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***Review article***

# *Azadirachta indica–Neem*-A natural gift for prevention and treatment of chronic diseases- A review

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**ABSTRACT**

*Neem plant (Azadirachta indica L.) was known since ancient times, one of the most significant medicinal herbs in the world. Every part of the plant viz., leaves, bark, stem, wood, seed are utilized for treatment and prevention of a large number of human diseases. It is due to containing more than 300 phytochemicals of which azadirachtin is the most prevalent. For avoidance and treatment of different human chronic illnesses neem is used in Indian subcontinent and worldwide in the ayurveda, Siddha, and Unani medical systems and recently specially for treatment of Covid related system of diseases. This article summarized the importance, health benefits, biological role, major phytochemicals present in different plant parts and their molecular action in curing diseases and cultivation tips of neem tree.*

***Keywords:*** *Azadirachta indica,* chronic diseases, COVID-19, cultivation tips, ethnobotanical uses, phyto-chemicals

## INTRODUCTION

*Azadirachta indica* (*Neem*) is seen as a treasured gift from nature. Since the prehistoric age, India and its adjacent countries have benefited from its enormous medicinal and ethnomedical values for humanity (Tiwari *et al*., 2014). It is also known in various names like holy tree, Indian lilac tree, Nim and Nimba. According to the Persian it is derived from three Latin words these are- Azad means "free"; dirakht means "tree"; i-Hind means (Gupta *et al*., 2017). Neem is one of the most significant multi-reason trees to the Indian subcontinent, but cultivated throughout the world mainly Southeast Asia, Australia, East and Sub-Saharan Africa, Fiji, Mauritius and many countries of central and South America (Kumar *et al*., 2019). Humans were using neem from immemorial time as a remedy for smallpox and other diseases. In addition, it has long been believed to have antibacterial properties and the ability to ward off evil spirits.

*Neem,* belongs to same family of the mahogany i.e. Meliaceae, is quick growing plant propagated naturally by seeds. The maximum productive life span of neem tree ranges from 150-200 years. Every part of the tree contain some phytochemicals with confirmed antiviral, antiseptic, anti- ulcer, anti-inflammatory, antifungal and antipyretic uses. Azadirachtin is one of the neem plant's most prevalent chemicals, which having insecticidal properties as well as used as a bio-pesticide (Chaudhary *et al*., 2017; Kilani-Morakchi *et al*., 2021). For maintaining dental hygiene by chewing sticks, millions of rural as well as urban people use neem twigs (Gupta *et al*., 2017).

In view of modern medicine and chronic disease recently, the *neem* tree has acquired popularity to the researchers. Because it contains new antimicrobials and it is also applicable to in the disciplines of endocrinology, dermatology, dentistry, and oncology etc. (Wylie and Merrell, 2022). A significant challenge has been presented to humanity by the recent epidemic brought on by the new coronavirus SARS-CoV-2 (COVID-19). Different variants (Alpha, Beta, Gamma, Delta & Omicron) are available in case of COVID-19. Now the distinctly observed variant is Omicron corona virus group. Omicron has a significantly greater rate of symptomatic carriage compared to others

variant of corona virus had given high preceding rates of SARS-COV-2 infection, and this high prevalence of symptomatic infection is probably a major role in the global and rapid spreading.

It is well known to people, SARS-CoV-2 cannot be effectively prevented by any potentially active medication or vaccination that was previously available. Despite the fact that a number of medications, including chloroquine and hydroxy chloroquine, are advised against COVID-19, few of these having unfavourable outcomes which was reported by many researcher (Baildya *et al*., 2020). Now a days, different kind of vaccines (Covaxin, Covishield, Covovax, Comirnaty etc.) are available which can be effective against COVID-19 but these also have some side effects (Beniwal *et al.*, 2021). In the beginning of pandemic different potential drugs from natural sources, like the restorative *neem* plant was find out effectively against COVID-19 by some research workers (Eze *et al.*, 2022; Sarkar *et al*., 2022). In this article, cultivation aspects and important biological role of *Azadirachta indica* has been discussed with special emphasized to COVID-19 and others chronic disease.

**Chemical composition of *neem***

More than 300 distinct chemicals have been taken from various *neem* components. The researcher claims that extracted chemicals can be generally divided into two kinds. Both isoprenoids and non-isoprenoids are present (Latif *et al.*, 2020). Diterpenoids and triterpenoids, which contain limonoids, azadirone, protomeliacins, and their derivatives, are the chemicals that make up isoprenoids. Carbohydrates (polysaccharides), proteins (amino acids), sulfate-containing substances, polyphenolics including glycosides and related flavonoids, dihydrochalcone, tannins, and coumarins are among the substances included in non-isoprenoids Diterpenoids and triterpenoids, which contain limonoids, azadirone, protomeliacins, and their derivatives, are the chemicals that make up isoprenoids. Carbohydrates (polysaccharides), proteins (amino acids), sulfate-containing substances, polyphenolics including glycosides and related flavonoids, dihydrochalcone, tannins, and coumarins etc. are among the substances included in non-isoprenoids *etc*. (Biswas *et al*., 2002). Beside this, some other compounds which were extracted from *neem viz.*, margalonone, margalone, and isomargalonone (Dixit, 2015).

The compounds have been extracted from bark of *neem* are catechin, gallic acid, epicatichin, polysaccharides and NB-2 peptidoglucan which having anti-tumor, anti-inflammatory, antioxidant and antibacterial activity (Pankaj and Lokeshwar, 2011; Ghimeray *et al*., 2009; Susmitha *et al*., 2013).

β-sitosterol and Quercetin (poly-phenolic flavonoids) were extracted from *neem* leaves and were famous for their anti-bacterial as well as anti-fungal properties. (Alzohairy, 2016). Beside this other essential compounds found in the *neem* leaves are nimbanene, nimbandiol, nimbin, nimbolide, amino acid and nimbiol (Gupta *et al*., 2017). Phytochemical analysis of methanolic leaf extracts of *Azadirachta indica* has shown the presence of biological compounds like, Alkaloids, Flavonoids, Saponins, etc which are then compared to aqueous leaf extracts of the plant (Dash and Dixit, 2017). Irodin A, isolated from leaves of neem, effective against contributing anxieties of HIV/AIDS and malaria (Anyaehie, 2009) and Azadivactrin, possess capability to perform against disease causing viruses, parasites and fungi (Raj, 2015).

Compounds present in *neem* seeds are liminoids or triterpenoids together with azadirachtin that would be one of the most significant (Tindo and Amusant, 2012). Azadirachtin, a tetranor triterpenoid, is an important biologically active constituent of *neem* seed kernel, generally used for pest control (Gupta and Tripathi, 1998). Specifically, the separation of three products nimbidin, nimbidic acid and nimbolide was from seed kernel oil (Bansal *et al*., 2010; Latif *et al*., 2020).

**Ethnobotanical utilizations of *neem***

*Neem* leaves are used as a diuretic, for headaches, heartburn, and boosting appetite, as well as for oral health, gastrointestinal problems, insect repellent, malaria, and a number of skin conditions. *Neem* leaves, on the other hand, are used to cure diabetes (Sujarwo *et al*., 2016). Traditionally in India, due to its medicinal qualities, we can get relief by lying on the leaves from chicken pox (Maithani *et al*., 2011). *Neem* stick is used to clean the teeth for preventing the tooth decay, bleeding gums and

foul smell. Traditionally *neem* oil is used for lightening purpose as fuel in village area. Additionally, it works well as an antiseptic for the treatment of intestinal worm infections, eczema, and furuncles (Eid *et al*., 2017).

Nigerians use this as a traditional malaria cure. Seed aqueous extracts are used to treat head lice. *Neem* is also used to combat insects and pests; its main form of action is the interruption of metamorphosis, and its bitter taste deters insects from feeding on its host plants. (Senthil Kumar *et al*., 2018).

**Uses of *Neem***

*Neem* tree remedies for a variety of human problems are frequently utilised on all sections of the tree. In the southern states of India, Sri Lanka, Malaysia, and Singapore, the Siddha system of medicine is widely practised. The Siddha medical system first makes reference to the medicinal herb *neem.*

*Neem* is effective against rheumatism, malaria, intestinal worms, jaundice, tuberculosis, skin and as well as arthritis. *Neem* oil is an effective antiseptic for the treatment of intestinal worm infections, eczema, and furuncles on the skin (Eid *et al*., 2017).Calcium mining, which is a unique property, capability to neutralize acidic soils is predicted in *neem* (Latif *et al*., 2020). Beside this it is having astringent effect, bitter property is useful for loss of appetite, cough, tiredness, helpful for healing wounds and excessive thirst infestation to combat vomiting (Dixit, 2015). The neem oil is also used for fighting pimples, acne as well as refining skin elasticity (Manisha and Sachin, 2014).

A significant anti-diabetic potential has been demonstrated by the extract of Neem leaves and possibly will be reduce the 30%-50% use of insulin (Latif *et al*., 2020). It is also considered as the possible substance for the treatment of cancer patients and AIDS. In south-Asia, a huge amount of *neem* oil is available and it is non-edible and it is used for cosmetics such as nail polish, purified *neem* oil is used (Latif *et al*., 2020; Balami and Aliyu, 2014). *Neem* seed cake, which contains the needed macronutrients for plant growth, is used as a bio-fertilizer after *neem* oil has been extracted (Ramachandran *et al*., 2007). Neem oil posses various phyto-chemicals, used for human health and insect-pest control (Campos *et al.*, 2016).

Jagannathan and Vasuki (2015) reviewed the properties of neem as insecticide, antifeedant, hormonal, antifungal, antiviral and nematicidal properties in agricultural applications through use of *neem* leaves, leaf extracts, oil, seed cakes, seed and fruit extracts. The *neem* and its products are used in seed treatment, soil application, foliar spraying, increasing nutrient efficiency by which the rice yield was found to enhance and its sustainability was seen in rice cropping system.

**Biological properties of *neem* and molecular action of its phyto-chemicals**

**Diabetes prevention**

Chronic hyperglycemia, which causes endothelial dysfunction and atherosclerosis, is a serious global health issue associated with diabetes (Zhang *et al*., 2015). Due to hyperglycemia and hyperlipidemia, there was an increase in the formation of free radicals or oxidative stress. (Barbosa *et al*., 2013). *Neem* is tested to see if it can lower intestinal glycosidase activity (Joshi *et al.*, 2011). *Neem* leaf extract may be helpful in the treatment of type-2 diabetes by increasing the production of the protein GLUT4 and insulin signalling molecules, according to an experimental investigation (Satyanarayan *et al.*, 2015).

**Anti-Inflammatory activity**

A defense mechanism of the body includes inflammation. Our immune system is triggered when our body is exposed to harmful substances such as viruses, bacteria, or poisonous chemicals or when it sustains an injury. Inflammatory cells and cytokines trigger our immune system's initial defenses. These cells may begin the healing process or work to trap germs and other harmful agents. The result can be shown in various ways like pain, swelling, bruising or redness. Mainly two types of inflammation: i) **Acute inflammation:** the reaction to an immediate physical injury, like cutting our finger. ii) **Chronic inflammation:** Even when there is no threat from the outside, our body keeps sending inflammatory cells. For instance, in rheumatoid arthritis, inflammatory chemicals and cells assault the tissues of the joints. **Acute inflammation may cause** pain, tenderness, swelling, heat, etc. Symptoms of **chronic inflammation** could be more difficult. It may also

include mouth sores, skin rashes, joint pain or stiffness, exhaustion, fever, and chest trouble.

Bhowmick *et al*. (2010) concluded that a compound found in *neem*, called nimbidin, might possess anti-inflammatory and anti-arthritic activity. Rheumatoid arthritis, which is distinguished by inflammation and pain in the muscles and joints as a result of auto-immune reactions, may also benefit from it. Schumacher *et al.* (2011) studied the ability of neem leaf extract to reduce inflammation through the nuclear factor-κB (NF- κB) signalling system, which is connected to apoptosis, inflammation, and cancer and concluded that *neem* extracts have strong effect on pro-inflammatory cell signaling and apoptotic cell death mechanisms. *Later* Alzohairy (2016) also reported that *Neem* act as anti-Inflammatory agent. It functions as an anti-inflammatory by regulating the activity of proinflammatory enzymes such the cyclooxygenase (COX) and lipoxygenase (LOX) enzymes.

**Hepatoprotective effect**

The body's many physiological processes depend on the liver, which is the most significant organ in this regard. A liver inflammation known as hepatitis is distinguished by the presence of inflammatory cells in the organ's tissue. Uorakkottil *et al*. (2016) stated that liver damage or dysfunction is a significant health issue that poses difficulties for the pharmaceutical business, medication regulatory organisations, and healthcare providers. For a very long time, liver illness has been treated with herbal medications. Polysaccharides, proteins, flavanoids, lignans, and other phytoconstituents originating from plants maintain liver disorders and boost the immune system. There are several herbs that have been reported to have hepatoprotective and immunomodulatory properties (Uorakkottil *et al*., 2016). *Neem* has been found to have hepatoprotective effects, according to numerous researchers. Kale *et al*. (2003) stated that hepatoprotective activity of *neem* leaf extract on antitubercular drugs-induced hepatotoxicity and resulted in significantly preventing changes in the serum levels of protein, bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase as well as significantly preventing the histological changes as compared to the group receiving antitubercular drugs.

Baligar *et al.* (2014) established azadirachtin's involvement in rat liver damage caused by carbon tetrachloride (CCl4). According to hepatoprotective investigations, there was liver damage induced by CCl4 since the CCl4 treatment group showed a drop in total protein and albumin levels compared to the vehicle-treated control. According to the study's findings, pretreatment with azadirachtin at higher dose levels only modestly improves the condition of the rat liver. This research demonstrates that azadirachtin has a stronger hepatoprotective effect.

**Antiviral activity**

Badam *et al.* (1999) noted that *neem* leaf extract has demonstrated virucidal efficacy against the B-4 cox sackie virus. The herpes simplex virus type 1 (HSV-1) can lead to encephalitis, chronic skin and corneal ulcers, and other serious health issues. Tiwari *et al.* (2010) reported that *Neem* plant bark blocks HSV-1 entry into cells at concentrations ranging from 50 to 100 ng/ml and is a powerful entry inhibitor against HSV-1 infection into natural target cells. Additionally, polykaryocytes and HSV-1 glycoprotein-mediated cell-cell fusion were suppressed in cells treated with *neem* bark extract. Later, Yerima *et al.* (2012) also verified the prior findings that, at doses ranging from 50 to 100 g/mL, neem bark extract effectively inhibited HSV-1 entrance into cells.

**Antiulcer activity**

Bandyopadhyay *et al*. (2004) showed that *neem* bark extract has therapeutic potential for reducing gastric hypersecretion and ulcers in the gastroduodenum and gastroesophageal junction. The duodenal ulcers were nearly fully cured after 10 weeks of treatment with the bark extract at a dose of 30–60 mg twice day. After six weeks, one patient's esophageal and stomach ulcers were completely healed. They came to the conclusion that the neem bark extract decreased the hypersecretion of stomach acid in those with gastro-duodenal and gastro-esophageal ulcers.

**Antioxidant activity**

Chronic conditions like cancer, diabetes, and cardiovascular conditions (CVD) are major worldwide health issues that claim the lives of millions of people and leave them disabled.

Numerous plants, including *neem,* have been shown to be protective against the emergence of these chronic disorders. Scavenging these oxidants is considered to be a useful strategy to reduce organisms' oxidative stress levels (Zhang *et al*., 2015). Antioxidants are the substances, bioactive non-nutrient compounds that inhibit oxidation or inhibits reactions promoted by oxygen or peroxides. They lessen the production of free radicals and support the body's defense against cell damage. Toxic metals cause the production of free radicals. They also cause cardiovascular diseases (CVD), cancer, diabetes, and oxidative stress. They are the source of the oxidative degradation of DNA, protein, and other essential components (Hla *et al*., 2011; Zhang *et al*., 2015). In a study using extracts of the Siamese *neem* tree's leaves, fruits, blossoms, and stem bark Sithisarn *et al*. (2005) reported that a substantial antioxidant potential has been found in leaf, flower, and stem bark extracts. Later Ghimeray *et al*. (2009) also noted that *neem* growing in the foothills' high antioxidant capabilities were also discovered in its leaf and bark extracts.

Experimental results showed that nimbolide and azadirachtin have reductive potential and concentration-dependent antiradical scavenging action in the following order: Nimbolid, Azadirachtin, and Ascorbate (Priyadarsini *et al*., 2009).

**Antibacterial activity**

*Neem* extracts' antibacterial activity was tested against a small number of pathogens, and the results showed that it may be effective for preventing the growth of spoilage organisms and foodborne diseases (Mahfuzul Hoque *et al.,* 2007).

Yerima *et al*. (2012) investigated the antibacterial activity of leaf, fruit, seed and bark extracts of neem by using agar well diffusion method. With increase in concentrations of the extracts, the zone of inhibition also increased. The antibacterial activity only at higher concentrations is shown by the extracts of fruit and seed. Therefore, the results confirmed the usage of neem in sustaining oral hygiene traditionally. Later, Mariana *et al.* (2017) concluded that Neem's effective antibacterial action against the oral strains under investigation, which may be attributed to the substance's flavonoids and saponins content.

**Antimalarial activity**

Deshpande *et al.* (2014) demonstrated that *neem* leaf extract has some active components that may be the cause of its effectiveness against *Plasmodium falcifarum* and *P. vivax.* Another experiment using albino mice infected with Plasmodium berghei was conducted to assess the antimalarial activity of extracts. The results showed that the extracts of *neem* stem, bark, and leaf reduce parasitemia in infected mice by 51–80% and 56–87%, respectively. Other research revealed that Azadirachtin, which is present in *neem* extracts, and other liminoids are potent against malaria vectors (Alzohairy, 2016).

**Antifungal activity**

The growth of the seed-borne fungus Aspergillus and Rhizopus was clearly suppressed and controlled by the antifungal activity of leaf extracts of neem (Alzohairy, 2016).

**Antimicrobial activity**

Three fungi, including *C. lunata, H. pennisetti,* and *C. gloeosporioides* f. sp. mangiferae, were inhibited from germination of their spores by the aqueous extracts of *neem* cake (Anjali *et al.,* 2013). The study demonstrated that neem extract in methanol and ethanol inhibited the growth of *Aspergillus flavus, Alternaria solani* and *Cladosporium* (Shrivastava and Swarnkar, 2014).

**Antisnake venom activity**

Mukherjee *et al*. (2008) reported that a compound, phospholipase A (an enzyme), extracted from the leaf of *neem* was effective against snake bite and worked as anti-snake venom drug. This substance prevented the cobra and Russell's viper (RVV) venoms from acting. The amount will be depending upon the dependent.

**Wound healing effect**

Osunwoke Emeka *et al.* (2013) demonstrated that leaf extracts stimulate inflammatory response and neovascularization, which boost wound healing activity.

**Antifertility activity**

*Neem* oil has a novel application that is described: reversible inhibition of fertility after a single intrauterine administration (Upadhyay *et al.,*1990). *Neem* extract can be used to improve birth

control, according to a report by researchers at the Defense Institute of Physiology and Allied Sciences (DIPAS). *Neem* oil can prevent pregnancy without having any negative effects on the vagina, cervix, or uterus when administered intravaginally before to sexual activity, according to the study (Bansal *et al*., 2010), but not absorbed from the vagina (Singha *et al*., 1984). Its active ingredients were discovered to be absorbed into the bloodstream through the vaginal mucosa and to have antifertility effects in addition to their direct spermicidal actions.

Khillare and Shrivastav (2003) determined that the aqueous extract of old and tender *neem* leaves could directly immobilise and destroy 100% of human spermatozoa within 20 seconds. When compared to untreated sperm, no morphological abnormalities were observed in the sperm head, mid-piece, or tail. Therefore, complete sperm death may result from a metabolic process, such as energy utilization, being blocked. Longer storage times (up to 4 years) have no effect on the potentiality or efficacy of lyophilized aqueous extract of old and tender leaves.

**Anti-dental caries**

Considering the health-awareness criteria scientists are exploring and recognized *neem* as one of the beneficial plant for the development of anti-dental carries medicine from plant origin. Gupta *et al.* (2017) studied and emphasised the therapeutic benefits of *neem* from the perspective of oral health, including its treatment of gingivitis, anti-microbial, anti-plaque, anti-candidiasis, anti-periodontitis, tooth erosion, and oral cancer.

**Anti-cancerous activity**

Cancer is a complex illness that is a huge global health issue. Allopathic medicine is helpful on one hand, but it also had negative effects on healthy cells (Alzohairy, 2016). The multistage carcinogenic process is thought to involve free radicals. DNA mutations, which are essential for the start of the carcinogenic process, can be brought on independently by peroxylradicals and lipid peroxidation. By preventing DNA damage, antioxidant phytochemicals may control the start of the carcinogenesis process. *Neem* and its components were thought to be crucial in the control of numerous cell signaling pathways. It contains a variety of components that can turn on tumor suppressor genes and deactivate the activity of several genes implicated in the onset and spread of cancer. According to reports, *neem* is an effective tumor suppressor gene activator. Additionally, it induces apoptosis, blocks NF- κB signaling, and activates the cyclooxygenase pathway (Alzohairy, 2016).

**Anti-HIV activity**

Acquired Immune Deficiency Syndrome (AIDS) is brought on by Human Immunodeficiency Viruses (HIV). *Neem* has historically been used to treat HIV-related illnesses. (Wylie and Merrell, 2022), have been investigated for their potential to shield the HIV-vulnerable $CD4^+$ T cell population. According to certain research, *neem* leaf extract can increase $CD4^+$ T cell counts in HIV patients on a daily basis while being safe to consume. Overall, the findings confirmed that *neem* possesses immunomodulatory properties that may be useful for some treatments and to enhance the health of people with persistent infections (such as HIV).

**Anti-Dengue activity**

Kaempferol 3-O-rutinoside and epicatechin were shown to be able to suppress dengue virus by 77.7% and 66.2%, respectively, after 49 different *neem* tree bioflavonoids were virtually screened for binding to the virus (Dwivedi *et al*., 2021). Triterpenoids called nimbin, which were extracted from neem leaves, were found to be efficient against the dengue virus's envelope protein (Lavanya *et al*., 2015). Due to its unique phytochemicals that functioned to inhibit the functions of both the protease and envelope proteins of the dengue virus, as well as may be for other viruses, *neem* may be a novel source for antiviral medications (Shanmugam *et al*., 2020).

**Anti-SARS-CoV-2 activity**

A family of viruses known as corona viruses can seriously harm the acute respiratory system and cause symptoms like the common cold. It was found to be the root of a disease outbreak in 2019 that originated in China. The virus is referred to as SARS-CoV-2, or severe acute respiratory syndrome coronavirus. The condition it brings on is referred to as coronavirus disease 2019 (COVID-19). The

World Health Organisation (WHO) classified the COVID-19 outbreak as a pandemic in March 2020. People with COVID-19 have reported experiencing a wide range of symptoms, from minor discomfort to serious sickness. 2 to 14 days after virus contact, symptoms may start to show. New variations and vaccination status may affect the severity and number of symptoms. The risk is larger for older folks and those with underlying illnesses including diabetes, heart disease, or lung disease. Acute respiratory infection and multiple organ failure should be present in extreme situations.

Over the past two years, COVID-19 has claimed the lives of more than five million people and has continued to pose serious hazards to the public's health (WHO, 2021). SARS-CoV-2 antiviral treatment is still not available. A thorough examination of this outbreak's dynamics indicated that Papain-like protease (PLpro), a multifunctional polyprotein, promotes SARS-CoV-2 replication and shields it from the host immune response via antagonistic cytokines and interferons, and may be viewed as a possible therapeutic target (Balkrishna *et al*., 2021). Elfiky (2020) suggested that Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir are the effective medicines against SARS-CoV-2 due to their ability to bind to its RdRp.

Numerous studies have successfully searched plant-based chemical compounds for SARS-CoV-2 viral inhibitors (Thota *et al*., 2020; Adithya *et al*., 2021). When compared to other medicinal plants, Neem's phytochemicals that combat SARS-CoV-2 performed a significant contribution (Wylie and Merrell, 2022). The action of phytochemicals in *neem* against SARS-CoV-2 has been demonstrated by various workers. For example, Baildya *et al*. (2020) studied the effect of *neem* extracts on the new coronavirus SARS-CoV-2's papain-like protease (PLpro). All of the Neem compounds under investigation exhibited respectable levels of inhibitory efficacy against the SARS-CoV-2 PLpro. Desacetylgedunin (DCG), which can be found in Neem seeds, had the strongest affinity for PLpro of all of them. They came to the conclusion that DCG on PLpro may aid in the treatment of SARS-CoV-2.

Parida *et al*. (2020) explored phytochemicals as potential inhibitors for SARS-CoV-2 by performing all atom molecular dynamics simulations using high performance computing for 8 rationally screened phytochemicals from *Withania somnifera* and *Azadirachta indica* and two repurposed drugs docked with the spike glycoprotein and the main protease of SARS-CoV-2. The results revealed that Withanolide R (−141.96 KJ/mol) and 2,3-Dihydrowithaferin A (–87.60 KJ/mol) were with the lowest relative free energy of binding for main protease and the spike proteins respectively. It was also observed that the phytochemicals exhibit a remarkable multipotency with the ability to modulate various human biological pathways especially pathways in cancer.

Balkrishna *et al*. (2021) experimentally proved that Nimbocinol and sage exhibited maximum inhibitory effect on replication against PLpro SARS-CoV-2 which was found to be better than remdesivir, chloroquine and favipiravir.

Potentiality of *neem* against SARS-CoV-2 was also supported by Lim *et al*. (2021) by highlighting antiviral research with favourable results specific to the SARS-CoV-2 coronavirus. Affect and remedy of SARS-CoV-2 upon the human body were clearly explained by Eze *et al*. (2022). Similar to SARS-CoV and the Middle East respiratory disease (MERS) virus, SARS-CoV-2 is an enclosed virus with a positive sense, single-stranded RNA genome. Because COVID-19 has a potential to damage many organs in a severe instance, which can result in multiple organ distress syndrome (MODS), it is unusual in that it can have a high morbidity and fatality rate. Severe COVID-19 risk factors include cardiovascular disease, diabetes and its consequences, and obesity. As a result of SARS-CoV-2 infection, the body produces excessive amounts of cytokines, chemokines, reactive oxygen species, nitric oxide, oxidative stress, acute phase proteins (such as C-reactive protein), and other pro-inflammatory compounds. A cytokine storm is produced in the worst case scenario.

Eze *et al*. (2022) hypothesised that an effective technique for preventing COVID-19 would be the displacement of the virus attached to the vascular endothelium (VE) and suppression of virus binding. As a result, *neem* leaf extract will be an efficient therapeutic formulation against COVID-19 by preventing the binding of SARS-CoV-2 to the vascular endothelium (VE).

The development of a vaccine and antiviral therapy are being challenged as a result of concurrent alterations in the SARS-CoV-2 genome. A useful investigation against SARS-CoV-2 was made by Sarkar *et al.* (2022) using *neem* bark extract (NBE). They looked into the SARS-CoV-2 and the m-CoV-RSA59 infections. On viral load, inflammatory response, and histological alterations in m-CoV-RSA59 infection, the effects of in vivo intranasal or oral NBE treatment were evaluated. Administration of neem bark extract (NBE) prevents SARS-CoV-2 and m-CoV-RSA59 infection and replication *in vitro* m-CoV-RSA59 infection is effectively inhibited *in vitro* by isolated fractions of *neem* bark extract (NBE) that are rich in nimbin isomers. *Neem* bark extract (NBE) contains triterpenoids, which may enable them to selectively target a variety of viral proteins to prevent mouse and various human coronavirus infections. It will be speculating on possible application as a pan-Coronavirus antiviral.

**Cultivation tips**

**Agro-climatic requirements**

It can be grown almost everywhere in the lowland tropics, with sub-arid to sub-humid conditions. It prefers tropical and sub-tropical climates at altitudes between 0-1500 m with annual temperature ranges between 21-32$^{o}$C but can tolerate up to maximum 40$^{o}$C and mean annual rainfall varies between 400-1200 mm. It does not tolerate cold temperature or saturated soils (Kumar *el al.*, 2019). It cannot tolerate the temperature below 5°C (Nisa *et al.*, 2022). It can also resistant against drought. Neem tree unable to withstand against waterlogged conditions and quickly dies in these conditions. It can grow on a range of soil types, including black cotton soils with a pH range of 5 to 10, from sandy to clayey soils, and other types of soil as well.

**Propagation and plating**

It can be propagated using seed as well as root shoot cutting. The viability of seeds lasts only for around two weeks. The endocarp is removed from seeds or the seed coat at the round end is cut off with a sharp knife in order to increase germination. Seeds are then immersed in cold water for 24 hours. In sandy nursery beds, de-pulped seeds should be distributed in lines (15 to 20 cm apart), 2.5 to 5 cm apart, at a depth of 1 to 2 cm, and lightly covered by soil. To avoid cracking, nursery beds should be irrigated frequently. It usually takes one to two weeks for germination. 70% to 90% of seeds sprout. Seedlings are transplanted in the main field during rainy season after 1 to 2 years at a spacing of 4.5 to 5.5 m (*Anon*., 2012).

**Planting root-shoot cuttings**

The stumps are made from seedlings that are 12 to 13 months old, with 2.5 cm of shoot section and 23 cm of root, and they are planted in crow bar holes at the end of the rainy season. In Tamil Nadu, stumps from plants that are two years old have a higher survival rate and better height growth than root stock that is one year old. 53% success with root-shoot cuts has been reported from Maharashtra. Rains are necessary for root-shoot cuttings to succeed; a protracted dry spell may significantly reduce survival rates (*Anon*., 2012).

**Interculture operation**

Young plantations can benefit from strip weeding for their survival and general health. The first year only needs two weedings, while the second year just needs one. Weeding can be carried out mechanically or manually. When seedlings are transplanted, the first mechanical thinning is carried out at the age of 5 years.

**Plant protection**

In nursery stage the plants are affected by different pests and diseases. After attaining 2-3 years age, they are capable to stand well against various pest and diseases attack. Tip borer (*Laspeyresia koenigiana*) and Tea mosquito bug (*Heliopeltis antonii*) are the two most frequent pests that attack plants in their seedling and younger stages. The main pest of *neem* is the scale insect *Pulvinaris maxima*, and *Heliothrips haemorrhoidalis* is a potential pest. Damping off disease, which is brought on by *Rhizoctonia* species, can have a serious impact on *neem* seedlings. There are other diseases as well, such as leaf web blight, leaf spot, and blights brought on by *Colletotrichum, Alternaria, and Pseudocercospora*. To manage the aforementioned insect pests and illnesses, systematic insecticides and fungicides are utilized.

**Harvest and yield**

Scented white flowers appear during March-April in abundance on auxiliary spikes. Fruits are ripening from June to August. Fruits are picked when they transform from green to a bright yellow tint. To collect the ripe fruits, the branches must be shaken firmly. About 8000- 10000 kg of fresh berries can be harvested from 1ha/ year (*Anon*., 1973). Fresh fruits give about 60% dry fruits, which yield 10% kernel and contain on an average 45% fixed oil.

**Cost of Production**

Approximate cost of production comes around Rs.37, 500/- per hectare (*Anon*., 1973).

**Post-harvest management or processing**

**Neem oil**

The seeds must first be cracked open and the kernels separated in order to produce *neem* oil. The kernels are subsequently squeezed in ghani or industrial expellers. Sometimes, the oil output might reach 50% of the weight of the kernel (Latif *et al.*, 2020).

The neem seeds were repeatedly washed to eliminate dirt and other clinging contaminants prior to oil extraction, and they were then dried in an oven at $50^0$C until they reached consistent moisture content (Anon., 2022).

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