IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 2, August 2024

Azadirachta indica (Neem) and its Active Ingredients' Therapeutic Significance in the Prevention and Treatment of Diseases

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Abstract: *Neem (Azadirachta indica) belongs to the Meliaceae family and is known for its health-promoting effects due to its high antioxidant content. It has been extensively utilised in Chinese, Ayurvedic, and Unani remedies globally, particularly in the Indian Subcontinent, for the treatment and prevention of several ailments. Prior research has established that neem and its components are involved in the removal of free radicals and the prevention of disease development. Research conducted using animal models has demonstrated that neem and its primary components play a crucial role in the management of cancer by influencing numerous molecular pathways, such as p53, pTEN, NF-κB, PI3K/Akt, Bcl-2, and VEGF. Medicinal plants are often regarded as safe and have the ability to regulate many biological processes without causing any negative effects. This article provides an overview of the role of Azadirachtaindica in the prevention and treatment of illnesses by regulating different biological and physiological pathways.*

Keywords: Neem (Azadirachta indica)

I. INTRODUCTION

Plant-derived compounds play a significant role in preventing and treating diseases by increasing antioxidant activity, inhibiting bacterial development, and influencing genetic pathways. The medicinal potential of several plants in illness management is currently being actively explored due to its minimal side effects and cost-effective features. It is widely acknowledged that allopathic medications are costly and can have harmful effects on both healthy cells and numerous biological processes. It is well acknowledged that many pharmacologically potent medications are obtained from natural sources, such as medicinal plants. The Bible and Quran, among other holy texts, also endorse the use of herbs in healthcare and disease prevention. The Islamic viewpoint also acknowledges the significance of herbs in managing diseases, and Prophet Mohammed (PBUH) advised the use of several plants and fruits for treating illnesses. Neem components are utilised in Ayurveda, Unani, Homoeopathy, and modern medicine to treat various infectious, metabolic, and cancerous conditions. Various forms of plant-based preparations, utilising different parts of plants or their components, are widely embraced in numerous countries for the purpose of managing ailments. Neem (Azadirachta indica), a plant belonging to the Meliaceae family, is abundantly found in India, Pakistan, Bangladesh, and Nepal. It has therapeutic implications for disease treatment and formulation due to its use in treating numerous ailments. Azadirachta indica has a combination of several components, including as nimbin, nimbidin, nimbolide, and limonoids. These compounds have a function in managing disorders by influencing numerous genetic pathways and other activities. Quercetin and ß-sitosterol were initially isolated from the fresh leaves of neem. These polyphenolic flavonoids are recognised for their antifungal and antibacterial properties. Multiple biological and pharmacological actions, such as antibacterial, antifungal, and anti-inflammatory effects, have been documented. Prior researchers have validated the efficacy of neem in reducing inflammation, treating arthritis, reducing fever, lowering blood sugar levels, preventing gastric ulcers, combating fungal and bacterial infections, and inhibiting cancer growth. A comprehensive review has provided an overview of the diverse medicinal applications of neem. This article provides an overview of the role of neem and its active components in preventing and treating diseases by influencing several biological pathways.

DOI: 10.48175/IJARSCT-19418

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TABLE 1: Taxonomic position of Azadirachtaindica (neem).

Order	Rutales
Suborder	Rutinae
Family	Meliaceae
Subfamily	Melioideae
Tribe	Melieae
Genus	Azadirachta
Species	indica

Botanical Description of Neem

The neem tree, a member of the Meliaceae family, is predominantly found in tropical and semitropical regions such as India, Bangladesh, Pakistan, and Nepal. The tree is characterised by rapid growth, reaching heights of 20-23 meters. Its trunk is straight and has a diameter of approximately 4-5 feet. The leaves are compound and imparipinnate, consisting of 5 to 15 leaflets. The fruits of this plant are green drupes that undergo a colour transformation to a golden yellow shade when they ripen between the months of June and August. The taxonomic classification of Azadirachta indica (neem) is presented in Table 1.

Active Compounds of *Azadirachta indica* L. (Neem)

Azadirachta indica L. (neem) has a medicinal role in health management due to its abundant supply of diverse components. Azadirachtin is the primary active compound, while the other constituents include nimbolinin, nimbin, nimbidin, nimbidol, sodium nimbinate, gedunin, salannin, and quercetin. The leaves of this plant contain a variety of compounds including nimbin, nimbanene, 6-desacetylnimbinene, nimbandiol, nimbolide, ascorbic acid, n-hexacosanol, amino acid, 7-desacetyl-7-benzoylazadiradione, 7-desacetyl-7-benzoylgedunin, 17-hydroxyazadiradione, and nimbiol. Quercetin and ß-sitosterol, which are polyphenolic flavonoids, were extracted from fresh neem leaves. These compounds are known to possess antibacterial and antifungal effects. Additionally, neem seeds include important elements such as gedunin and azadirachtin.

Mechanism of Action of Active Compounds

Neem (Azadirachta indica), a plant belonging to the Meliaceae family, possesses therapeutic properties that can be utilised for the prevention and treatment of several ailments. However, the precise biochemical mechanism involved in preventing the development of disease is not fully comprehended. Azadirachta indica is believed to have a therapeutic effect because it has a high concentration of antioxidants and other useful active chemicals, including azadirachtin, nimbolinin, nimbin, nimbidin, nimbidol, salannin, and quercetin.

The potential mode of action of Azadirachta indica is outlined below.

The various portions of the Neem plant (Azadirachta indica) exhibit antimicrobial properties by inhibiting the growth of microorganisms and their ability to break down cell walls. Azadirachtin, a multifaceted tetranortriterpenoid limonoid found in seeds, is the primary component accountable for the antifeedant and poisonous effects on insects. The findings indicate that the ethanol extract derived from neem leaves had antibacterial effects against Staphylococcus aureus and MRSA in a laboratory setting. The most significant inhibitory effects were observed at a concentration of 100%.

(1) Neem has free radical scavenging activities as it is a rich source of antioxidants. The antiradical scavenging activity and reductive potential of azadirachtin and nimbolide were seen to be concentration-dependent, with nimbolide demonstrating the highest activity, followed by azadirachtin, and then ascorbate.

(2) The neem component plays a significant function in managing cancer by regulating cell signalling pathways. Neem regulates the function of different genes that limit cancer growth (such as p53 and pTEN), the formation of new blood

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vessels (angiogenesis) through VEGF, transcription factors (such as NF-κB), and cell death (apoptosis) through bcl2 and bax.

(3) Neem also acts as an anti-inflammatory agent by regulating the activity of proinflammatory enzymes, such as cyclooxygenase (COX) and lipoxygenase (LOX) enzymes.

Therapeutic Implications of Neem and Its Various Ingredients in Health Management

The activation of antioxidative enzymes, the disruption of bacterial cell walls, and the modulation of cellular pathways are all important roles played by active constituents in the treatment of illnesses and as chemopreventive agents. The pharmacological actions of neem are thoroughly addressed (Figure 1).

Antioxidant activity. Free radicals, also known as reactive oxygen species, play a significant role in the development of numerous diseases. Neutralising free radical activity is a crucial step in preventing illnesses. Antioxidants neutralise free radicals, typically before they can harm biological cells. They also contribute to the activation of antioxidative enzymes, which help regulate the damage caused by free radicals and reactive oxygen species. Medicinal herbs have been documented to possess antioxidant properties. The various parts of plants, such as fruits, seeds, oil, leaves, bark, and roots, have a significant role in preventing diseases since they are rich in antioxidants.

The antioxidant activity of leaf and bark extracts from A. indica has been examined, and the study's findings demonstrate that all evaluated extracts/fractions from neem trees cultivated in the foothills had noteworthy antioxidant characteristics. A significant study was conducted to evaluate the antioxidant activity of extracts obtained from the leaves, fruits, flowers, and stem bark of the Siamese neem tree. The findings indicate that the extracts derived from the leaf, flower, and stem bark had robust antioxidant properties.

A study of high value was conducted to assess the antioxidant activity in vitro of various crude extracts derived from the leaves of Azadirachta indica (neem). The antioxidant capacity of the different crude extracts was determined as follows: Chloroform is superior to butanol. The ethyl acetate extract is superior to the hexane extract, which is superior to the methanol extract. The recent findings indicate that the chloroform crude extracts of neem have the potential to be utilised as a natural antioxidant.

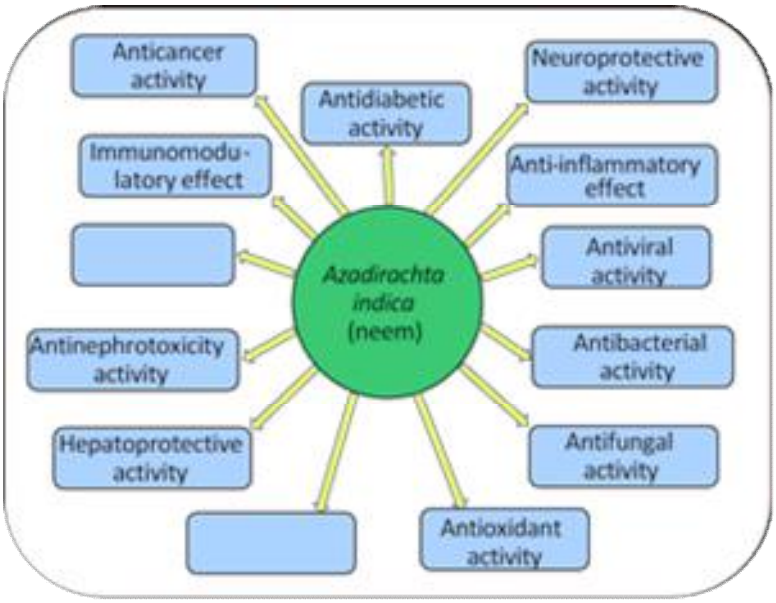

FIGURE 1: Pharmacological activities of *Azadirachta indica* L. neem in diseases management through the modulation of various activities.

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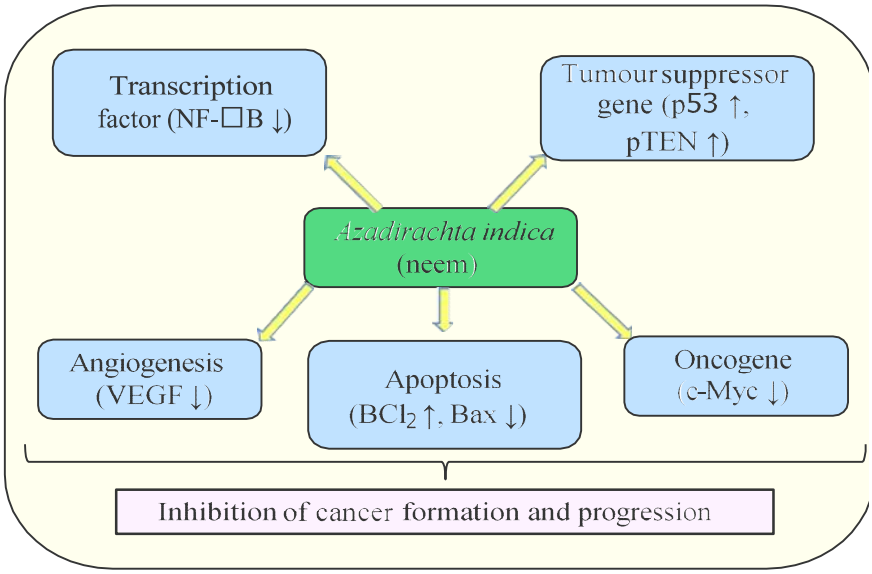

FIGURE 2: Anticancerous activities of Azadirachta indica L. neem through the modulation of various cell signaling pathways.

Additional findings indicated that azadirachtin and nimbolide exhibited antiradical scavenging activity and reductive potential that varied based on concentration, with nimbolide demonstrating the highest activity, followed by azadirachtin, and then ascorbate. In addition, the treatment of azadirachtin and nimbolide effectively prevented the formation of DMBA-induced HBP carcinomas by inhibiting the activation of procarcinogens and oxidative DNA damage. Furthermore, these compounds upregulated antioxidant and carcinogen detoxification enzymes. An experiment was conducted to assess the antioxidant activity of the flowers and seed oil of the neem plant, Azadirachta indica A. Juss. The results showed that the ethanolic extract of the flowers and seed oil, at a concentration of 200 μg/mL, exhibited the highest ability to scavenge free radicals, with percentages of 64.17 ± 0.02% and 66.34 ± 0.06%, respectively.

The study findings indicated that the extract from the root bark shown a greater ability to eliminate free radicals, with a scavenging activity of 50% at a concentration of 27.3 μg/mL. Additionally, the total antioxidant activity of this extract was determined to be 0.58 mM, equivalent to that of standard ascorbic acid. Additional findings from the study indicated that the leaf and bark extracts/fractions of neem cultivated in the foothills (sub-tropical zone) possess notable antioxidant effects.

The antioxidant properties of extracts obtained from the leaves, fruits, flowers, and stem bark of the Siamese neem tree were assessed. The study revealed that the aqueous extract from the leaves and the ethanol extracts from the flowers and stem bark exhibited a stronger ability to scavenge free radicals, with 50% scavenging activity observed at concentrations of 26.5, 27.9, and 30.6 microg/mL, respectively. In addition, the extracts exhibited a total antioxidant activity of 0.959, 0.988, and 1.064 mM of standard trolox, respectively.

Anti-cancer activity. Cancer is a complex disease with multiple contributing factors and is a significant global health issue. The modification of molecular/genetic pathways is involved in the genesis and advancement of cancer. The allopathic therapy module is efficacious, although it also has deleterious effects on healthy cells. Prior research has documented that plants and their components exhibit inhibitory effects on the formation of cancerous cells via altering cellular proliferation, apoptosis, tumour suppressor genes, and several other biochemical pathways. Neem possesses flavonoids and other compounds that actively suppress the development of cancer (Figure 2). A plethora of epidemiological studies suggests that a substantial consumption of flavonoids may be associated with a reduced risk of cancer.

Neem oil contains several neem limonoids that inhibit the mutagenic effects of 7,12-dimethylbenz(a)anthracene. A study was conducted to examine the toxic effects of nimbolide, a compound found in leaves and flowers, on human

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choriocarcinoma (BeWo) cells. The results demonstrated that treatment with nimbolide led to a reduction in the growth of BeWo cells, which was dependent on the dosage and duration of treatment. The IC50 values for nimbolide were determined to be 2.01 and 1.19 μM after 7 and 24 hours of treatment, respectively. A study was conducted to evaluate the chemopreventive properties of the limonoids, azadirachtin and nimbolide. The results demonstrated that both azadirachtin and nimbolide effectively hindered the formation of DMBA-induced HBP carcinomas. This was achieved by influencing various mechanisms, including the prevention of procarcinogen activation and oxidative DNA damage, the increase in antioxidant and carcinogen detoxification enzymes, and the inhibition of tumour invasion and angiogenesis.

Azadirachta indica and its active components are crucial in preventing the development and progression of cancer. The precise chemical mechanism underlying this phenomenon remains incompletely known. Through experiments, it has been determined that neem and its components have a significant impact on the regulation of different cell signalling pathways. Azadirachta indica has many elements that stimulate the expression of tumour suppressor genes and inhibit the function of various genes associated with the genesis and progression of cancer, including VEGF, NF-κB, and PI3K/Akt. Neem has been documented as an effective stimulator of tumour suppressor genes and a blocker of VEGF and phosphoinositol PI3K/Akt pathways. Additionally, it triggers apoptosis, inhibits NF-κB signalling, and affects the cyclooxygenase pathway.

Neem and its components contribute to the prevention of malignancies via influencing molecular pathways, as explained below.

The Impact of Neem and its Components on Genes that Inhibit Tumour Growth. The p53 gene is a crucial tumour suppressor gene that functions by suppressing the growth of aberrant cells, hence impeding the formation and advancement of cancer. A study has verified that treatment with the ethanolic fraction of neem leaf (EFNL) successfully increased the expression of proapoptotic genes and proteins, such as p53, Bcl-2-associated X protein (Bax), Bcl-2-associated death promoter protein (Bad), caspases, phosphatase and tensin homolog gene (pTEN), and c-Jun N-terminal kinase (JNK). A study revealed that the use of an alcoholic extract from neem leaves increased the activity of genes that promote cell death (proapoptotic genes), specifically caspase-8 and caspase-3. Additionally, it reduced the activity of genes that inhibit cell death (Bcl-2 and mutant p53) in cancer cells produced by 7,12-dimethylbenz(a)anthracene.

Nimbolide, a kind of tetranortriterpenoid limonoid, plays a significant role in the cytotoxic effects of neem extracts. Nimbolide decreased the expression of proteins that promote cell survival, such as I-FLICE, cIAP-1, cIAP-2, Bcl-2, Bcl-xL, survivin, and X-linked inhibitor of apoptosis protein. Additionally, it increased the expression of proapoptotic proteins p53 and Bax.

The activity of pTEN is frequently disrupted through mutations, deletions, or suppression of the promoter methylation in different primary and metastatic malignancies. The inactivation of pTEN has been observed in multiple tumour types. A study has verified that treating neem leaf with an ethanolic fraction substantially enhanced the expression of pTEN. This increase in expression can effectively hinder the development of breast tumours by inhibiting the activity of Akt.

The Impact of Neem and its Components on Apoptosis. The proteins bcl2 and bax are crucial for controlling the process of apoptosis. Any modification in the genes bcl2 and bax leads to the formation and advancement of tumours. Aberrant expression of these genes has been observed in numerous cancers. A study was conducted to examine the impact of an extract on an in vivo 4T1 breast cancer model in mice. The findings revealed that the CN 250 and CN 500 groups had a greater occurrence of apoptosis compared to the cancer control group. Another study has documented that the extract has demonstrated the ability to induce apoptosis, leading to the death of prostate cancer cells (PC-3).

The study discovered that the leaf extract decreased the expression of Bcl-2 and increased the expression of Bim, caspase-8, and caspase-3 in the buccal pouch. This suggests that the extract has the ability to induce apoptosis in the targeted organ. Furthermore, the study confirmed that the leaf extract caused a reduction in the viability of chronic lymphocytic leukaemia (CLL) cells in a dose-dependent manner. Significant apoptosis was observed at a concentration of 0.06% (w/v) within 24 hours. The isolated substance and primary ingredients derived from neem exhibit a diverse variety of activities that impact many targets. Additionally, they also contribute to the initiation of apoptotic cell death in cancer.

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The impact of Neem and its components on angiogenesis. Angiogenesis is an intricate biological process that facilitates the delivery of blood to tissues, playing a crucial role in the formation and spread of tumours.

Angiogenesis is controlled by both stimulators and suppressors. The advancement of antiangiogenic medicines to impede neovascularisation is a pivotal measure in the suppression of tumour proliferation. Medicinal plants and their constituents contribute to the prevention of tumour growth by exerting antiangiogenic effects.

A significant study demonstrated that the use of the ethanolic fraction of neem leaf (EFNL) substantially suppressed the production of proangiogenic genes, specifically vascular endothelial growth factor A and angiopoietin. This suggests that EFNL has the ability to limit angiogenesis, the formation of new blood vessels. Moreover, the suppression of the formation of new blood vessels (angiogenesis) by the ethanolic fraction of neem leaf (EFNL) may explain the decrease in the size of breast tumours and the prevention of new tumour growth, as found in recent research. A separate investigation was conducted to assess the antiangiogenic properties of a leaf extract on human umbilical vein endothelial cells (HUVECs). The findings revealed that treating HUVECs with the extract effectively hindered the angiogenic response induced by VEGF, both in laboratory settings and in living organisms. Additionally, the extract was found to suppress the in vitro proliferation, invasion, and migration of HUVECs. A study was conducted on zebrafish embryos to investigate the effects of different concentrations of water-soluble fractions of crude methanolic extract of neem root, imatinib (a standard substance), and a control group. The study results indicated that the water-soluble fractions of methanolic extract of neem root demonstrated the ability to inhibit angiogenesis.

The impact of Neem on oncogenes. An oncogene is a gene that has undergone a mutation and has a major impact on the formation and advancement of tumours. An experiment was conducted to examine the impact of leaf extract on the expression of the cMyc oncogene in 4T1 breast cancer BALB/c mice. The findings demonstrated that the group treated with 500 mg/kg of neem leaf extract (C500) exhibited a noteworthy reduction in cMyc oncogene expression compared to the cancer control group.

Impact of Neem on PI3K/Akt signalling pathways. The PI3K/Akt pathways play a crucial role in promoting tumour growth. However, the suppression of PI3K/Akt pathways is a crucial step in regulating tumour development. The study examined the impact of leaf extract on the PI3K/Akt and apoptotic pathways in prostate cancer cell lines (PC-3 and LNCaP). The findings indicated that the leaf extract causes apoptosis and hinders cell proliferation by inhibiting the PI3K/Akt pathway in both PC-3 and LNCaP cells.

A separate study was conducted to assess the molecular mechanisms responsible for the initiation of programmed cell death and inhibition of cell growth caused by the leaf extract on human breast cancer cell lines. The findings of this study confirmed that the cells treated with the extract exhibited a significant reduction in the expression of various proteins involved in the IGF signalling pathway, including IGF-1R, Ras, Raf, p-Erk, p-Akt, and cyclin D1.

A separate study was conducted to assess the impact of nimbolide on apoptosis and insulin-like growth factor (IGF) signalling molecules in androgen-independent prostate cancer (PC-3) cell lines. The findings of the study indicate that nimbolide functions as a powerful anticancer agent by promoting apoptosis and suppressing cell proliferation through the PI3K/Akt pathway in PC-3 cells.

The impact of Neem on the NF-κB factor. The NF-κB transcription factor has a significant impact on cancer and associated illnesses. Nevertheless, the suppression of NF-κB activity is a crucial measure in the prevention of cancer initiation and advancement. A significant study was conducted to examine the effectiveness of bioactive phytochemicals in preventing the activation of NF-κB, a protein involved in radiotherapy-induced cell signalling and regulation of cell death. The results revealed that curcumin, leaf extract, and black raspberry extract (RSE) effectively inhibited both the natural and radiotherapy-induced activation of NF-κB. additionally, another important finding from the study demonstrated that nimbolide, a compound derived from neem, simultaneously blocked the canonical NF-κB and Wnt signalling pathways and triggered intrinsic apoptosis in human hepatocarcinoma (HepG2) cells.

Effect of Neem as Anti-Inflammatory

Plants or their separated compounds are commonly used as anti-inflammatory medications. The study has verified that administering a dose of 200 mg/kg of A. indica leaf extract orally resulted in considerable anti-inflammatory effect in rats, as observed in the cotton pellet granuloma assay. Additional research findings indicate that neem leaf extract exhibits a notable anti-inflammatory impact, however its efficacy is inferior to that of dexamethasone. Moreover, the

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study suggests that nimbidin inhibits the activities of macrophages and neutrophils that are associated with inflammation.

Prior research has demonstrated the immunomodulatory and anti-inflammatory properties of extracts from the bark and leaves, as well as the antipyretic and anti-inflammatory effects of oil seeds. An experiment was conducted to assess the analgesic properties of neem seed oil on albino rats. The results of the study demonstrated that neem seed oil had a notable analgesic impact at doses of 1 and 2 mL/kg, and this effect was dependent on the dosage of the oil.

A separate study was conducted to examine the anti-inflammatory properties of neem seed oil (NSO) on albino rats by inducing hind paw oedema using carrageenan. The findings demonstrated that NSO exhibited a greater suppression of paw oedema as the dosage increased from 0.25 mL to 2 mL per kilogramme of body weight. NSO exhibited a peak inhibition of oedema at a dose of 2 mL/kg body weight, with a maximum inhibition rate of 53.14% observed at the 4th hour after carrageenan administration.

The study's findings indicated that mice treated with a dose of 100 mg kg−1 of carbon tetrachloride extract (CTCE) from the fruit peel of Azadirachta indica, as well as the isolated component azadiradione, exhibited notable antinociceptive and anti-inflammatory effects.

Hepatoprotective Effect

Medicinal plants and their constituents are crucial in providing protection to the liver without causing any negative side effects. A study was conducted to examine the hepatoprotective effects of azadirachtin-A in rats with carbon tetrachloride (CCl4)-induced liver damage. The results from histology and ultrastructure analysis indicated that pretreatment with azadirachtin-A reduced hepatocellular necrosis in a dose-dependent manner. Additionally, the study's findings indicate that pretreatment with azadirachtin-A at higher doses partially returns the rat liver to its normal state.

A separate study was conducted to assess the safeguarding impact of the active component of neem, specifically nimbolide, against liver toxicity induced by carbon tetrachloride (CCl4) in rats. The findings indicate that nimbolide exhibits a hepatoprotective effect against CCl4-induced liver damage, comparable in efficacy to the standard silymarin. Additionally, another study discovered that the leaf extract of neem provides protection against liver necrosis induced by paracetamol in rats.

A study was conducted to evaluate the hepatoprotective effects of Azadirachta indica (AI) leaf extract on hepatotoxicity induced by antitubercular drugs. The results demonstrated that the aqueous leaf extract of AI effectively prevented alterations in the levels of bilirubin, protein, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase in the serum. Additionally, it significantly prevented histological changes when compared to the group that received only antitubercular drugs. In addition, further findings indicated that the ethanolic and aqueous leaf extracts of A. indica demonstrated a modest level of effectiveness in rats treated with carbon tetrachloride. The hepatoprotective activity of methanolic and aqueous extracts of Azadirachta indica leaves was assessed in rats, and the study findings confirmed that the plant exhibits significant promise as a hepatoprotective agent.

A study was conducted to examine the defensive impact of neem extract on ethanol-induced damage to the lining of the stomach in rats. The findings revealed that administering neem extract prior to ethanol exposure provided protection against the harm caused to the stomach lining.

Wound Healing Effect

Many plants and their components have a significant impact on the process of wound healing. An investigation was conducted to assess the efficacy of A. indica and T. cordifolia leaf extracts in promoting wound healing. The study utilised excision and incision wound models in Sprague Dawley rats. The findings demonstrated that the extracts from both plants effectively enhanced wound healing in both models. Moreover, the tensile strength of the healing tissue in both groups of plants treated with incision wounds was significantly greater than that of the control group. Additional findings shown that extracts derived from Azadirachta indica stimulate wound healing by enhancing the inflammatory response and promoting the formation of new blood vessels.

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Antidiabetic Activity

A study was conducted to assess the efficacy of a 70% alcoholic extract derived from the neem root bark (NRE) in treating diabetes. The findings demonstrated that the neem root bark extract exhibited statistically significant effects at a dosage of 800 mg/kg. A further study was conducted to investigate the pharmacological hypoglycemic effects of Azadirachta indica in diabetic rats. The findings revealed that administering neem extract at a dosage of 250 mg/kg resulted in significantly lower glucose levels compared to the control group during a glucose tolerance test. Additionally, Azadirachta indica effectively reduced glucose levels in diabetic rats on the 15th day of treatment.

The effects of chloroform, methanolic, and aqueous extracts of A. indica and B. spectabilis were studied using a diabetic mouse model. The results demonstrated that the chloroform extract of A. indica and the aqueous and methanolic extracts of B. spectabilis exhibited favourable oral glucose tolerance and significantly decreased intestinal glucosidase activity. A separate significant study indicated that extracts derived from the leaves of Azadirachta indica and Andrographis paniculata possess notable antidiabetic properties and may serve as a promising resource for the management of diabetes mellitus.

Antimicrobial Effect

Neem and its constituents contribute to the suppression of the proliferation of many microorganisms, including viruses, bacteria, and harmful fungi. The individual description of neem's involvement in preventing microbial growth is as follows.

Activity with the ability to kill or inhibit the growth of microorganisms. A study was conducted to assess the antimicrobial effectiveness of herbal alternatives as endodontic irrigants, comparing them to the standard irrigant sodium hypochlorite. The results confirmed that leaf extracts and grape seed extracts exhibited zones of inhibition, indicating their antimicrobial properties. In addition, the leaf extracts exhibited considerably larger areas of inhibition compared to 3% sodium hypochlorite.

The study assessed the antibacterial efficacy of guava and neem extracts against 21 strains of foodborne pathogens. The findings indicated that these extracts contain compounds with antibacterial properties, which have the potential to effectively control foodborne pathogens and spoilage organisms.

A further experiment was conducted to assess the antibacterial efficacy of the extracts derived from the bark, leaf, seed, and fruit of Azadirachta indica (neem) on bacteria obtained from the oral cavity of adults. The findings indicated that the extracts from the bark and leaf exhibited antibacterial properties against all the bacteria strains tested. In addition, it was shown that the antibacterial action of seed and fruit extracts was only evident at greater concentrations.

Antiviral activity. The findings demonstrated that the neem bark extract (NBE) effectively inhibited the entry of HSV-1 into cells within the dose range of 50 to 100 μg/mL. Moreover, the inhibition of NBE activity was observed when the extract was preincubated with the virus, but not with the target cells, indicating a direct antiviral effect of the neem bark against HSV-1.

The neem (Azadirachta indica A. Juss.) leaf extract (NCL-11) has demonstrated the ability to inactivate and reduce the production of coxsackievirus viral B-4. It also interferes with an early stage of the virus's replication cycle.

Activity against fungi. An experiment was conducted to assess the effectiveness of different neem leaf extracts on seed-borne fungus Aspergillus and Rhizopus. The results revealed that the growth of both fungal species was greatly suppressed and regulated by both alcoholic and water extracts. Moreover, the alcoholic extract of neem leaf shown superior efficacy in inhibiting the growth of both fungal species as compared to the aqueous extract. The study found that aqueous extracts of neem cake have antimicrobial properties and can inhibit spore germination in three types of fungi: C. lunata, H. pennisetti, and C. gloeosporioides f. sp. mangiferae. Additionally, the study showed that methanol and ethanol extracts of Azadirachta indica can inhibit the growth of Aspergillus flavus, Alternaria solani, and Cladosporium.

Previous researchers have shown that aqueous extracts of many portions of the neem tree, including neem oil and its main components, exhibit antifungal properties. A study was conducted to investigate the antifungal properties of Azadirachta indica L. against Alternaria solani Sorauer. The findings revealed that the ethyl acetate fraction exhibited the highest efficacy in inhibiting fungal growth, with a minimum inhibitory concentration (MIC) of 0.19 mg. Furthermore, this fraction was more effective than the fungicide (metalaxyl + mancozeb), which had a MIC of 0.78 mg.

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Activity against malaria-causing parasites. An experiment was conducted to assess the effectiveness of extracts in treating malaria. Plasmodium berghei infected albino mice were used, and the results demonstrated that neem leaf and stem bark extracts reduced the parasitemia levels in the infected mice by approximately 51-80% and 56-87% respectively. Additionally, other studies have indicated that neem extracts containing azadirachtin and other limonoids have a positive effect on malaria vectors.

A study was conducted using a crude extract of leaves, obtained by mixing acetone and water in a 50/50 ratio, to assess its effectiveness against the asexual and sexual forms of the malaria parasite, Plasmodium falciparum, in a laboratory setting. The results revealed that when the extract, known as IRAB, was applied to separate cultures of asexual parasites and mature gametocytes for a period of 72 hours at a concentration of 0.5 microg/mL, the number of parasites was reduced to less than 50% compared to control cultures. The control cultures had parasitemia levels of 8.0% and 8.5% for asexual parasites and mature gametocytes, respectively.

Role of Neem in Dentistry

A study was conducted to evaluate the effectiveness of a neem-based mouth rinse in terms of its ability to reduce gum inflammation. The study concluded that using a mouth rinse manufactured from the neem tree (A. indica) is just as effective as using chlorhexidine in reducing measures of gum disease.

A further investigation was conducted to assess the antibacterial characteristics of organic neem extracts against three bacterial strains responsible for dental caries. The findings indicated that the petroleum ether and chloroform extracts exhibited potent antimicrobial activity against S. mutans. The chloroform extract exhibited significant activity against Streptococcus salivarius, whereas the third strain of Fusobacterium nucleatum had high sensitivity to both the ethanol and water extracts. Prior research has verified that dried neem chewing sticks have the highest level of antibacterial effectiveness against S. mutans, in comparison to S. salivarius, S. mitis, and S. sanguis.

Antinephrotoxicity Effect

A study was conducted to examine the impact of methanolic leaves extract of Azadirachta indica (MLEN) on nephrotoxicity and oxidative stress induced by cisplatin (CP) in rats. The findings revealed that the extract successfully protects the kidney from oxidative damage caused by CP. In addition, the PCR data indicated a decrease in the expression of caspase-3, caspase-9, and Bax genes in the groups treated with MLEN.

Neuroprotective Effects

A study was conducted to examine the neuroprotective properties of Azadirachta indica leaves against cisplatin-induced neurotoxicity. The results indicated that the neem leaves exhibited a conserved brain tissue structure both before and after cisplatin injection. The neem treated group did not show any alterations in biochemical markers.

Immunomodulatory and Growth Promoting Effect

An experiment was conducted to examine the effects of neem leaves infusion on the growth and immune system of broiler chicks. The results demonstrated that neem infusion effectively enhanced antibody levels, growth performance, and overall profit when administered at a concentration of 50 mL per litre of fresh drinking water.

A separate study examined the impact of administering powdered dry leaves of A. indica (AI) on the immune responses of broilers, specifically in terms of humoral and cell mediated immunity. The findings revealed that treatment with AI at a dosage of 2 g/kg significantly increased the levels of antibodies against the new castle disease virus (NCDV) antigen.

Safety, Toxicities, and LD_{50} Values of Neem

Prior to their implementation in health management, it is essential to measure the toxicities of natural compounds. Multiple studies utilising animal models and clinical trials have substantiated that neem is safe when administered at specific doses. Conversely, neem and its constituents have demonstrated toxic and deleterious effects.

Multiple studies have documented cases of neem oil poisoning in children, resulting in symptoms such as vomiting, liver damage, metabolic acidosis, and encephalopathy. Additionally, a study conducted on rats found that the administration of

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 2, August 2024

neem leaf sap had a calming effect at low doses, while high doses did not produce the same effect. A significant study utilising a rat model shown that azadirachtin exhibited no toxicity, even at a dosage of 5 grammes per kilogramme of body weight. A toxicological analysis study was conducted on rabbits to assess the effects of neem extract. The results indicated a gradual increase in body weight in both the test and control groups throughout the entire duration of the neem extract administration. No signs of toxicity were observed in either group.

The investigation revealed that the LD50 values of neem oil in the acute toxicity test were determined to be 31.95 g/kg. A further study was conducted to assess the harmful effects on chickens. The results indicated that the neem leaf extract, when administered intraperitoneally, had an LD50 value of 4800 mg/kg, and the observed clinical indications were directly proportional to the dosage.

A study found that the lethal median dosages (LD50) for neem leaf and stem bark extracts were 31.62 and 489.90 mg/kg body weight, respectively. The lethal dose (LD50) of the water extract from the leaves of A. indica was 6.2 mL kg−1, while the LD50 of the water extract from the seeds was 9.4 mL kg−1. The lethal dose values were determined using probit analysis, resulting in LD50 and LD90 values of 8.4 and 169.8 μg/fly of neem extract, respectively. The test conducted on mice to determine acute oral toxicity yielded an LD50 value of around 13 g/kg body weight.

Clinical Studies Based on Neem

Multiple clinical experiments have substantiated that herbal medicines or derivatives from natural sources play a crucial role in the prevention and treatment of diseases. Only a small number of studies have been conducted on active substances, such as nimbidin, to assess their effectiveness in health management. A significant study was conducted using human subjects to examine the significance of neem bark extract in its ability to reduce secretion and prevent ulcers in humans. When the lyophilised powder of the extract was given to patients for 10 days, at a dose of 30 mg twice a day, there was a notable reduction (77%) in the production of stomach acid. Administering the bark extract at a dosage of 30-60 mg twice daily for a duration of 10 weeks resulted in nearly total healing of duodenal ulcers. Additionally, one case of esophageal ulcer and one case of gastric ulcer were entirely cured when treated with a dosage of 30 mg twice daily for a period of 6 weeks.

A double-blind clinical trial was conducted to assess the effectiveness of a drug containing an aqueous extract of neem leaves in 50 cases of uncomplicated psoriasis who were also receiving conventional coal tar treatment. The results indicated that patients who received the drug along with coal tar showed a faster and more favourable response compared to the placebo group. A six-week clinical study was conducted to evaluate the effectiveness of neem extract dental gel compared to a mouthwash containing chlorhexidine gluconate (0.2% w/v) as a positive control. The results of the study demonstrated that the dental gel with neem extract significantly decreased both the plaque index and bacterial count in comparison to the control group. A study demonstrated that nimbidin greatly improved the healing process in albino rats and dogs with persistent stomach ulcers caused by acetic acid in ulcer healing tests.

II. CONCLUSION

The global popularity of natural products and their derivatives in the treatment and prevention of diseases is on the rise, mostly due to their reduced adverse effects. Neem and its constituents possess therapeutic implications and have been traditionally utilised globally, particularly in the Indian Subcontinent, since ancient times. Empirical research have substantiated that neem has a crucial function in the prevention of several ailments. The chemopreventive impact of active components has been observed in various tumours through the modulation of many cell signalling pathways. A comprehensive investigation should be conducted using animal models to determine the precise mechanism of action in illness treatment.

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Impact Factor: 7.53
Volume 4, Issue 2, August 2024

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