolymer-based coatings (such as chitosan, starch, or pectin) with additional neem oil are completely safe for both human health and the environment, in contrast to synthetic wax-based films or coatings [64].

Fig 6: Some neem insecticides available in the market

Conclusion

In this review study (*Azadirachta Indica*), the applications of *Azadirachta Indica* in terms of phytochemistry, pharmacology, and sustainability were covered. It is reasonable to suggest that they can be used safely and without risk for various disorders. Due to the abundance of flavonoids, as well as diterpenes, triterpenes, polyphenols, and many other compounds, *Azadirachta Indica* has a significant medicinal potential. The evidence suggests that *Azadirachta Indica* could become a marketable medication with the identification and separation of its active ingredients for the treatment of leprosy, intestinal helminthiasis, respiratory issues, constipation, blood morbidity, rheumatism, biliary infections, itching, skin ulcers, and a variety of other conditions. In COVID-19, it is also highly beneficial. In light of the fact that we discussed phytochemistry, pharmacology, and the sustained benefits of *Azadirachta Indica* in this review, it may be helpful for future research because it backs up the claims of numerous traditional systems of medicine.

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