Technical Report

Significance of Neem Extract in CanXida Remove (Formula RMV)

Neem extract in CanXida Remove (Formula RMV) is a versatile botanical ingredient with natural antimicrobial, anti-inflammatory, and antioxidant properties. When combined with other ingredients, neem extract synergistically contributes to pathogen clearance and healing.

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Executive Summary

Neem extract, derived from the Neem tree, is a versatile natural remedy known for its wide-ranging health benefits and therapeutic properties. The historical significance of this extract is evidence of its safety and efficacy in addressing a range of health concerns. The extraction process is relatively straightforward, primarily involving water-based solvents, resulting in a non-toxic and relatively pure substance enriched with a multitude of bioactive compounds.

Neem extract is a valuable ingredient in formulations like CanXida due to its rich bioactive compounds, targeted effects, and wide range of health benefits. Neem extract is a natural antimicrobial, anti-inflammatory, and antioxidant agent. This extract contains a variety of compounds, including azadirachtin, nimbin, and other triterpenoids. These compounds are responsible for its strong antiparasitic effects. In addition, the extract's antimicrobial properties are extremely effective against a wide range of bacterial and fungal strains. It is also capable of combating viral infections and parasitic nematodes, as well as treating Candida infection. *

1. Introduction

Azadirachta indica, holds significant importance as a medicinal plant throughout human history. The plant is classified under the Meliaceae family and is commonly referred to as neem. The utilization of A. indica has been observed from ancient times to the present day. It comprises various parts, including leaves, bark, seeds, and oil. (Sarkar et al., 2021)

Recent research trends have uncovered the substantial potential of neem-derived bioactive compounds, particularly from its leaves, for their remarkable health and agricultural applications. Neem extract contains over 300 bioactive compounds, divided into isoprenoids (diterpenoids and triterpenoids) and non-isoprenoids (flavonoids, sterols, glycosides, alkaloids, and polyphenols).

These compounds offer various health benefits, including anti-inflammatory, antioxidant, anti-fungal, antibacterial, and cholesterol-lowering properties. (Hemdan et al., 2023; Melese Damtew, 2022) Neem is known for its pesticidal and insecticidal properties, but people also use it for medicinal purposes. Neem is a strong antioxidant, neutralizing free radicals that may influence the development of some conditions. It is also a strong anti-inflammatory agent.

Neem has antimicrobial effects and may be effective against several types of bacteria, viruses, and fungi. It effectively combats bacteria (Gram-positive and Gram-negative), and fungi (including dermatophytes and Candida species), and shows potential antiviral effects. Moreover, it exhibits antiprotozoal activity against Plasmodium species responsible for malaria and may inhibit nematode growth, potentially reducing their harmful effects.

Neem extract is usually derived from different parts of the neem tree, such as leaves, seeds, or bark, using methods like solvent extraction or cold pressing. The extraction process of neem leaves involves water-soluble bioactive compounds, ensuring a safe and chemicalfree procedure. Although it has a long history of safe traditional use in dietary supplements and potential health benefits, its safety for consumption can vary depending on factors such as dosage and individual responses. When used responsibly and obtained carefully, neem extract can be a valuable addition to medicinal and nutraceutical products. * (Wasim et al., 2023)

2. Bioactive Compounds of Neem Extract

The neem tree is widely acknowledged for its impressive adaptability and its vast collection of more than 300 bioactive compounds. Numerous scientific studies have provided evidence for the presence of bioactive compounds in different parts of the neem tree, including the bark, husk, seeds, seed oil, tree, leaves, and flowers.(de Alba et al., 2022) The chemical compounds found in neem can be categorized into two main groups (de Alba et al., 2022; Tiwari et al., 2014):

- Isoprenoids
- Non-Isoprenoids.

Table 1 provides a comprehensive list of the key bioactive compounds present in neem.

2.1. Isoprenoids:

Isoprenoids, also called terpenoids, are a wide-ranging group of natural compounds that can be found in different parts of the neem plant. Isoprenoids have been found to possess various health-related properties, such as anti-inflammatory, antibacterial, and potential antifungal effects. These compounds are derived from isoprene units.

and are mainly classified into two major subgroups:

- Diterpenoids
- Triterpenoids

These include protomeliacins, limonoids, derivatives of azadirone, gedunin, and secomeliacins like salannin, nimbin, and azadirachtin. (Atawodi & Atawodi, 2009) Nimbin is a compound that is typically inactive, but it has the potential to be transformed into salannin through enzymatic reactions. Additional enzymatic modification and oxidation result in the creation of azadiractin.

Although, Nimbin was the center of interest at first, subsequent developments have allowed for the full laboratory synthesis of azadirachtin, a major bioactive ingredient in neem due to its antioxidant and antiinflammatory properties.

2.2. Non-isoprenoids

In contrast, neem extract contains a wide range of bioactive compounds, such as tannins, flavonoids, saponins, glycosides, alkaloids, reducing sugars, hydrogen cyanide (HCN), polyphenols, and terpenes. **Table 1:** List of Bioactive Compounds present in neem extract. Source: (Hemdan et al., 2023;Melese Damtew, 2022)

Phytochemical Groups	Subgroups	Bioactive Compound
	Diterpenoid & Triterpenoid	Nimbolide
		Sugiol
		Nimbiol
		Nimbin
		Nimbinin
Isoprenoids		6-deacetyl nimbinin
		Nimbinene
		6-deacetyl nimbinene
		Nimocinol (6α-hydroxy-azadirone)
		Azadirone
	Flavanoids	Quercetin
		Kaemferol
		Quercetin-3-galactoside (Heprin)
		Quercetin-3-galactoside
		(Astragalin)
		Rutin
		Chrysin
Non-isoprenoids	Sterols & Glycosides	β-sitosterol
		β-sitosterol-β-D-glucoside
		Rhamnoside of quercetin
		Caffeic acid
		Catechin
		Chlorogenic acid
		Cinnamic acid
		Ferulic acid

	Gallic acid
Polyphenolic Acids	Gentisic acid
	p-hydroxybenzoic acid
	Protocatechuic acid
	Syringic acid
	Vanillic acid
	Neem leaf glycoprotein
	5-hydroxy-methyl furfural
	Nomolin
	Nimolicin
Others	17-Hydroxy-azadiradione
	17β-Hydroxy-azadiradione
	17-Epi-azadiradione

• Flavonoids:

These are a type of natural compound found in neem, contributing to the plant's complex array of phytochemicals. Quercetin and β-sitosterol are the initial flavonoids extracted from neem. These compounds exhibit significant anti-fungal and antibacterial properties.

These are recognized for their ability to combat oxidative stress, reduce inflammation, and potentially offer therapeutic benefits. (Sarkar et al., 2021)

• Polyphenolic Compounds:

The neem extract contains a range of polyphenolic compounds, such as

catechins, cinnamic acid, and gallic acid. The polyphenols found in neem contribute to its antioxidant properties, which may have potential health benefits. They are known for their antiinflammatory effects and ability to protect against oxidative damage.

Alkaloids, flavonoids, glycosides, and saponins are the most notable bioactive elements because of their diverse and advantageous properties, which include anti-inflammatory, anti-allergic, antioxidant, anti-diabetic, anti-viral, antileprosy, and antimicrobial actions.

• Sterols and Glycosides

Furthermore, the bioactive compounds include sterols such as beta-sitosterol and glycosides. The presence of these components in the extract contributes to its possible health advantages, including its anti-inflammatory and cholesterollowering capabilities.

• Other bioactive compounds

The extract of neem contains various compounds that have immune-regulating and antioxidant effects. It also contains amino acids, tannins, and small amounts of vitamins and minerals, which contribute to its nutritional profile and diverse medicinal properties.

3. Health Benefits of Neem Extract

Neem extract, derived from the various parts of the neem tree (Azadirachta indica), is renowned for its wide-ranging health benefits including antioxidant, antimicrobial, antiinflammatory and healing properties. Table 2 Some of the notable health advantages associated with neem extract include:

3.1. Antioxidant Properties:

Free radicals are naturally produced by the body, but these molecules are unstable and can harm other cells. High levels of free radicals can lead to a range of disorders, such as cardiovascular disease, eye health issues like cataracts and macular degeneration, and age-related neurodegeneration.

Neem plant extract plays a significant role as a free radical scavenger due to its rich antioxidant content. Specifically, compounds like *azadirachtin and nimbolide* exhibit a concentration-dependent ability to scavenge free radicals and possess reductive potential, with nimbolide being more effective than azadirachtin and ascorbate. (Hossain et al., 2013).

Furthermore, a comprehensive analysis was conducted, considering extracts from various parts of the Siamese neem tree, including leaves, fruits, flowers, and stem bark, to assess their antioxidant activity. The results of this study strongly indicate that extracts derived from the leaves, flowers, and stem bark possess robust antioxidant potential. (Alzohairy, 2016).

3.2. Antimicrobial Properties:

Neem extract has potent antimicrobial properties against a wide range of microorganisms. The presence of bioactive compounds such as nimbin, nimbidin, gedunin, and azadirachtin largely contribute to these effects. These compounds interact with different microbial targets, disrupting cell membranes, inhibiting enzymatic processes, and hindering pathogen growth and replication.

Recent studies have confirmed the antimicrobial properties of neem extract. It has been studied for its potential to prevent STDs, gum disease, and cavities. Neem extracts also effectively combat malarial parasites, including drug-resistant strains, inhibiting the growth and development of P. falciparum, a human malarial parasite, as well (Kumar et al., 2018).

Additionally, neem extract has proven effective against various fungal infections, including athlete's foot, ringworm, and Neem extract has also shown potential in combating biofilm-forming bacteria through multiple mechanisms. The antibacterial properties of this substance can effectively inhibit the growth of bacteria within biofilms.

Additionally, it has the capability to disrupt the formation and adhesion of biofilms, thereby preventing the development of these microbial communities. Neem's disruption of quorum sensing, an essential communication mechanism among bacteria in biofilms, provides an additional method to hinder their growth. In addition, the antiinflammatory and antioxidant properties of neem may assist in reducing the inflammatory response and oxidative stress commonly linked to infections caused by biofilms.

Candida-related conditions such as yeast infections and thrush. Neem extract has also been shown to exhibit antiviral potential against both the Dengue virus, linked to hemorrhagic fever, and the highly infectious coxsackie B virus, belonging to the 'enterovirus' category. (Bhowmik et al., 2010)

3.3. Anti-inflammatory Properties

Neem has bioactive compounds like nimbin, nimbinin, nimbidin, and quercetin that can inhibit the production of inflammatory molecules in the body. Neem can help reduce inflammation by decreasing the synthesis of these compounds. (Lee et al., 2017)

Neem contains antioxidants such as flavonoids and polyphenols, which help protect cells against oxidative stress and free radical damage. Neem has the ability to reduce inflammation by neutralizing free radicals, which are major trigger. Neem's antimicrobial properties also enhance its antiinflammatory potential. Infections can be a cause of inflammation, and Neem's ability to combat multiple pathogens can aid in reducing the inflammation caused by these infections.(Wasim et al., 2023)

In oral health, neem is incorporated into toothpaste and mouthwash due to its antiinflammatory and antimicrobial properties. By reducing gum inflammation and preventing oral infections, neem promotes oral health.(Aftab et al., 2023) (Niha Naveed et al., 2014).

Neem extracts possess the ability to manage inflammatory disorders such as rheumatoid arthritis by diminishing joint inflammation and alleviating pain. They also potentially help manage conditions like inflammatory bowel disease (IBD) by reducing gut inflammation.

3.4. Wound Healing:

A common use for neem extract is as a wound healer. (Melese Damtew, 2022)

- It gives the skin moisture, softens it, and supports the skin's natural healing process.
- Its strong antimicrobial properties. It helps keep wounds free from harmful

microorganisms, which speeds up the healing process and promotes skin restructuring

- Neem extract has been found to effectively reduce inflammation, which aids in faster healing.
- It also supports the development of essential components like granulation tissue, elastin, and collagen.

3.5. Other Benefits:

The Azadirachta indica has various health benefits. It has shown hepatoprotective effects by enhancing liver function. Neem's neuroprotective qualities help alleviate nerverelated problems and combat oxidative stress.

In addition, it has been found to protect against kidney damage, modulate the immune system, exhibit antidiabetic effects, and possess properties that protect the heart. Neem is highly regarded for its wide range of applications in both traditional and modern medicine. * (Rahmani, 2018)

4. Biosafety Profile

Research conducted using animal models and clinical trials has provided conflicting results regarding the safety of neem and its components.

^{*} These statements have not been evaluated by Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

Table 2: Clinical Trials Utilizing Neem Extract as an Active Ingredient in Treatment andPrevention. Source: clinicaltrials.gov

Clinical Trial ID	Health Condition	Status
NCT03065504	Skin Inflammation	Completed
NCT06050174	Periodontitis	Completed
NCT03166163	Gingival Bleeding	Unknown status
NCT01251250	 Refractory Chronic Lymphocytic Leukemia Stage II Chronic Lymphocytic Leukemia Stage III Chronic Lymphocytic Leukemia Stage IV Chronic Lymphocytic Leukemia 	Withdrawn
NCT01731756	Arsenical Keratosis	Completed
NCT02943759	Periapical Abscess	Completed
NCT01321645	Acne Vulgaris	Unknown status
NCT02352987	Chronic Arsenic Poisoning	Completed
NCT01898091	Oral Mucositis	Completed
NCT04341688	Covid-19	Unknown status
NCT04949932	Acne Vulgaris	Completed
NCT04537585	Covid19	Completed
NCT04210336	HPV Infection	NCT04210336

Several studies have confirmed that neem is safe when used at certain doses, with no significant adverse effects on human health or animals. On the other side, there is evidence suggesting that neem and its components may have harmful effects, particularly when consumed or applied excessively or inappropriately. (Alzohairy, 2016).

Neem compounds show great potential in the field of medicine. By modifying the chemical structures and bioactive molecules derived from the neem tree, it is possible to minimize any potential side effects and toxicity. Additional research is required to fully utilize the potential of neem for the development of safer and more effective drugs.

The absorption of neem extract in the body can be influenced by various factors, including its type, compound composition, and method of administration (whether oral or topical). Many other plants and natural sources provide similar bioactive chemicals as those found in neem. For instance, quercetin, a flavonoid known for its antioxidant and anti-inflammatory effects, is not exclusive to neem and is widely distributed in fruits, vegetables, and other plant sources, such as apples, citrus fruits, onions, grapes, and leafy vegetables.

Neem extract is typically derived from different parts of the neem tree, such as leaves, seeds, and bark, using methods like solvent extraction or cold pressing. This extract contains a wide range of bioactive compounds, including water-soluble ones, known for their potential health benefits. The extraction process of neem leaves involves water-soluble bioactive compounds, ensuring a safe and chemical-free procedure. Neem has an ancient history in medicine and dietary supplements for its antibacterial, antiinflammatory, and antioxidant properties. Neem has been used to address a wide range of health issues, such as skin conditions, digestive problems, and as a wound healer.

5. Effective Targets

The extract of Neem is recognized for its strong antimicrobial properties, making it highly effective against a wide range of microbial targets. Some of the common microbial targets of neem extract include:

5.1. Bacterial species:

The Neem plant extract has been found to possess potent antibacterial properties,

capable of effectively suppressing the growth of various types of bacteria. It is effective against both Gram-positive and Gramnegative strains, making it a versatile antimicrobial agent. Some important bacterial targets are as follows. (Atawodi & Atawodi, 2009)

Staphylococcus aureus: Neem has been found to have antibacterial properties against Staphylococcus aureus, including antibiotic-resistant strains like MRSA (Methicillin-Resistant Staphylococcus aureus). This bacterium can cause skin infections

Escherichia coli (E. coli): Neem extracts have demonstrated antibacterial activity against Escherichia coli, a bacterium often associated with foodborne illnesses and urinary tract infections.

Salmonella: Neem has been shown to inhibit the growth of Salmonella bacteria, which can cause various gastrointestinal infections, including salmonellosis.

Pseudomonas aeruginosa: This bacterium is responsible for a range of infections, especially in people with weakened immune systems. Neem has exhibited antibacterial activity against Pseudomonas aeruginosa. *Klebsiella pneumoniae:* It is known for causing respiratory and urinary tract infections.

Acne-Causing Bacteria: Neem has been used traditionally manage acne due to its antibacterial properties. It targets bacteria like Propionibacterium acnes, which play a role in the development of acne.

5.2. Fungal species

The antifungal properties of neem extract have been shown against a range of fungi, including:

Dermatophytes: The causative agents of skin and nail infections, including Trichophyton species, which are responsible for conditions like ringworm.

Candida species: Neem has also shown antifungal efficacy against various Candida species. Candida is known for causing fungal infections, including oral thrush, vaginal yeast infections, and systemic candidiasis.

Sporulating Fungi: Neem extract has been found to inhibit the spore germination of several sporulating fungi, including

- C. lunata,
- C. gloeosporioides,

• H. pennisetti.

Aspergillus flavus: Aspergillus flavus is a common fungus known for producing aflatoxins in contaminated food.

Alternaria solani: A fungal pathogen that affects a variety of plants, causing diseases like early blight in tomatoes and potatoes.

Neem extract possesses a wide range of antifungal properties, making it a potential natural remedy for treating various fungal infections and preventing the growth and spore germination of different fungal species.*

5.3. Viral species

Neem extract has been the subject of extensive research for its potential antiviral properties, particularly in relation to several viral species. While it may not directly eliminate viruses, its effects have been studied in depth, and it may have the potential to disrupt viral replication. Some viral categories and examples include:. (Atawodi & Atawodi, 2009)

Dengue Virus: Neem extract has been studied for its possible antiviral effects against the Dengue virus.

Coxsackieviruses: Research has explored the use of neem extract in relation to Coxsackieviruses, which can cause various infections, including hand, foot, and mouth disease.

5.4. Protozoan Parasites

Neem extract has been extensively studied for its anti-protozoal activity, specifically targeting protozoan parasites such as Plasmodium species, known for their role in causing malaria. The neem extract contains active compounds like azadirachtin and other triterpenoid compounds, which have demonstrated potential in fighting against these protozoan parasites.

5.5. Nematodes

This extract shows the potential to inhibit nematode growth within the body. Nematodes are a diverse group of parasitic worms that have the ability to infect both humans and animals, resulting in a range of health problems. Neem extract is thought to possess various properties that can potentially hinder nematode growth and minimize their effects on the body.

The potential uses of neem in fighting these pathogens reflect its broad spectrum of

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activity against a variety of disease-causing agents.

6. Significance of Neem Extract in CanXida Remove

The addition of Neem extract to CanXida Remove (Formula RMV) greatly improves the product's efficacy as a powerful antimicrobial and anti-inflammatory dietary supplement. Neem, with its various beneficial properties, is a valuable addition to the formulation and works well with other active ingredients.

CanXida RMV contains 4:1 neem extract which signifies its remarkable potency and concentrated active compounds, making it an ideal choice for effectively combating candida overgrowth and promoting gut health

The antimicrobial properties of neem extract are highly diverse, making it effective against a wide range of bacterial strains, including both Gram-positive and Gram-negative. This strengthens the ability of CanXida Remove to combat infections. It effectively combats a wide range of fungal infections including Candida. Neem's potential in combating viruses and parasitic nematodes is in line with the product's objectives.* The immune modulation, anti-inflammatory, antioxidant properties, and wound-healing attributes of this substance contribute to the overall wellbeing of the digestive system.

In conclusion, the product CanXida Remove's antibacterial. anti-inflammatory, and antiparasitic properties are significantly improved by the addition of Neem extract. It enhances the product's capacity to effectively address a range of digestive system issues, including parasite infestations, viral threats, and bacterial and fungal infections. The bioactive components of neem extract further enhance its significance by regulating the immune system, promoting healing, and supporting digestive health within the formulation. *

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