NEEM EXTRACTS: REVOLUTIONIZING HEALTH, WELLNESS, AND BEYOND

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INTRODUCTION

Neem, also known as Azadirachta indica,, is an evergreen tree from the Meliaceae family and is a highly renowned medicinal plant in the Indian subcontinent for over two millennia due to its remarkable versatility and broad range of biological activities. It goes by the name "neem" in English, "Al Shurisha " in Arabic and ‘Arishtha’ in Sanskrit meaning "relief from illness," and is hence referred to as "Sarbaroganibarini". Neem is a tall tree with a semi-straight trunk that grows to a height of around 25 meters. It is a blooming plant that usually starts producing fruit after three to five years and reaches peak productivity after ten years [2]. The neem tree has rough, gray bark, and its leaves can become as long as 30 centimeters. Ten to twelve serrated leaflets, each averaging 7 centimeters long and 2.5 centimeters broad, make up each leaf. Neem is typically grown in the southern parts of Asia and Africa where it has long been used in traditional medicine. Neem thrives in low-rainfall areas.. It is found in various states such as Andhra Pradesh, Assam, Delhi, Haryana, Bihar, Meghalaya, Odisha, Gujarat, Punjab, West Bengal and Rajasthan. Azadirachta indica preparations are highly popular in many countries for managing different ailments.The significance of neem is also supported by various holy books such as the Bible and the Quran, highlighting its role in healthcare and disease prevention.The US National Academy of

Sciences acknowledged the significance of the neem tree in a 1992 paper titled "Neem - a tree for solving global problems."

The medicinal properties of neem have been recognized since ancient times, making it a revered tree in India for centuries. Every component of the neem tree, including the bark, fruit, leaves, flowers, gum, and oil, has been used in traditional medicine to treat problems including cancer, hypertension, heart disease, and diabetes. Traditional uses include employing the leaves and their paste to alleviate allergic skin reactions and as antiviral remedies for conditions such as smallpox and chickenpox [4]. In urban areas of Nepal, India, and Bangladesh, it is common practice for people to brush their teeth using neem twigs. Neem leaf juice is consumed as a tonic to increase appetite and get rid of intestinal worms [5]. Neem is widely known for its capacity to help regulate fever as well as its hypolipidemic, hypoglycemic, hypotensive and hepatoprotective qualities [6]. In addition, the leaf extract's antimicrobial properties against tooth diseases are used therapeutically. [7]. Neem oil is currently accessible in northeastern India and is used extensively in the production of mosquito-repellent pills and is used in the Ayurvedic medical system to treat malarial fever [7], [8]. [5], [6], [7]. Furthermore, neem has numerous medicinal applications, with formulated products targeting conditions such as AIDS, cancer, digestive disorders, and skin diseases [9].Neem has long been used in Oman to treat fever and diabetes.

Today, neem holds significant importance in medicine due to its diverse chemical constituents, In-depth investigation has been made on the chemical constituents of numerous components derived from the neem tree. Among these components, the neem leaf stands out as a rich source of organic compounds, serving as a veritable repository of beneficial substances. Notably, neem leaves contain approximately 0.13% essential oil, which imparts the characteristic aroma to the leaves.. Furthermore, researchers have successfully isolated more than 140 active substances from different parts of the neem tree, exhibiting diverse chemical structures and

complex compositions. These compounds can be broadly categorized into two main classes: isoprenoids and nonisoprenoids.Isoprenoids, a class of compounds found in neem, encompass diterpenoids, triterpenoids, vilasinin compounds, limonoids and their derivatives, as well as C-secomeliacins. On the other hand, non isoprenoids consist of proteins, sulfurous compounds, polysaccharides, polyphenolics like flavonoids and their glycosides, coumarin, dihydrochalone,tannins, and aliphatic compounds [3-7].The highly active chemical compounds have a slight hydrophilic nature but are predominantly lipophilic, exhibiting better solubility in organic solvents such as alcohol,water, esters, and ketones [12].

BIOACTIVE COMPOUNDS PRESENT IN AZADIRACHTA INDICA

Neem, scientifically known as Azadirachta indica, possesses numerous active compounds with therapeutic properties. Different parts of the neem tree, including the leaves, bark, fruits, oil and seeds, are utilized for their therapeutic properties. Over 135 phytocompounds have been isolated from different parts of Neem trees. Among them, nine limonoids classified as triterpenes, namely azadirachtin A–G (primarily found in leaves), have been extensively studied due to their potent insecticidal properties. Additionally, the bark contains a significant amount of lignans [3]. Other bioactive compounds found in Neem oil studies include salannin, meliantriol,nimbin, meliacin, tignic acid, gedunin (also present in leaves), nimbidin, nimbidinin, nimbidic acid,nimbolide (found in leaves), deacetylnimbin, meliacin, linoleic acid, linalool oxide, palmitic acid, oleic acid, azadiradione, hexadecanoic acid, stearic acid, valassin, caryophyllene oxide, mahmoodin, margolone, azadirone, nimbinene ,nimbolin and nimbosterol. Neem kernels contain 30–50% oil, primarily utilized in soaps, biopesticides, and pharmaceuticals [3,11–13]. Furthermore, non isoprenoid compounds present in Neem trees encompass proteins (amino acids), sulfurous compounds, carbohydrates (polysaccharides), polyphenolics such as flavonoids and their glycosides,ferulic acid, dihydrochalcone, carotenoids, rutin,catechin, β-sitosterol, quercetin,steroids (found in leaves and/or bark), coumarin and tannins (produced in the bark),

ellagic acid, aliphatic compounds, lupeol, saponins (leaves), alkaloids (leaves), gums, resins, margisine, cyclic trisulphide, ketones and steroid. [3,4,13,14].

Azadirachta indica, a plant known for its various physiological defense mechanisms against potentially hazardous environmental influences, contains phyto components whose concentrations can be influenced by factors like harvesting method and storage conditions. Recent literature highlights the plant's medicinal properties, including chemopreventive, antiseptic, and anti-inflammatory activities. Additionally, it possesses pharmacological effects such as antidiabetic, antioxidant, and antileishmaniasis properties.

UNVEILING THE THERAPEUTIC POTENTIAL OF AZADIRACHTA INDICA

Neem (Azadirachta indica) is a tree native to the Indian subcontinent known for its medicinal properties. Neem leaves have been traditionally utilized in a variety of ways, including powder, oil, and extracts, to treat a broad range of health conditions owing to their potent antimicrobial properties. The antimicrobial activity of neem leaves can be attributed to several key mechanisms:

Antimicrobial

Neem (Azadirachta indica) contains secondary metabolites like glycosides, alkaloids, flavonoids, and saponins, which have antibacterial, antifungal, and antioxidant properties, aiding in its defense against pathogens [14,22]. Neem oil from the seeds, bark, and leaves showed antimicrobial efficacy against both Gram-positive and Gram-negative bacteria, whereas methanolic neem leaf extracts inhibited Bacillus. Notably, neem extracts effectively combated bacteria commonly found on the skin, such as Staphylococcus aureus , Streptococcus mutans, and M. pyogenes[4]. Isolated compounds from neem, such as β-sitosterol, nimbolide, and nimbidin, demonstrated antibacterial and antifungal activities against various species [4,14]. Neem

extracts also proved effective against dermatophytes like Trichophyton mentagrophytes and T. rubrum [24]. Additionally, the antifungal and antioxidant effects of neem were attributed to sulfur-containing compounds and flavonoids present in its leaves [14]. Nimbolide, when combined with antibiotics, exhibited significant inhibition against bacteria, including methicillin-resistant S. aureus (MRSA) [27].

A comparison was made between the alcoholic extract of neem leaves and the standard gentamicin, revealing the former's antimicrobial properties. Notably, the alcoholic neem extract demonstrated the most substantial inhibition against bacillus pumillus, pseudomonas aeruginosa, and staphylococcus aureus. Additionally, the neem extract was found effective in inhibiting the growth of the carcinogenic bacterium S. sobrinus, as reported by Md. Mohashine Bhuiyan et al. in 1997 (11).

Another research study was carried out to assess the potential bioactive compound for developing a new antimicrobial agent. The study utilized cultured bacteria, specifically staphylococcus aureus and enterococcus faecalis. The findings showed that neem bark extract had considerable antimicrobial action against pseudomonas aeruginosa, proteus mirabilis, and enterococcus faecalis at all doses tested, whereas neem leaf extract had strong antibacterial activity. Neem oil from the seeds, bark, and leaves showed antibacterial efficacy against both Gram-positive and Gram-negative bacteria, whereas methanolic neem leaf extracts inhibited Bacillus. Additionally, the seed extract demonstrated antifungal activity, particularly at concentrations of 1000 and 2000 μg/ml, showing effectiveness against candida albicans. However, the seed extract did not exhibit any antibacterial activity under the conditions tested (12).On the other hand, when compared to the chloroform extract, the latter (C.E) demonstrated more potent antimicrobial activity against gram-positive bacteria, including S. aureus, S. pneumoniae, B. subtilis and B. cereus.

These findings indicate that the neem leaf extract contains diverse phytochemicals, and their potential additive or synergistic effects, position it as a promising resource for developing antimicrobial treatments.

Antibacterial

Neem oil, obtained from neem leaves, bark and seeds, exhibits broad-spectrum antibacterial activity against both Gram-negative and Gram-positive microorganisms, including drug-resistant strains like M. tuberculosis. It also shows inhibitory effects against specific bacteria such as Vibrio cholerae, Klebsiella pneumoniae, Streptococcus mutans, and Enterococcus faecalis. Moreover, a new vaginal contraceptive derived from neem oil, called NIM-76, has demonstrated inhibitory effects on various pathogens, including bacteria, fungi, and viruses. Recent studies have also assessed the antibacterial activity of neem seed oil against 14 strains of pathogenic bacteria in vitro.

Gayathri R Menon et al. (2016) found that neem oil showed the maximum inhibition against Streptococcus mutans, Enterococcus faecalis, and Lactobacillus acidophilus. Uwibabazi Francin et al. (2015) compared the effects of neem extracts on Staphylococcus aureus and Escherichia coli, with ethanol extracts from neem bark and leaves showing greater efficiency. Oluwajobi Iyanuloluwa et al. (2019) examined the antibacterial activity of the aqueous extract of neem leaves compared to Psidium guajava and Vernonia amygdalina, and found that neem displayed superior antibacterial effects.Overall, neem extracts offer promising antibacterial effects and hold potential for diverse applications in combating bacterial infections.

Anti-Cancer

Neem (Azadirachta indica) has been extensively studied for its potential anticancer properties. Different studies have explored its various chemical constituents, such as azadirachtin, nimbolide, limonoid, and azadiramide A, have demonstrated promising anti-cancer effects. Nimbolide and azadirone have induced apoptosis through ROS-mediated mechanisms. Azadiramide A, a recently discovered alkaloid, has exhibited anti-cancer effects in breast cancer cell lines.These compounds interfere with various pathways that control cell growth, apoptosis, and chemo-protection. Neem extracts have been shown to suppress the NF-κβ pathway and reduce the expression of certain proteins associated with cell proliferation. Neem extracts, including aqueous and ethanolic extracts, have been found to enhance the activity of enzymes involved in maintaining cell integrity and detoxifying carcinogens. These extracts also show cytotoxic effects on cancer cells in a time and dose-dependent manner.

Neem leaf extracts have also demonstrated apoptosis-inducing activity by inhibiting IGF signaling molecules. Furthermore, compounds like NLGP have shown immunomodulatory effects by regulating immune cells and cytokines, helping to normalize the immune microenvironment of tumors.Overall, the studies emphasize the potential of neem and its compounds as effective anti-cancer agents with diverse mechanisms of action, making them a promising area of research in cancer therapy.

Anti-Malarial

Neem (Azadirachta indica) has been traditionally used by various tribes in the subcontinent to treat malaria. Studies have explored the chemical constituents of neem seed and leaf extracts and their effects on malaria-causing parasites including drug-sensitive and drug-resistant strains

of Plasmodium falciparum. The extracts contain various active compounds such as tannins, glycosides, alkaloids, flavonoids, terpenoids, saponin, reducing sugar, and volatile oil. The alcoholic extracts from neem leaves and seeds contain flavonoids, saponin, tannins, and reducing sugar , show efficacy against these parasites while acetone and ethanol extracts contained saponin, and methanol extract had terpenoids. These constituents exhibited antiprotozoal activity and demonstrated anti-plasmodium effects against the malaria parasite. Compounds like azadirachtin, gedunin, and meldenina found in neem have also shown antimalarial properties. Studies on male Wistar rats confirmed the safety and non-toxic nature of neem leaf extract, further supporting its potential as a safe and effective anti-malarial treatment. Overall, neem's chemical constituents and their anti-plasmodium activity make it a promising natural remedy for malaria, aligning with its traditional medicinal use by various communities.

Anti-inflammatory

Neem extracts possess significant anti-inflammatory properties, attributed to bioactive compounds like limonoid and epoxy-azadiradione. These compounds inhibit the production of inflammatory mediators and cytokines, reducing inflammation and its associated effects. Neem's ability to inhibit cyclooxygenases 1 and 2 (COX1 and COX2) also contributes to its anti-inflammatory activity by modulating eicosanoid metabolism. Furthermore, Neem extracts interfere with NF-kβ, a key factor in the production of inflammatory cytokines, thus reducing the overall inflammatory response. This anti-inflammatory potential makes Neem extracts a promising candidate for addressing various diseases involving inflammation, including cancer and autoimmune disorders.

Anti-Diabetic

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Antioxidant

Neem extracts have been studied for their antioxidant properties, and they have shown to boost the body's natural defenses.Several studies have demonstrated the antioxidant effects of Neem extracts. For instance, an extract from Neem leaves and methanol was tested on rats with induced intestinal ischemic-reperfusion injury (IIRI). The extract reduced inflammation markers and increased glutathione levels, enhancing the body's defense mechanisms. In another study, Neem extract was administered to rats with colitis induced by acetic acid, resulting in a reduction of colonic tissue damage and inflammation. The extract also restored the activity of antioxidant enzymes.In the another study, the ethanolic fraction of neem flower showed the highest scavenging activity against the 2,2-diphenyl-2-picrylhydrazyl (DPPH) free radical, with a percentage of 64.17%. In comparison, the methanol and water extracts exhibited scavenging activities of 52.30% and 41.03%, respectively.In summary, Neem extracts have shown promising antioxidant activity and the ability to enhance the body's natural antioxidant defenses, making them a potentially valuable addition to the diet for combating inflammation and oxidative stress.

UTILIZING NEEM'S EXTRACTS FOR INDUSTRIAL INNOVATIONS

Neem, a versatile botanical treasure, has found diverse applications due to its potent extracts. From serving as fungicides and antibacterial agents to aiding wound healing, wound contraction, and even acting as a potential male contraceptive, neem's properties have attracted significant interest and research.

IN PEST CONTROL AND SURFACE COATINGS

Neem extracts, notably Azadirachtin, serve as effective fungicides, insecticides, and antibacterial agents. The disruption of mitochondrial oxidative phosphorylation by Azadirachtin inhibits respiratory chains, and other compounds like nimbidin further enhance antibacterial properties. These extracts have emerged as effective tools in agricultural and residential pest control. With an estimated market cap of $16.2 billion, expected to soar to over $27 billion by 2025, these extracts play a pivotal role in this rapidly growing sector. Additionally, they have expanded into surface coatings for diverse applications such as residential, medical, and commercial use, driven by the demand for sterile environments and the benefits of neem's antimicrobial attributes.

Wound Healing and Exciting Potential:

Neem's wound healing prowess has been under the spotlight. Studies on neem's stem bark extract showcased its remarkable efficacy in wound closure and contraction, surpassing standard treatments. This potential is further underscored by the accelerated wound healing observed in diabetic rats using neem ointment and gel. Such findings indicate a promising future for neem in wound healing applications.

MALE CONTRACEPTIVE AND UNIQUE ATTRIBUTES

Neem has been explored as a novel male contraceptive, offering an alternative to traditional methods. Injecting neem oil into the vas deferens of rats led to successful contraception without impacting hormones or libido. Neem oil extracts formulated in vaginal creams demonstrated contraceptive efficacy without disrupting the ovulation cycle. Notably, neem's application circumvents hormonal regulation issues associated with traditional contraceptives, presenting an appealing option for birth control.

DIABETES MANAGEMENT AND HEALTH ENHANCEMENT

The role of neem in diabetes management is significant. Neem's potential to stimulate beta cells and enhance insulin production marks a breakthrough. Research also validates its glycemic control properties, attributed to compounds like nimbidin. Encapsulated neem extract pills exhibit blood antioxidant activity and counter cardiovascular markers. The presence of Tannins in these formulations offers oxidative stress reduction and potential weight loss benefits.

SUN PROTECTION AND COSMETIC POTENTIAL

Neem's influence extends to cosmetics, where its oil enhances sun protection factor (SPF) values in creams. This signifies neem's potential as a multifunctional sunscreen ingredient. With satisfactory safety profiles established in cosmetic applications, neem is poised to revolutionize the skincare industry.

Neem's extracts, harnessed for diverse purposes, hold immense promise for pest control, wound healing, contraception, diabetes management, sun protection, and cosmetic innovation. As scientific exploration continues, the multifaceted properties of neem extracts offer a compelling avenue for improving quality of life and expanding possibilities across various fields.

CONCLUSION

In conclusion, Neem (Azadirachta indica) emerges as a remarkable botanical asset with versatile applications driven by its potent extracts. Its historical significance in traditional medicine finds resonance in modern research, unveiling a spectrum of mechanisms and benefits. From its antimicrobial, anti-inflammatory, and antioxidant properties to potential anti-cancer effects, Neem's compounds offer diverse therapeutic potential.The multifaceted nature of Neem's chemical constituents, soluble in various solvents, equips it for combating diseases and promoting well-being. Its industrial applications, notably in pest control and coatings, reflect its market impact. Neem's wound healing and diabetes management potential, unique male contraceptive attributes, and contributions to sun protection and cosmetics highlight its healthcare and cosmetic relevance.

Looking forward, Neem's potential remains vast. Further research can uncover novel applications, refine existing formulations, and uncover new mechanisms of action. Neem's rich legacy, paired with its modern exploration, positions it as a bridge between tradition and innovation, offering an array of possibilities for improved health, well-being, and industrial advancement. As scientific investigation advances, Neem's promising future continues to inspire exploration and innovation.