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ANTICANCERACTIVITYOFDRUGSFROM AZADIRACHTA INDICA [NEEM] PLANT

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Abstract
Azadirachta indica (Neem), a cornerstone of traditional Indian medicine, has emerged as a promising source of anticancer agents due to its rich repertoire of bioactive limonoids, including nimbolide, azadirachtin, and gedunin. These compounds exhibit potent cytotoxic, antiproliferative, anti-angiogenic, and anti-metastatic effects across diverse cancer models. Nimbolide, the most extensively studied neem constituent, induces apoptosis through both intrinsic and extrinsic pathways, modulates Bcl-2 family proteins, and causes cell-cycle arrest by regulating cyclins and cyclin-dependent kinases (CDKs). Neem limonoids suppress angiogenesis by inhibiting VEGF- and IGF-1R-mediated PI3K/Akt/HIF-1α signaling, while also reducing metastatic potential through the downregulation of matrix metalloproteinases and epithelial-to-mesenchymal transition markers. Gedunin disrupts Hsp90 chaperone function, destabilizing oncogenic proteins and triggering endoplasmic reticulum stress. Neem extracts further enhance antitumor immunity by promoting dendritic cell maturation, boosting CD8+ T-cell responses, and inhibiting immunosuppressive cells such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). Additionally, neem demonstrates chemopreventive effects by elevating antioxidant defenses and activating detoxification enzymes. Despite compelling preclinical evidence, translational progress is hindered by poor solubility, limited bioavailability, and insufficient clinical data. Therefore, standardized formulations and rigorous clinical trials are essential to validate neem-derived compounds as effective anticancer therapeutics.

Keywords: *Neem (*Azadirachta indica*); Nimbolide; Anticancer activity; Limonoids; Apoptosis.*

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INTRODUCTION

(Neem Azadirachta indica) is a medicinal tree long used in traditional Indian medicine and has attracted modern research interest for anticancer properties because its leaves, seeds and bark contain biologically active limonoids (notably nimbolide, azadirachtin, gedunin and related tetranortriterpenoids) that show cytotoxic and chemo preventive effects in many preclinical models (cell lines and animals) [1,2,3]. The most studied neem constituent, nimbolide, exhibits potent antiproliferative activity and induces apoptosis via both intrinsic and extrinsic pathways (caspase activation, modulation of Bcl-2 family proteins), while also causing cell-cycle arrest in multiple cancer cell types [4,5]. Nimbolide and other limonoids inhibit metastatic behaviours (migration/invasion) by downregulating matrix metalloproteinases and epithelial-to- mesenchymal transition markers, and they reduce angiogenesis in tumor models by blocking. VEGF/IGF-1R→PI3K→AKT/HIF-1α signaling [6,7].

Another neem limonoid, gedunin, destabilizes oncogenic client proteins by interfering with Hsp90/cochaperone activities, which contributes to its anticancer effects [8]. Neem extracts and limonoids have anti-inflammatory and antioxidant properties (e.g., suppression of NF-κB and modulation of detoxifying enzymes) that go beyond direct cytotoxicity and contribute to chemopreventive benefits in chemical carcinogenesis models [9,10]. Translational development is constrained by gaps in pharmacokinetic and toxicology data, formulation/bioavailability issues (many limonoids are poorly water soluble), and a lack of large, well-controlled clinical trials to establish safety and efficacy in humans, despite the abundance of in-vitro and in-vivo evidence supporting multi- target anticancer activity [11,12].

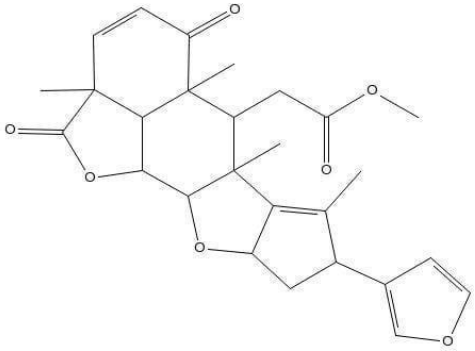

Fig 01: chemical structure of Azadirachta indica (Neem)

NIMBOLIDE

ANTI-CANCER ACTIVITY OF NEEM

Neem has bioactive substances, particularly nimbolide, have demonstrated promise in triggering apoptosis and preventing the development of cancer cells. Neem's principal anti-cancer properties. Rich in Antioxidants, Neem has substances like flavonoids and polyphenols that reduce oxidative stress, a major factor in the development of cancer, by neutralizing free radicals [13]. Anti-Inflammatory Effects, Progression of cancer is associated with chronic inflammation. The anti-inflammatory qualities of neem aid in the suppression of inflammatory pathways that may result in the development of tumors. Induction of Apoptosis, Bioactive substances like nimbolide cause cancer cells to undergo programmed cell death without endangering healthy cells [14]. For cancer treatment to be effective, this selective cytotoxicity is essential. Inhibition of Cell Proliferation: It has been demonstrated that neem extracts prevent the growth of several cancer cell lines, such as those from colon, breast, and prostate malignancies [15].

Immune Modulation: Neem strengthens the immune system, which makes it easier for the body to identify and eliminate cancer cells. Hepatic Protection: Neem's antioxidant action in the liver promotes detoxification and lowers the chance of malignancies linked to the liver.

Nimbolide

Preclinical research has shown that nimbolide, a limonoid present in neem, has potent anti-cancer properties. It slows metastasis, disrupts cancer cell signaling pathways, and makes tumors more susceptible to treatment.

SYNTHESIS:

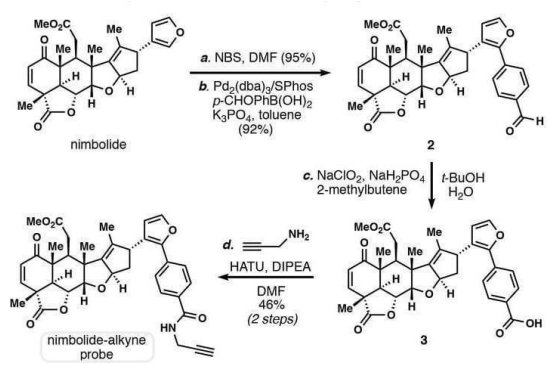

Fig 02: Synthesis of nimbolide-alkyne probe

Structure–Activity Relationship (SAR) of Nimbolide

1. α,β-Unsaturated γ-Lactone Ring (Ring D) – Key Pharmacophore

Functions as a Michael acceptor, reacting with nucleophilic thiol groups (–SH) of cysteine residues in target proteins that are crucial for anticancer activity (induction of apoptosis, suppression of NF-κB) anti-inflammatory properties. There is a noticeable decrease in activity when the double bond is reduced or saturated [16].

2. α,β-Unsaturated Ketone (Enone System)

Increases electrophilicity, which makes it easier for signaling proteins to interact covalently. causes cell cycle arrest. suppression of the PI3K/Akt and STAT3 pathways. Reduced cytotoxic potency due to modification or elimination [17].

3. The Furan Ring (Ring E)

The Furan Ring (ring E), is crucial for biological target binding affinity. membrane permeability and lipophilicity. Reduced biological activity due to furan ring replacement or oxidative cleavage.

4. Moiety of Epoxide

Increases the number of reactive sites available for protein interactions. aids in the selective cytotoxicity of cancer cells. Selectivity and potency are lost due to epoxide opening or removal [8.9.18].

5. Hydroxyl Groups

Improve solubility, receptor interaction, and hydrogen bonding. On the other hand, too much hydroxylation could decrease the permeability of the membrane. Bioavailability can be maximized through strategic derivatization.

6. Rigid Limonoid Skeleton

Preserves the functional groupings correct spatial alignment. For stability and target specificity, structural stiffness is essential. Excessive flexibility or ring opening leads to decreased activity [10, 11, 19].

7. Overall Electrophilic Character

Lactone, enone, and epoxide are several electrophilic center that work in concert. In charge of broad-spectrum anticancer actions and covalent alteration of carcinogenic proteins [20].

SAR Summary Table:

Table 01: Breakdown of Structural Indicators

Structural Feature	Role in Activity
α,β-Unsaturated γ-lactone	Essential pharmacophore
Enone system	Enhances cytotoxicity
Furan ring	Improves target binding
Epoxide	Increases selectivity
Hydroxyl groups	H-bonding & solubility
Rigid skeleton	Structural integrity

RESULT

Neem and its bioactive compounds demonstrated strong anticancer effects across various experimental studies. Neem extracts and limonoids inhibited the growth of several cancer cell types by inducing cell-cycle arrest, disrupting mitochondrial function, and activating both intrinsic and extrinsic apoptotic pathways. These compounds also showed significant antiangiogenic activity by suppressing endothelial cell survival and reducing new blood vessel formation. In vivo studies reported enhanced natural killer (NK) and NKT cell activity, contributing to reduced tumour growth. Neem leaf glycoprotein (NLGP) further strengthened antitumor immunity by improving dendritic cell maturation and enhancing T-cell responses. Additionally, neem reduced carcinogen-induced mutagenicity, enhanced detoxification enzyme activity, and inhibited cancer cell migration and invasion by downregulating matrix metalloproteinases and suppressing key oncogenic signaling pathways. Overall, neem exhibited consistent cytotoxic, immunomodulatory, antiangiogenic, and anti-metastatic properties, supporting its potential as a promising anticancer agent.

DISCUSSION

Breast cancer

Priya R et al., reported antibiofilm and anticancer activities of unripe and ripe Azadirachta indica seed extracts. These extracts demonstrated potent anticancer activity against triple-negative MDA-MB-231 breast cancer cells. Ethanolic extracts were prepared from neem seeds and evaluated using MTT assay and FACS analysis yielding superior activity of ripe seed extract with low cytotoxicity to normal lymphocytes. Newly studied extracts mainly from ripe seeds showed higher anticancer potency due to limonoid content like gedunin modulating apoptosis pathways in breast cancer cell lines [21].

Lung cancer

Kumar S et al., reported limonoid-rich fraction from Azadirachta indica A. Juss. (neem) stem bark with anticancer activity against lung cancer cells. This fraction demonstrated potent anti- neoplastic effects specifically against A549 lung adenocarcinoma cells. Dichloromethane (DCM) extract was fractionated using thin-layer chromatography and the active F2 fraction was evaluated using cell viability, clonogenic assay, cell cycle analysis, and apoptosis assays yielding strong dose-dependent cytotoxicity with low effects on normal cells. Newly studied F2 fraction mainly containing limonoids showed higher anticancer potency due to induction of ROS-independent ER stress and apoptosis in lung cancer cell lines [22].

Ovarian cancer

Priya R et al., reported anticancer activities of Azadirachta indica extracts against ovarian cancer cell lines. These extracts demonstrated potent antiproliferative effects specifically against SKOV3 ovarian cancer cells. Ethanolic leaf extracts were prepared from neem leaves and evaluated using MTT assay, apoptosis detection, and cell migration studies yielding dose- dependent inhibition with IC50 values in micromolar range. Newly studied extracts mainly from neem leaves showed higher anticancer potency due to nimbolide and azadirachtin content inducing caspase-3 activation and G2/M cell cycle arrest in ovarian cancer cell lines [21,23].

Prostate cancer

Batra N et al., reported exploring the therapeutic potential of Neem (Azadirachta indica) for prostate cancer treatment. This review demonstrated potent anticancer effects specifically against PC-3 and LNCaP prostate cancer cells. Ethanolic neem leaf extracts (ENLE) and supercritical extracts (SENL) were evaluated using cell viability assays, apoptosis detection, and tumour growth studies yielding significant inhibition of AR signaling and PSA expression. Newly studied extracts mainly ENLE and nimbolide showed higher anticancer potency due to suppression of PI3K/Akt pathway, integrin signaling, and induction of apoptosis in prostate cancer cell lines.

Oral cancer:

Agrawal S et al., reported a review of the anticancer activity of Azadirachta indica (Neem) in oral cancer. This review demonstrated potent anticancer effects specifically against oral squamous cell carcinoma cells. Ethanolic neem leaf and seed extracts were evaluated using cell proliferation assays, apoptosis studies, and DMBA-induced hamster buccal pouch carcinogenesis models yielding significant tumour inhibition and increased apoptotic indices. Newly studied extracts mainly from neem leaves showed higher anticancer potency due to nimbolide and azadirachtin content inducing caspase activation and suppressing Bcl-2 expression in oral cancer cell lines [21,24, 25].

CONCLUSION

Neem (Azadirachta indica) and its major bioactive limonoids-especially nimbolide, azadirachtin, and gedunin-demonstrate strong, multi-target anticancer activity in preclinical studies. These compounds consistently induce apoptosis, cause cell-cycle arrest, suppress angiogenesis, inhibit metastatic pathways, and modulate key oncogenic signaling cascades. In addition, neem enhances antitumor immunity and exhibits notable chemo preventive effects by reducing oxidative stress, improving detoxification enzyme activity, and limiting carcinogen- induced damage. Together, these mechanisms

highlight neem as a potent natural candidate for cancer management. However, challenges such as poor solubility, limited bioavailability, and insufficient clinical data still restrict its therapeutic translation. Therefore, future research must focus on standardized formulations, detailed pharmacokinetic and toxicity studies, and well- designed clinical trials to validate neem-derived compounds as safe and effective anticancer agents.

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CONFLICT OF INTEREST
Authors are declared that no conflict of interest

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Not Applicable

AUTHOR CONTRIBUTION
All authors are contributed equally.

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