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Therapeutic Applications of Neem and Its Various Ingredients in Health Management

[1]Ram Ratan, [2]Dr. Vivek Gupta and [3]Dr. Jitendra Malik

[1]Ph.D., Research Scholar, Department of Pharmacology, Faculty of Pharmacy, PK University, Shivpuri, Madhya Pradesh, India
[2]Principal (Professor), Department of Pharmaceutical Chemistry, Faculty of Pharmacy, PK University, Shivpuri, Madhya Pradesh, India
[3]Professor, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, PK University, Shivpuri, Madhya Pradesh, India

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Corresponding Author: Ram Ratan

Abstract

The Meliaceae family includes the health-promoting neem (*Azadirachta indica*), which gets its beneficial effects from the abundance of antioxidants it contains. Traditional Chinese, Ayurvedic, and Unani medicine practitioners have long relied on it for the treatment and prevention of a broad range of illnesses, particularly on the Indian subcontinent. Cancer is a multi-faceted disease with many potential origins; it is a major worldwide health problem. Some of the biochemical and genetic processes that cause cancer to start and spread are altered. Normal cells have certain adverse consequences from the allopathic treatment module, despite its beneficial advantages. By soaking in a neem leaf infusion, their skin stayed supple and healthy. Their facial treatments included neem leaf powder or mashed, which has emollient and anti-aging properties. The antibacterial properties of neem make it an effective tool in the fight against acne. Crucial for regulating cell death is the role of bcl2 and bax. Whenever bcl2 and bax levels alter, cancer develops and progresses.

Keywords: Neem, Antioxidants, *Azadirachta indica*, Cancer and biochemical

Introduction

Neem, margosa, nimtree, and Indian lilac are all names for the same tree-*Azadirachta indica* - It is a mahogany tree species belonging to the Meliaceae family. The genus Azadirachta counts it among its two species. Originally from the Indian subcontinent and several Southeast Asian countries, it is now cultivated and naturalized all over the globe in tropical and subtropical climates. The oil derived from the neem tree's fruits and seeds is called neem oil. The Hindustani term nim comes from the Sanskrit word nimba (निंब). It is not uncommon for margosa trees to reach a height of 35–40 meters (115–131 feet), although most often they reach 15-20 meters (49–66 feet). It continues to grow year-round but loses a significant quantity of winter leaves. A vast expanse of branches extended forth. In potential growth, the rather thick and round crown may reach a diameter of 20–25 meters, or 66–82 feet.

On one side, you have 20 to 30 dark green leaflets that are around 3-8 cm (1+1⁄4-3+1⁄4 in) long, while on the other side, you have 20-40 cm (8-16 in) long pinnate leaves. Frequently, the concluding pamphlet is absent. There aren't many petioles. Axillary panicles, which may reach a length of 25 cm (10 in), are adorned with fragrant white flowers. Between two hundred and three hundred blooms are produced by inflorescences that branch to a third degree. The length inside a single bloom measures 5-6 mm (3⁄16-1⁄4 in) and its width is 8-11 mm (5⁄16-7⁄16 in). There are male blooms and protandrous, bisexual flowers on the same tree. As people have spread throughout the country, the legendary Indian medicinal tree has grown in importance and become an integral part of Indian culture. In many ways, the neem tree represents the past and present of Indian

culture. Native Indians have looked up to the neem tree for generations, seeing it as a protector and friend. The indigenous people of this land have long held the belief that this tree has curative powers for a variety of ailments.

Additionally, it has a long history of usage as a storage herbicide, fertilizer for fields, and natural pesticide for food and grains. Compared to other trees, it has the most practical uses. The neem tree, scientifically known as Perhaps the most well-kept secret in India was *Azadirachta indica* A. Juss. Historically, Europe has been the recipient of much-desired commodities originating from ancient India, such as black pepper, cardamom, saffron, turmeric, sandalwood, and silk. This tree's extensive distribution throughout India-apart from the coastal regions and the Himalayas-was another aspect that the British Raj failed to comprehend. Perhaps the neem tree would have achieved worldwide prominence much earlier if its incredible versatility had been known to them. For several reasons, the neem tree captivated the Indians.

We chose this tree because it is said to provide the coolest shade of any tree and to keep insects and vermin at bay. When it came to women's natural beauty practices, neem was the bedrock. Additionally, it was used as a remedy for more than a hundred different diseases and ailments, including diabetes, malaria, and skin rashes and scrapes. It served the ladies well all year round, protecting their stored grains and pulses. The seeds, leaves, and bark that the tree provided helped the men with insect control and fertilization. They might also use the therapeutic combinations it produced for their cattle and other animals. Their houses were also kept cool and virus-free by the air that swept through the branches of the tree throughout summer. Ancient Indians often interacted gently with this remarkable plant and planted it near their houses. Women, in particular, benefited greatly from the free and invaluable neem oil, which improved their health, cleanliness, and appearance.

Their skin remained soft and healthy by bathing in an infusion made from neem leaves. The anti-aging and emollient benefits of neem leaf powder or crushed were a part of their face treatments. Because of its antimicrobial characteristics, neem is useful for clearing up acne. In certain regions of India, particularly among young ladies who like to flaunt their eyes, it was customary practice to apply coryllium, often called lamp black, to the outer corner of the eye. Traditional lamp black was made by placing a cotton wick and neem oil inside an earthen lamp. Lighted wicks produce copious amounts of smoke, which, when collected in a bronze cup with water inside to cool, may be used to make lamp black.

Literature Review

Españo, *et al*. (2021) [1]. There are currently no approved drugs to treat acute viral diseases, and the 2019 coronavirus disease pandemic (COVID-19) has brought this issue to attention. Despite the lack of efficacy of compounds derived from plants as antivirals, plants are thought to be an endless supply of medications for many illnesses and clinical situations. In this paper, we argue that vascular plant chemicals such as tannins, polyphenols, alkaloids, and flavonoids might be useful as antivirals, especially against the COVID-19 virus. We provide their possible targets in the SARS-CoV-2 replication cycle and examine the existing evidence for the use of these phytochemicals against SARS-CoV-2 infection.

Velmurugan, *et al*. (2018) [2]. Typically, conditions characterized by the demise of neurons are identified as neurodegenerative diseases. While there are a number of substances under investigation for the treatment of neurodegenerative disorders (NDs), many only provide limited symptom relief and come with a laundry list of unwanted side effects. Phytochemicals have shown promise in certain studies aimed at treating neurodegenerative diseases including Alzheimer's and Parkinson's. Phytochemicals such as limonoids, resveratrol, quercetin, berberin, curcumin, and epigallocatechin-3-galate were investigated for their potential anti-AD and PD effects in this study. Further investigation is necessary to confirm the positive effects of these phytochemicals on slowing the development of AD and PD, but preliminary data suggests they may be useful.

Healy, *et al*. (2022) [3]. There has been minimal advancement in treating primary progressive MS and secondary progressive MS, despite the development of highly effective treatments for relapsing-remitting MS. Both forms of the disease cause the irreversible accumulation of disability and the loss of oligodendrocytes, neurons, and axons. All kinds of multiple sclerosis revolve on neuroinflammation. The peripheral immune system is the focus of the present successful therapeutics for relapsing-remitting MS; nevertheless, these medications have shown a consistent inability to slow the progression of progressive MS. To find new ways to treat inflammation, we need a better grasp of how cells found in the CNS, including microglia and astrocytes, cause it. New insights from genetics, imaging, and biomarker studies point to microglia and astrocytes as key players in the development of illness. We summarize the role of astrocytes and microglia at key pathological locations in the progression of multiple sclerosis in this Review. We go over some of the existing and potential future treatments that aim squarely at glial cells, with the goal of reversing pathogenic activities or reestablishing homeostatic processes that have been lost as a result of the illness.

Antioxidant Activity

Reactive oxygen species, sometimes known as free radicals, significantly aid in the advancement of many illnesses. One of the critical stages in preventing the illness, however, is neutralizing free radical activity. To regulate damage induced Antioxidants neutralize and stabilize free radicals and reactive oxygen species (ROS) before they damage or destroy biological cells. They also activate antioxidative enzymes. There have been reports of medicinal plants exhibiting antioxidant properties.

Because they contain a lot of fruits, seeds, oil, leaves, bark, and roots are all elements of plants that contain antioxidants and may help keep diseases at bay. In particular, all of the fractions of neem grown in the foothills that were studied had outstanding antioxidant properties, and studies on the antioxidant activity of A. indica bark and leaf extracts have showed encouraging findings. The antioxidant activity of several extracts from the Siamese neem tree, such as leaves, fruits, blossoms, and stem bark, has been the subject of

much investigation. The results show that these fractions possess considerable antioxidant potential.

Important research is a study that looked at the antioxidant activity of several crude extracts of neem leaves (*Azadirachta indica*). The most effective antioxidants were determined to be these crude extracts: The extraction procedures were carried out in the following sequence: chloroform, butanol, ethyl acetate, hexane, and methanol/ethanol. This study's results provide support for the possibility that neem's chloroform crude extracts have antioxidant properties.

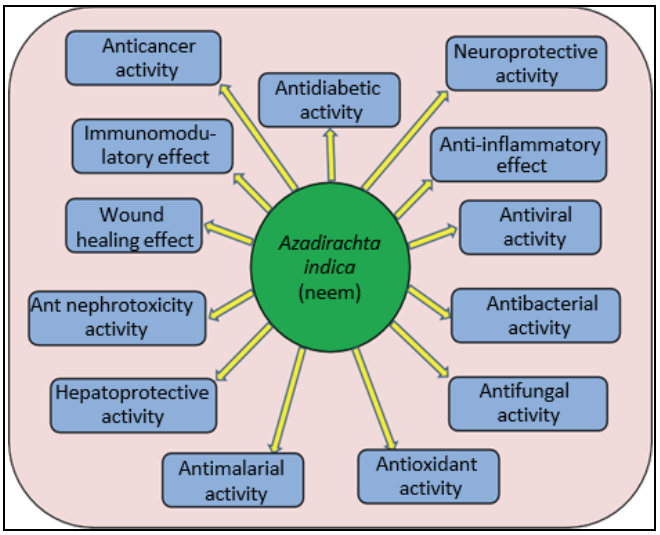

Fig 1: Pharmacological activities of *Azadirachta indica* L. neem in diseases management through the modulation of various activities

Additionally, the findings indicated that nimbolide had the highest reductive potential and antiradical scavenging activity, The sequence of concentration is ascorbate, azadirachtin, and subsequent compounds. The development of DMBA-induced HBP carcinomas might be avoided by treating with azadirachtin and nimbolide. These compounds inhibited procarcinogen activation and oxidative DNA damage while upregulating enzymes that detoxify carcinogens and antioxidants. Experiments were conducted to determine the antioxidant activity of the neem plant's seed oil and floral components. According to the findings, the free radical scavenging activity was 64.17 ± 0.02%, which was the greatest for the ethanolic floral extract. and the seed oil at 66.34 ± 0.06%, when tested at 200 μg/mL.

Anticancerous Activity

A severe health concern on a global scale, cancer is a complex illness with several causes. Cancer begins and advances due in part to changes in molecular and genetic pathways. Although the allopathic therapy module has some positive effects, it also has some negative effects on normal cells. Through influencing several biochemical pathways, such as cellular proliferation, apoptosis, and the tumor suppressor gene, previous studies have shown that plant components may inhibit the formation of cancer cells. Just think of all the components in neem, including flavanoids, that suppress the progression of cancer (Figure 2). A large body of epidemiological evidence suggests that a lower cancer risk may be associated with a greater flavonoid consumption.

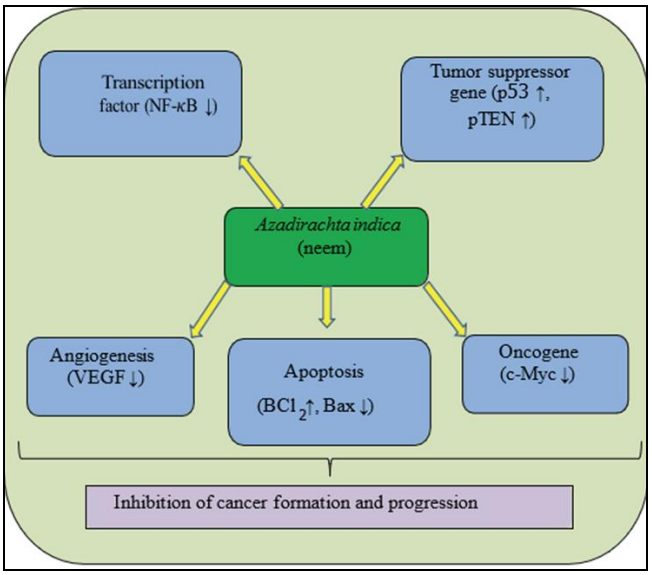

Fig 2: Anticancerous activities of *Azadirachta indica* L. neem through the modulation of various cell signaling pathways

A number of neem limonoids found in neem oil mitigate the carcinogenic effects of 7,12-dimethylbenz(a)anthracene is the chemical name. The cytotoxic effects of nimbolide, which is present in both flowers and leaves, were examined in a study on human choriocarcinoma (BeWo) cells. Nimboide treatment suppressed BeWo cell proliferation with dose- and time-dependent effects, as shown by the IC50 values. of 2.01 μM for 7 hours and 1.19 μM for 24 hours, respectively. Researchers looked at the limonoids azadirachtin and nimbolide to see if they could stave off DMBA-induced HBP carcinomas. They found that both compounds inhibited tumor invasion and angiogenesis, enzymes that detoxify carcinogens and antioxidants were increased, and prevented procarcinogen activation and oxidative DNA damage.

Effect of neem and its constituents on tumour suppressor genes

An essential p53, a tumor suppressor gene, aids in reducing the development and metastasis of cancer by halting the proliferation of malignant cells. A formulation using an ethanolic fraction of neem leaf (EFNL) was discovered by researchers to boost levels of many proapoptotic genes and proteins in rats. These genes and proteins include p53, Bax, Bad, caspases, phosphatase and tensin homolog gene (pTEN), and c-Jun N-terminal kinase (JNK). Scientists have found evidence indicating produced by 7,12-dimethylbenz (a) anthracene had their Bcl-2 and mutant p53 expression inhibited by ethanolic neem leaf extract, while proapoptotic genes like caspase-8 and caspase-3 were stimulated.

A major component nimbolide, a tetranortriterpenoid limonoid, is responsible for the cytotoxicity of neem extracts. Nimbolide had the opposite effect on cell survival proteins, increasing levels of proapoptotic p53 and Bax and reducing levels of surviving, X-linked inhibitor of apoptosis, Bcl-2, Bcl-xL, and I-FLICE. Many times, promoter methylation silencing, deletions, or mutations lead to the depletion of pTEN function in numerous kinds of malignancies, both primary and metastatic. Multiple tumor forms have been shown to have pTEN inactivation.

Research has shown that treating mice with an ethanolic fraction of neem leaves considerably upregulated pTEN expression, which may prevent mammary tumorigenesis by inhibiting Akt.

Effect of neem and its constituents on apoptosis

When it comes to controlling the cell death process, bcl2 and bax are crucial. Cancer starts and grows in response to changes in bcl2 and bax. Many malignancies have altered the expression of these genes. Results using an *in vivo* 4T1 breast cancer model in mice, demonstrated that apoptosis was more common in the CN 250 and CN 500 groups than in the cancer control group. The research aimed to evaluate the impact of extract on this model. Another research found that the extract induced apoptosis, which led to the cell death of PC-3 prostate cancer cells. Results showed that leaf extract reduced the viability found it elevated the expression of Bim, caspase-8, and caspase-3 in the buccal pouch, indicating that it triggers cell death in the target organ, and that it caused dose-dependent apoptosis in chronic lymphocytic leukemia (CLL) cells, with considerable cell death happening at 0.06% (w/v) after 24 hours. Cell death during apoptosis in cancer is one among the many targets impacted by the wide variety of actions shown by isolated compounds and primary components of neem.

Effect of neem and its constituents on angiogenesis

A tumor's ability to grow and metastasize depends on angiogenesis, transporting blood to the tissues via a complex procedure. In addition to activators, inhibitors have a role in controlling angiogenesis. A critical step in inhibiting or preventing tumor growth is the discovery of antiangiogenic medicines, which act as roadblocks to the formation of new blood vessels. The antiangiogenic action of medicinal herbs and their constituents helps to inhibit tumor development.

Results from significant research showed that EFNL has antiangiogenic potential by inhibiting development of genes that promote angiogenesis, vascular endothelial growth factor A, and angiopoietin. It is also possible to understand why neem leaf ethanolic fraction (EFNL) suppresses angiogenesis, as shown in the current study there has been a decrease in breast tumor volume and no new tumors have developed. Another study examined the ability of the leaf extract to inhibit the growth of blood vessel endothelial cells in the human umbilical vein (HUVECs). Results showed that EENL reduced VEFG-induced angiogenic response in both animal models and laboratory settings, and it also reduced HUVEC migration, invasion, and proliferation. Zebra fish embryos were exposed to several concentrations of imatinib (control), standard, and a crude methanolic extract of neem root containing water-soluble fractions. The results showed that the latter may inhibit angiogenesis.

Effect of neem on oncogene

The expansion and progression of malignancies are significantly impacted by oncogenes, which are altered genes. The experimental group given neem leaf extract at a dose of 500 mg/kg (C500) demonstrated a statistically significant reduction in c-Myc oncogene expression compared to the cancer control group in a study examining the effects of leaf extract on c-Myc oncogene expression in 4T1 breast cancer BALB/c mice.

Effect of neem on pi3k/akt pathways

The pathway PI3K/Akt mediates a critical role in tumor promotion. One key step in regulating tumor formation, however, is suppression of PI3K/Akt pathways. Researchers looked at how leaf extract affected the pathways involving PI3K/Akt and cell death in PC-3 and LNCaP prostate cancer cell lines. The findings showed that the leaf extract inhibited cell growth and induced apoptosis in both cell lines.

Research into the molecular pathways by which Inhibiting cell growth and inducing cell death in human breast cancer cell lines is achieved by use of a leaf extract. has shown that cells treated with extract exhibit a marked reduction in the expression of proteins including cyclin D1, p-Erk, p-Akt, and IGF signaling molecules Ras and Raf. Nimbolide is a powerful anticancer drug because it Another research looked at its effects on apoptosis and insulin-like growth factor (IGF) signaling molecules in androgen-independent prostate cancer (PC-3) cells, and found that it causes apoptosis and suppresses cell proliferation via the PI3K/Akt pathway cell line.

Effect of neem as anti-inflammatory

The use of anti-inflammatory medications derived from plants or their constituents is widespread. A. indica leaf extract's anti-inflammatory properties were validated in rat research using the cotton pellet granuloma test, with a dosage of 200 mg/kg. Additional research detected a significant decrease in inflammation when administered neem leaf extract, but to a lesser extent than dexamethasone. The data also indicated that nimbidin inhibits the inflammatory-related activities of neutrophils and macrophages.

Previous research shown that oil seed extracts had antipyretic and anti-inflammatory properties, while the anti-inflammatory and immunomodulatory effects were mediated by extracts of bark and leaves. Neem seed oil's analgesic properties were studied in albino rats. At 1 and 2 mL/kg dosages, the oil had a significant analgesic effect, and the effect was dose-dependent.

Albino rats were used in another research to examine neem seed oil's (NSO) anti-inflammatory properties. Results showed that the quantity of NSO required to prevent swelling in rats subjected to carrageenan-induced hind paw edema increased from 0.25 mL to 2 mL/kg body weight. At 4 hours post-carrageenan injection, the most effective dose of NSO for edema suppression was 2 mL/kg body weight (53.14%). The research found that rats administered a 100 mg kg^{-1} dose of *Azadirachta indica* fruit skin carbon tetrachloride extract (CTCE) and the isolated chemical azadiradione showed significant efficacy against inflammation and pain.

Conclusion

Traditional medicine practitioners all throughout the globe, but notably on the Indian subcontinent, have long recognized the medicinal properties of neem and its constituents. You won't find a tree with more useful applications than this one. The neem tree, formally known as *Azadirachta indica* A. Juss, is one of India's best-kept secrets. Black pepper, cardamom, saffron, turmeric, sandalwood, and silk are just a few of the ancient Indian goods that have long been prized by Europeans. Neem has a

long history of usage as a medicine, with mixed results in preventing and treating illness. A lack of repeatability in production is a result of the fact that these extract-based therapies are being utilized as supplemental medicine today and are often acquired via the artisanal way. Diabetes, malaria, and skin rashes and scrapes were among the over a hundred illnesses and maladies for which it was prescribed. It kept the women's grains and pulses safe throughout the year, which was a great service.

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