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A review on recent biological and chemical worth of Neem (*Azadirachta indica* A. Juss)

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Abstract
Neem (*Azadirachta indica*), a useful multipurpose tree species, is a member of the Meliaceae family. Indians have revered Neem for millennia for its use in organic fertilizers, medicines, and pesticides, among other everyday necessities. Neem oil is used to treat worm infections, stomach ulcers and other conditions. Mulch and fertilizer made from Neem leaves and twigs have shown to be effective. Azadirachtin is a systemic insecticide that is extracted from Neem seed oil. Additionally, Neem trees have antibacterial, antiviral, anti-inflammatory, antifungal, and antiallergic properties. Biodiesel is also made from Neem seeds. Biodiesel is the alternative fuel that is most similar to diesel engines. Numerous compounds isolated from Neem have been shown to inhibit the SARS-CoV-2 (COVID-19) PLpro protein.

Keywords: Meliaceae, Azadirachtin, Biodiesel, SARS-CoV-2, PLpro protein, insecticide

Introduction
Azadirachta indica A. Juss, referred to as neem, is a significant fast-growing member of the Meliaceae family. The tree can grow in a wide range of soil types and climates. It is typically found in regions of Africa and South Asia. Up to 1500 meters above sea level, thorny, tropical, dry deciduous forests are inhabited to neem trees in India. It is a resilient, quickly growing tree that occasionally sheds its leaves in harsh situations like protracted drought seasons (Tiwari, 1992) [47]. It has been shown that a wide variety of components found in neem seeds affect biological activity. According to Kumar and Parmar (1996) [24], the neem kernel has a significant oil content of up to 52% w/w. This commercial neem oil's fatty acid content is primarily made up of oleic (58%), palmitic (14%) and stearic (15%) acids, with trace levels of myristic, arachidic, linoleic, and behenic acids. Sterols and triterpenoids (e.g. *azadirachtin, nimbin, salannin*) having insecticidal properties, produced by oil. These compounds are acknowledged as components with biological activity (Pandey *et al*., 2014) [35]. All parts of the Neem tree like flowers, leaves, seeds, fruits, roots, and bark have produced more than 140 compounds that have been identified for their antiulcer, anticancer, antimalarial, antifungal, antibacterial, antiviral, and anti-inflammatory properties (Sairam *et al*., 2000, Subapriya and Nagini, 2005) [38, 42]. Because of its systemic and transmembrane properties, neem oil exhibits a broad spectrum activity, making it useful against a wide variety of pests. It works as a repellant, inhibits feeding, lowers ecdysone, motion, and flight activity, deregulates development, and suppresses fertility and reproduction (Campos *et al*., 2016) [14]. Neem oil also functions as a fertilizer, enhancing soil quality for crop growth and supporting organic farming in a sustainable manner.

Review and Discussion
Role of Neem in treatment of COVID-19
Severe acute respiratory syndrome coronavirus (SARS-CoV-2) is a virus that cause respiratory illness in humans and first reported in Wuhan, China. Endothelial cell death has been noted in COVID-19 patients as a result of the identification of the SARS-CoV-2 element. The vascular endothelium is impacted by the SARS-CoV-2 virus, which also activates the innate and adaptive immune system. Eze MO, *et al.* (2022) [19] reported that vascular endothelium may be disinfected of SARS-CoV-2 using Neem acetone water extract.

As a monomeric protein, PLPro (Papain-like protease) is known to be crucial for the cleavage and maturation of viral polyprotein assembly, replicase-transcriptase assembly, and disruption of the host response. Baildya N, *et al*. (2021) [9] concluded 19 major compounds found in different parts of neem are chosen to analyse their potential inhibitory capacity against PLPro of Corona virus. Currently 7 drugs being tested against COVID-19. Among them, DCG (desacetylgedunin) gives highest docking score. Neem bark extract and its Nimbin isomers restrict beta-Corona viral infection and its replication and shows inhibitory effect on severe acute respiratory syndrome coronavirus-2 (Sarkar L, *et al.* 2022) [39]. Khan T, *et al.* (2021) [51] obtained an active compound Deacetyl-3-cinnamoyl azadirachtin from bark of neem which is very effective against Newcastle disease virus (NDV) Hepatitis C virus (HCV) and COVID-19.

Role of Neem in treatment of tumour and cancer

Neem having the anticancer and tumour inhibiting properties. The glycoprotein found in neem leaves increases the activation of genes that suppress tumours by increasing the tri-methylation acetylation of histone H3 (Chatterjee, A. *et al.* 2023) [15]. The anticancer properties of Neem were assessed, and it is undeniable that its active ingredients have the ability to both prevent and treat oral cancer through therapeutic means (Agrawal S, *et al.* 2020) [4]. Some active components of neem obtained from different parts of plant are anticarcinogenic. 2'3'-dihydronimbolide, 2'3'-dehydrosalannol both are anticarcinogenic compounds obtained from neem leaves.28-deoxonimbolide, azadirachtin both are anticarcinogenic compounds obtained from neem seeds. 6-deacetynimbinene is also anticarcinogenic obtained from bark of neem plant (Batra N, *et al.* 2022) [11].

Antibacterial properties of neem

A multitude of studies on the antibacterial properties of neem against various human infections have been documented.Many parts of *A. indica* (such as seeds, bark, leaves, etc.) generate extracts with moderate to significant levels of antimicrobial activity against a number of pathogens, including *Salmonella typhi, E. coli, E. faecalis, P. aeruginosa, Streptococcus agalactiae, Shigella boydii, B. subtilis, Klebsiella pneumoniae*, and *Candida tropicalis* Susmitha *et al*., 2013; Tesso *et al*., 2015; Melese *et al*., 2016; Panchal *et al*., 2020; Essuman *et al*., 2021) [44, 45, 30, 34, 18]. Neem oil extract and nimbolide, a phytochemical related to neem, have demonstrated strong in vitro bactericidal activity against *H. pylori* in liquid cultures and biofilms, according to two recent investigations (Blum *et al*., 2019) [12].

Antifungal activity of Neem

On different concentration like 1000, 2000, 4000, 8000 and 10000 ul/l plant extract including alcoholic,aqueous and oil were extracted from *Azadirachta indica* seeds control the growth of mycelium. Alcoholic extract has highest antifungal effect. Neem and *Citronella* oil shows antifungal activity when using nano emulsions of both plant oils against phytopathogenic fungi, *Sclerotium rolfsii* and *Rhizoctonia solani*. Results shows that *Citronella* nano emulsions 10 (CNE 10) and Neem nano emulsion 10 (NNE10) were active against *S. rolfsii and R. solani*. Schizophyllum commune, a white rot fungus growth was inhibited on solid medium containing 1.8% (w/w) *Azadirachta indica* extract or 5% (w/w) *Azadirachta indica* with copper sulphate and boric acid. These extract shows protective effect against fungal deterioration of *Mangifera indica* and *Albizia saman* wood. (Islam MM, *et al*. 2009) [21]. The ethanolic and methanol extract of Neem against *Alternaria solani*, *Cladosporium*, *Aspergillus flavus* was found growth inhibitory (Shrivastava *et al.* 2014) [40].

Role of Neem in insecticide and pest management

According to Vineesh PJ, *et al*. 2023 [49]. The oil of neem having bioactive properties and useful in pest management. Different chemicals like alfa-pinene, p-cymene limonene, gamma-terinene etc. are found in Neem oil which are having the potential to control agents against home invading acid flies (*Paederus fuscipes*) and darkling beetles. Some insect repelling compounds are present in Neem seed oil. So we are using this character in making anti mosquito soap (Adjei F, *et al.* 2022) [3]. Extract from leaves and seed of Neem having insecticide property and working against armyworm (*Spodoptera frugipera*). We can use lufenuron and Neem seed extract for harmful paste management (Asrar M, 2022) [8].

Neem as biofertilizer and manure

Certain organic and inorganic components found in neem enhance both the quality and quantity of crops. Neem seed cake provides critical macronutrients for plant growth. Now a days Neem seed cake is a good substitute of chemical fertilizer because it is cost effective, ecofriendly and biodegradable (Ramachandran *et al.* 2007) [36]. Nitrogen is very important for plant growth and urea is the chief source of nitrogen in present scenario and used worldwide to fulfill the nitrogen requirement of crops. The control of urea hydrolysis and nitrification is one of the principal strategies employed to avoid nitrogen losses in agriculture. Neem plant works as nitrification inhibitor, helping to slow the bacterial activities that is responsible for denitrification, hence minimizing the loss of urea from soil (Musalia *et al*. 2000, Mohanty *et al*. 2008) [32, 31]. The manure is the plant or animal waste matter used to fertilized land for improving the fertility of soil and enhancing plant growth (Tiwari, 2002) [46]. Neem manure is ecofriendly and rich in Nitrogen, potassium, sulphur, calcium etc. (Adeoye *et al.* 2008) [2]. Neem manure provide different micro and macro-nutrients to the soil and increases the productivity of cops.

Anti-inflammatory effects of Neem

The capacity of neem extracts to function as anti-inflammatory agents is a significant characteristic (Rupani & Chavez, 2018) [37]. Numerous illnesses, including diabetes and cancer, as well as other conditions like alcoholism and poor digestion, are caused by inflammation, a pathophysiological state (Eldeen *et al*. 2016) [17]. In the cotton pellet granuloma assay, the water-soluble portion of the alcoholic extract of Neem leaves, administered orally at a dose of 200 mg/kg, demonstrated strong anti-inflammatory effect and also markedly reduced the biochemical mechanism of action on inflammation. Neem leaf extract's anti-inflammatory properties may result from lysosomal membrane stabilization and anti-proliferative (Chattopadhyay, 1998) [16]. According to findings from other studies, neem leaf extract shown notable anti-inflammatory action, although it is not as effective as dexamethasone (Mosaddek *et al*. 2008) [1]. Using

carrageenan-induced hind paw edema, another study examined the anti-inflammatory effects of neem seed oil (NSO) on albino rats. The findings showed that NSO demonstrated greater inhibition of paw edema with a progressive increase in dose from 0.25mL to 2mL/kg body weight (Naik *et al*. 2014) [27].

Antioxidant effects of Neem

The antioxidant properties of *A. indica* leaf and bark extract have been investigated (Ghimeray *et al*., 2009; Sultana *et al*., 2007) [20, 43]. With minor modifications, the method outlined in Brand-Williams *et al*.,1995 was used to assess the antioxidant activity of neem (Barks and Roots) based on the scavenging activity of the stable 2, 2-diphenyl-2-picrylhydrazyl (DPPH) free radical. A straightforward and economical method of introducing antioxidants appears to be the use of natural extracts, such as those from neem, in supplements in the form of teas and oils (Alzohairy, 2016) [6]. Neem seed extract's antioxidant properties have been shown in vivo during horse grain germination, which is linked to low levels of lipid peroxides and lipooxygenase activity (Balasenthil *et al*., 1999) [10].

Neem as a source of biodiesel

The 40% oil content of neem seeds makes them highly promising for biodiesel generation. Compared to diesel fuel, it has a higher molecular weight, density, flash point, and viscosity. Neem oil is often light to dark brown, bitter, and strongly scented, with a combination of garlic and peanut scents (Sahin-uz-zaman *et al*. 2007) [7]. Only 25 to 30 percent of the 442.3 tons of potential seeds from the billions of neem trees planted across India were harvested for oil extraction. It was believed that using the esterification and trans esterification procedures to produce biodiesel from neem oil may result in a yield of 98.7% (Chhabra *et al*. 2021) [26]. The term "biodiesel" describes a group of goods known as mono alkyl esters of fatty acids that are produced from vegetable or animal fats and alcohol, such as methanol or ethanol. According to a study, biodiesel has around 12% less energy than diesel fuel made from petroleum on a bulk basis. Compared to diesel-fueled engines, it produces more nitrogen oxides (NOx), less carbon monoxide (CO), and less unburned hydrocarbons (HC). Natural oil, such as neem oil, is used to make this domestic, sustainable diesel engine fuel. In engine tests, biodiesel is an environmentally friendly liquid fuel that performs similarly to traditional diesel fuel in terms of power and fuel consumption (Gerpen *et al.* 2007, Galib *et al.* 2009) [22, 7].

Conclusion

Neem (*Azadirachta indica*) stands out as a botanical powerhouse with remarkable biological and chemical significance. Its extensive range of medicinal qualities including antibacterial, anti-inflammatory, antioxidant, antidiabetic and insecticidal activities are attributed to its rich array of bioactive chemicals which include azadirachtin, nimbin, nimbolide, and others. From a chemical perspective, its therapeutic effectiveness is attributed to its abundance of terpenoids, flavonoids, and limonoids. Biologically, it has been utilized for centuries in conventional medicine and is currently becoming more widely known for its possibilities in personal care, pharmaceuticals and agriculture. Finally, it should be noted that Neem is a natural resource that has been scientifically proven to have enormous potential for long-term health and environmental uses. More advantages for contemporary medicine and eco-friendly innovation may become available with further research and responsible application

Conflict of Interest

Not available

Financial Support

Not available

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