Synergistic Potential and Nano-Delivery of Neem Extract in Oral Oncology

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Abstract

Oral cancer continues to pose a major global health challenge, with current treatment options often leading to considerable side effects and inconsi stent therapeutic success. Recently, there has been growing interest in natural compounds assafer and more effective alternatives or adjuncts to conventional treatments. Neem (*Azadirachta indica*), a widely recognized medicinal plant, exhibits potent anticancer, antioxidant, and anti-inflammatory activities, making it a strong candidate for use in oral cancer management.

This study investigates the combined potential of neem extract and nanotechnology-based delivery systems. The conventional use of plant-derived compounds is often limited by issues such as poor solubility, reduced bioavailability, and inadequate targeting. Incorporating neem extract into nanoscale carriers can help address these challenges by improving targeted delivery to cancerous cells while reducing harm to normal tissues.

Nanocarrier systems also enhance the stability and allow controlled release of neem's active constituents, thereby increasing their therapeutic effectiveness. Furthermore, the synergistic interaction between neem bioactives and nano-delivery platforms may strengthen anticancer effects, such as suppressing tumor growth, triggering apoptosis, and limiting cancer spread.

However, limited clinical translation highlights the need for further trials to validate its therapeutic potential

Keywords:

Oral cancer; Neem (*Azadirachta indica*); Nano-delivery systems; Nanotechnology; Anticancer activity; Phytochemicals; Targeted drug delivery; Apoptosis; Bioavailability; Synergistic therapy

1. Introduction:

Oral cancer remains a major global health problem, especially in developing countries where habits like

tobacco use, alcohol consumption, and poor oral hygiene are common. Even though medical science has made progress with treatments such as surgery, chemotherapy, and radiotherapy, survival rates have not improved as much as expected. In addition, these treatments often come with serious side effects, can harm healthy tissues, and may significantly affect a patient's quality of life. Because of these limitations, there is increasing interest in finding safer and more effective treatment options.

One promising area of research involves natural plant-based compounds, which are known for their therapeutic benefits and lower toxicity. Neem (*Azadirachta indica*) is one such plant that has been widely studied for its medicinal properties. It contains several active compounds like azadirachtin, nimbolide, and quercetin, which are known to have anticancer, antioxidant, anti-inflammatory, and antimicrobial effects. These characteristics make neem a strong candidate for use in the prevention and treatment of oral cancer.

However, using neem extract in clinical settings is not without challenges. Issues such as poor solubility in water, low absorption in the body, and lack of targeted delivery to cancer cells limit its effectiveness. To address these problems, researchers are turning to nanotechnology-based drug delivery systems. These systems, including nanoparticles, liposomes, and nanoemulsions, can improve how the drug is delivered by enhancing its stability, solubility, and ability to specifically target cancer cells. They also allow for a slow and controlled release of the active compounds, which can increase effectiveness while reducing side effects.

2. Challenges in Conventional Delivery of Neem Phytochemicals

Neem (*Azadirachta indica*) has long been valued for its wide range of medicinal properties, including antimicrobial, anti-inflammatory, antioxidant, and anticancer effects. Its important bioactive compounds—such as nimbolide, azadirachtin, nimbin, and quercetin—have shown strong pharmacological potential in several preclinical studies [1,2] However, despite these

promising benefits, the practical use of neem phytochemicals in clinical settings is still limited due to several challenges associated with traditional delivery methods.

Key Challenges

One of the biggest limitations is poor water solubility. Many active compounds in neem, especially limonoids, are lipophilic, meaning they do not dissolve easily in water. This limits their absorption in the body and leads to low oral bioavailability [3].Another important issue is reduced bioavailability due to first-pass metabolism. When taken orally, neem compounds are quickly metabolized and cleared from the body, which reduces their effective concentration in the bloodstream [4].Stability is also a concern. Neem phytochemicals are sensitive to environmental factors like light, heat, oxygen, and changes in pH. These conditions can degrade the compounds, affecting their shelf life and therapeutic effectiveness.

Maintaining consistent dosing is another challenge. The composition of neem extracts can vary depending

on factors such as geographic origin, cultivation conditions, and extraction techniques. This variability makes it difficult to ensure uniform dosage and reliable results.The bitter taste of neem can further reduce patient acceptance, particularly in oral formulations.In addition, conventional systems lack targeted delivery mechanisms. They are unable to deliver the active compounds specifically to diseased tissues or provide controlled drug release, which is especially critical in cancer treatment [5].

Finally, there are regulatory and manufacturing limitations. Variability between batches and a lack of sufficient clinical evidence make it difficult to standardize neem-based products and bring them into large-scale pharmaceutical use.

The Way Forward

To overcome these limitations, researchers are increasingly focusing on advanced drug delivery systems such as nanoparticles, liposomes, nanoemulsions, and phytosomes. These modern approaches can improve solubility, enhance stability, increase bioavailability, and enable targeted delivery of neem phytochemicals [6].

Although neem has been used for centuries in traditional medicine, its full potential is yet to be realized in modern healthcare. Addressing issues related to solubility, stability, and standardization is essential. By combining traditional knowledge with advanced nanotechnology, it may be possible to unlock neem's complete therapeutic potential [7,8].

3. Neem as a Chemosensitizer for Standard OSCC Drugs

Neem (*Azadirachta indica*) and its key phytochemicals, especially nimbolide and quercetin, show promise as chemosensitizers for standard Oral Squamous Cell Carcinoma (OSCC) drugs such as cisplatin, 5‑fluorouracil (5‑FU), and paclitaxel. By modulating critical survival pathways and enhancing apoptosis, they can increase tumor‑cell killing while allowing lower chemotherapeutic doses and potentially reducing systemic toxicity.[9,10,]

Key mechanisms in OSCC models

- NF‑κB and PI3K/Akt inhibition: Nimbolide covalently modifies Cys179 of IKK‑β, suppressing NF‑κB activation and downregulating NF‑κB‑regulated survival proteins, thereby sensitizing tumor cells to cisplatin and other agents. Similar studies show that neem components broadly inhibit NF‑κB signaling, which is often constitutively active in OSCC.[11,12]
- Autophagy–apoptosis switch: In OSCC cells, nimbolide initially induces cytoprotective autophagy but then shifts the balance toward apoptosis by negatively regulating PI3K/Akt and activating GSK‑3β, which promotes mitochondrial dysfunction and caspase‑dependent cell death.[13]

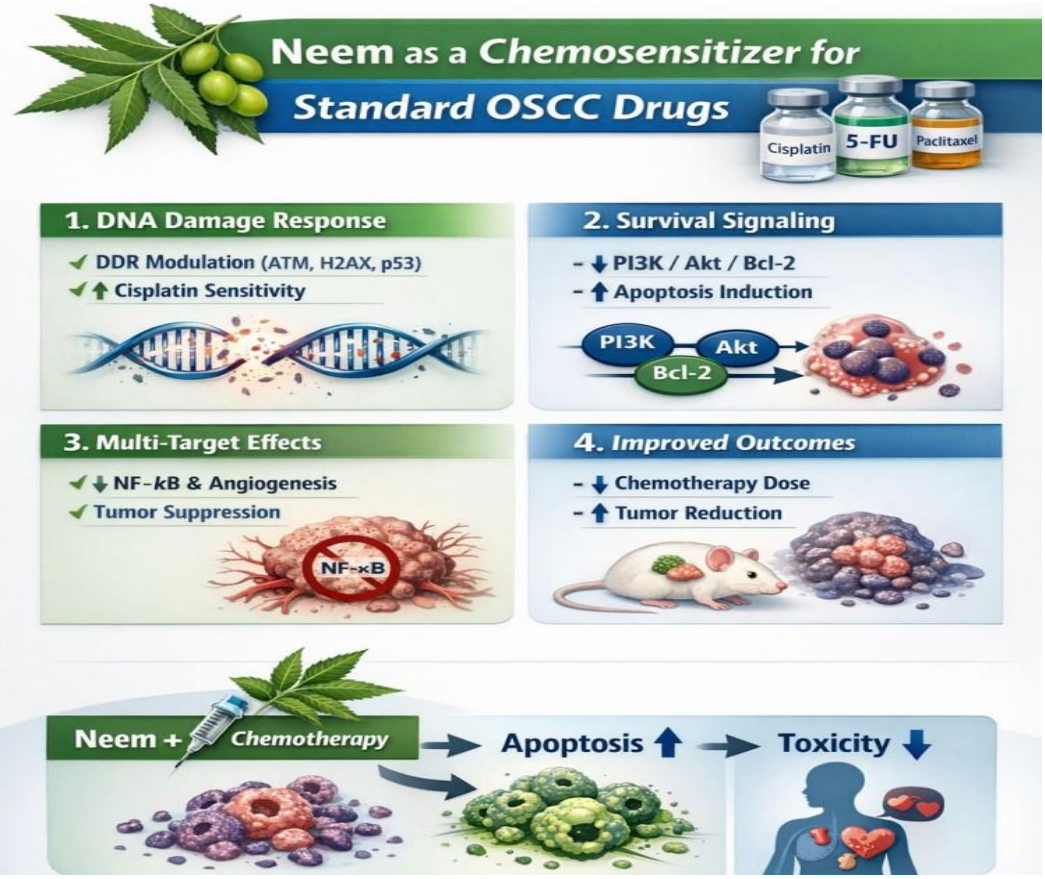

Figure.1 Chemosensitizing effect of Neem (Azadirachta indica) on standard OSCC drugs.

- Synergy with standard drugs: Neem-leaf extract and limonoids enhance the cytotoxicity of cisplatin and paclitaxel in various cancer models, with clear evidence of synergistic growth inhibition and reduced inflammatory signaling at lower drug doses.[14]

In vivo and translational relevance

- In OSCC-relevant models, high-purity neem leaf extract (SCNE) and nimbolide significantly inhibit tumor growth and progression, and they can also reprogram the tumor microenvironment (e.g., polarizing macrophages toward an M1 phenotype).[15]
- Nanoparticle- and nanoformulation-based delivery of neem limonoids further enhances tumor targeting, chemo-drug–synergy, and therapeutic index, while lowering toxicity in preclinical cancer systems.[16]

4. Formulation and Characterization of Neem-Loaded Nanoparticles

Neem-loaded nanoparticles are a promising strategy to overcome the pharmaceutical limitations of neem phytochemicals such as nimbolide, azadirachtin, and quercetin, which otherwise suffer from poor

solubility, low bioavailability, chemical instability, and dose variability. By encapsulating these bioactives into polymeric nanoparticles, liposomes, nanoemulsions, and solid lipid nanoparticles (SLNs), one can achieve stable, controlled-release, and often site-directed delivery that is particularly relevant for enhancing anticancer and chemosensitizing effects in Oral Squamous Cell Carcinoma (OSCC).17

Purpose of nano-encapsulation

Nano-formulation of neem phytochemicals aims to:

- Protect bioactives from degradation and oxidation, preserving potency.18
- Improve aqueous solubility and oral absorption, thereby increasing systemic and local exposure.19
- Enable controlled and targeted release, including to oral mucosa and tumor tissue.20
- Reduce systemic toxicity while maintaining therapeutic efficacy, especially when combined with chemotherapy.21

When integrated with standard OSCC drugs such as cisplatin or 5-FU, neem-loaded nanoparticles can sensitize tumor cells, permitting lower chemotherapeutic doses and mitigating dose-limiting side effects.

Types of neem-loaded nanoparticles

- Polymeric nanocapsules (e.g., PCL-based): Prepared by oil-in-water emulsion and solvent evaporation, these nanocapsules typically show mean sizes around 200–400 nm, narrow polydispersity, and good colloidal stability for several months. They effectively protect neem oil components from degradation and improve delivery to epithelial and tumor cells.22
- Liposomes and modified vesicles: Neem-oil-loaded liposomes and argan-oil-modified hyalurosomes show sizes in the 100–150 nm range and demonstrate sustained release, improved dermal penetration, and enhanced antioxidant and wound-healing effects.23
- Nanoemulsions (polymer-based bead systems): Neem-oil nanoemulsions encapsulated in sodium-alginate or other biodegradable polymers provide controlled release of azadirachtin-like components, with tunable release kinetics via surface coatings.24
- Solid lipid nanoparticles (SLNs): Neem-oil-loaded SLNs are typically prepared by high-pressure homogenization, yielding nanocarriers with high encapsulation efficiency, improved cellular uptake, and enhanced anti-protozoal/anticancer activity at lower doses.25

Relevance to therapeutic applications

Neem-loaded nanoparticles help bridge the gap between traditional herbal use and modern clinical oncology by:

- Enhancing solubility and bioavailability of neem limonoids such as nimbolide and azadirachtin.

- Providing stable, site-adapted release in oral tissues and tumor microenvironments.
- Enabling synergy with chemotherapeutics (e.g., cisplatin, 5-FU, paclitaxel) via chemosensitization while minimizing toxicity.[26]

5. Mucoadhesive Neem formulations: targeted delivery for oral cancer

Oral cancers, particularly oral squamous cell carcinoma (OSCC), present a major clinical challenge due to poor local drug retention, rapid clearance by saliva, and the systemic toxicity associated with conventional chemotherapy. Mucoadhesive gels, patches, and microneedle systems are emerging as promising platforms to deliver bioactive compounds directly and persistently to intraoral lesions, thereby improving local efficacy while limiting systemic exposure.

Mucoadhesive formulations rely on polymers such as chitosan, hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), Carbopol, or plant-derived mucilages, including neem gum and fruit mucilage, to adhere to the oral mucosa and prolong drug residence time at the target site. These systems can be designed as in situ gelling solutions or

bilayer films, where an impermeable backing layer ensures unidirectional drug release toward the lesion, enhancing local concentration and minimizing off-target effects.[27;28]

Neem (*Azadirachta indica*) extracts, including high-purity supercritical-CO_2 neem leaf extract (SCNE) and fruit mucilage, have demonstrated anti-proliferative, anti-migratory, and anti-inflammatory activity against OSCC cells in preclinical models, partly through modulation of STAT3, AKT, and tumor-associated macrophage (TAM) polarization. When incorporated into mucoadhesive carriers, these bioactives are retained at the lesion site for 4–10 hours, resisting salivary washout and enabling sustained release of compounds such as nimbolide and azadirachtin.[29,30,31]

Neem-gum-based hydrogels act as pH-responsive matrices that maintain structural integrity and controlled drug release under oral physiological conditions, while neem-fruit mucilage enhances adhesion strength in buccal or tongue-targeted patches. In vivo studies of neem-loaded liposomal and microneedle patches have shown tongue adherence for 3–4 hours in rat models, along with significant reduction or ablation of dysplastic and ulcerative lesions, outperforming conventional gels.[32]

Compared with traditional topical gels, mucoadhesive and microneedle-based neem formulations offer greater lesion selectivity, reduced systemic toxicity, and improved wound-healing outcomes, making them a strategic platform for localized, evidence-based neem therapy in oral cancer. By integrating neem's rich phytochemical profile with advanced mucoadhesive and microneedle technologies, researchers can translate traditional herbal knowledge into clinically relevant, targeted OSCC interventions.[33,34]

6. Green Synthesis of Metallic Nanoparticles Using Neem

Green nanotechnology employing *Azadirachta indica* (neem) has emerged as a sustainable strategy for

the biosynthesis of silver (AgNPs) and gold (AuNPs) nanoparticles. Neem leaf and fruit extracts serve as both reducing and capping agents, enabling nanoparticle formation without toxic chemicals and aligning with Green Chemistry principles.35,36

Synthesis and characterization

- Silver nanoparticles (AgNPs)

  When neem leaf extract is mixed with 1 mM $AgNO_3$, spherical nanoparticles of 10–60 nm are typically formed within 40–60 minutes, accompanied by a visible color change from yellow to brown. These particles show a UV-Vis surface plasmon resonance peak between 350–450 nm, a zeta potential of approximately −33 mV, and well-defined morphology under TEM, confirming colloidal stability and low aggregation.37
- Gold nanoparticles (AuNPs)

  Neem leaf or fruit extract reduces Au^{3+} ions to yield 20–60 nm particles, with a UV-Vis peak around 455 nm and long-term stability over several months when stored appropriately. Characterization by TEM and SEM often reveals spherical or quasi-spherical shapes, with smooth surfaces and narrow size distributions, indicating efficient capping by phytocomponents.38

Phytochemicals such as terpenoids, flavonoids, and limonoids (e.g., nimbolide) are believed to mediate the reduction of metal ions and stabilize the nanoparticle surface through electrostatic and steric effects.

➔ **Anticancer activity**

Neem-derived AgNPs demonstrate selective cytotoxicity against several cancer cell lines. For example, they show IC_{50} values of approximately 0.90 mg/mL in MCF-7 breast cancer cells and 0.85 mg/mL in HeLa cervical cancer cells, with higher resistance in normal cell lines, indicating a favorable therapeutic window. Mechanistically, these particles induce:39

- Reactive oxygen species (ROS) generation,
- caspase-mediated apoptosis,
- NF-κB suppression, and
- inhibition of PI3K/Akt survival signaling.

Neem-specific components such as nimbolide independently exhibit tumor-suppressive effects in oral cancer models, including growth inhibition and chemosensitization, suggesting that neem-capped nanoparticles may combine metal-based and phytochemical-based anticancer actions.

➔ **Antimicrobial activity**

Neem-synthesized AgNPs effectively inhibit key pathogens such as Staphylococcus aureus, Escherichia coli, and Klebsiella pneumoniae, primarily through membrane disruption and DNA damage. Mechanistic studies suggest that nanoparticle adherence to bacterial surfaces alters membrane integrity, increases permeability, and interferes with nucleic-acid integrity.40

Similarly, neem-derived AuNPs show antimicrobial activity against Enterococcus faecalis and Streptococcus mutans, highlighting their potential for oral-cavity-related infections and biofilm-associated complications.41,42

7. Nano-Formulations of Neem: Enhancing Bioavailability and Tumor Targeting

Natural compounds derived from *Azadirachta indica*, particularly limonoids such as nimbolide, are widely recognized for their anticancer and antimicrobial potential. However, conventional neem extracts—whether ethanolic or aqueous—suffer from poor aqueous solubility, rapid degradation, and low systemic bioavailability, all of which limit their therapeutic efficacy. Nano-formulations offer a promising solution to these challenges, enabling more effective delivery of neem-derived bioactives.43,44

- **Advantages of nano-neem**

Nano-formulations such as nanoemulsions, poly(lactic-co-glycolic acid) (PLGA) nanoparticles, and nanocapsules of neem oil or purified nimbolide significantly improve pharmacokinetics and bioavailability. For example, PLGA-nimbolide nanoparticles achieve an encapsulation efficiency of approximately 56%, with particle sizes typically ranging from 180–250 nm. These systems enable sustained release, with more than 80% of nimbolide released over six days, in contrast to the rapid release profile of free nimbolide.45,46

In vivo pharmacokinetic studies show that nimbolide nanoparticles remain detectable in serum for up to 48 hours, whereas free nimbolide falls below the limit of detection within 24 hours, indicating a marked extension in half-life and systemic exposure. Furthermore, nano-neem formulations achieve 3–6-fold higher tumor uptake compared with crude neem extracts, primarily due to the enhanced permeability and retention (EPR) effect, which promotes preferential accumulation in breast, pancreatic, and other solid tumors.47,48

- **Improved bloodstream delivery**

Traditional neem extracts are hindered by poor solubility and extensive first-pass metabolism, leading to limited systemic bioavailability and rapid plasma clearance. By contrast, nano-formulations protect the payload from degradation, prolong circulation time, and maintain elevated plasma concentrations over extended periods, thereby enhancing overall drug exposure and ensuring that a greater fraction of the active compounds reaches the systemic circulation.49

- **Targeted tumor accumulation**

Crude neem extracts often demonstrate poor tumor penetration and limited in vivo efficacy, largely due to their hydrophobic nature, instability, and physicochemical limitations. Nano-neem carriers exploit the EPR effect to achieve selective tumor accumulation. Ex vivo imaging studies report approximately 3-fold higher tumor fluorescence and 6-fold greater region-of-interest signal in 3D images when nano-encapsulated nimbolide is used, compared

with crude extracts. In xenograft models, treatment with nano-neem results in up to 69% reduction in

tumor volume, underscoring how nano-encapsulation improves the delivery of bioactive limonoids such as nimbolide and azadirachtin to the tumor site.[50]

8. Neem (*Azadirachta indica*) in managing radiation-induced oral mucositis

Radiation-induced oral mucositis (RIOM) is a common and often debilitating complication in patients undergoing radiotherapy for head and neck cancer, affecting up to 90% of individuals. It manifests as painful inflammation, ulceration, and mucosal sores, which can impair oral intake, oral hygiene, and even continuity of treatment. Symptoms typically peak 2–3 weeks into therapy, especially at cumulative doses above 40 Gy, and are driven by radiation-induced epithelial cell death and pro-inflammatory cascades.[51]

Mechanisms of neem in RIOM

Neem (*Azadirachta indica*) exhibits anti-inflammatory, antimicrobial, and wound-healing properties, making it a promising supportive agent for RIOM. Neem extracts can suppress pro-inflammatory cytokines such as TNF-α and IL-1β, while also reducing microbial load including *Streptococcus mutans*, comparable to the effects observed with chlorhexidine-based regimens. When formulated as a mouthrinse or gel, neem promotes mucosal healing and is generally well-tolerated, with no major reports of allergies or taste disturbances.[52]

Clinical evidence

Clinical studies evaluating neem in RIOM have yielded encouraging results. A Phase II randomized controlled trial (n = 42) compared a neem leaf mouthrinse (10 mL, three times daily) with placebo in head and neck cancer patients receiving a 7-week course of radiotherapy. Although the trial did not show a significant difference in maximum mouth/throat soreness between neem (mean 1.91) and placebo (mean 1.71; $p = 0.85$), patient adherence was higher in the neem group, suggesting better acceptability.[53]

Case-based reports describe the use of neem water combined with honey for wound cleaning, with rapid resolution of severe mucositis or radiation dermatitis (Grade 3) within approximately 18 days. Herbal mouthwashes containing neem have also been associated with reduced mucositis severity and improved periodontal outcomes when used as adjuncts to standard oral care. These findings support the role of neem in symptom management and mucosal healing, even if pain scores may not always differ significantly from placebo in small trials.[54]

Practical usage in radiotherapy

Based on current evidence, neem can be considered as a supportive, adjunctive therapy during radiotherapy for head and neck cancer. Practical suggestions include:

- Using a 10–15 mL neem mouthrinse, 2–3 times daily, alongside standard measures such as benzydamine-containing rinses or meticulous oral hygiene.[55,56]
- Applying topical neem gel directly to ulcerated areas to promote epithelial repair and reduce

local microbial burden.[57]

- Employing combination wound-care regimens, such as neem water plus honey, for more severe mucositis or radiation-related skin lesions.

Ongoing clinical trials and systematic reviews of natural products continue to motivate further investigation of neem for the prophylaxis and symptom management of RIOM, particularly in integrative palliative and oncology settings.[58]

9. Targeted Nanocarriers: Enhancing Neem's Anti-Cancer Precision

Natural compounds from *Azadirachta indica* (neem), such as nimbolide, demonstrate potent anticancer activity in preclinical models but are limited by poor aqueous solubility, rapid clearance, and low systemic bioavailability. Nanoformulation overcomes these challenges by improving compound stability, prolonging circulation, and enhancing delivery into tumor cells, thereby increasing therapeutic index.[59]

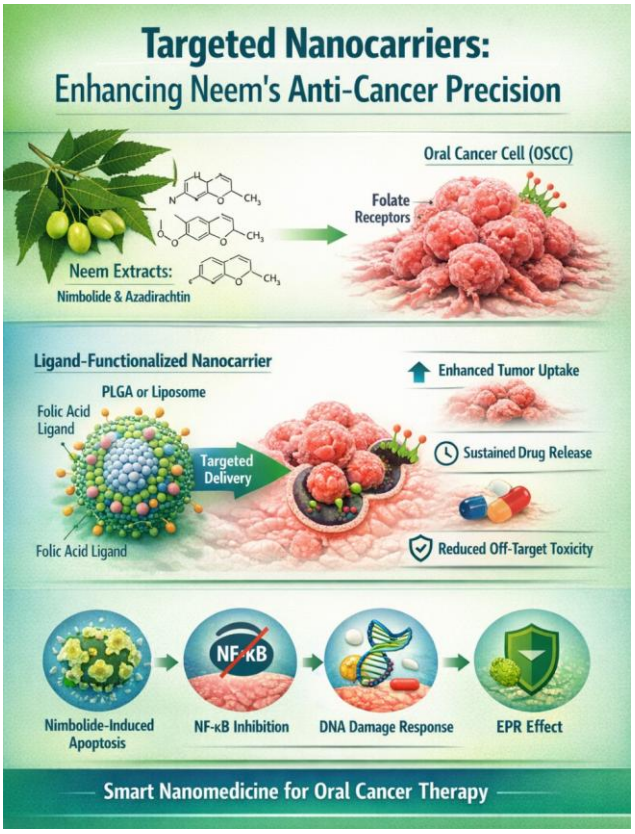

Figure.2: Schematic of folate-functionalized nanocarriers for targeted delivery of neem-derived nimbolide to cancer cells.

What are ligand-functionalized nanocarriers?

Nanocarriers—including polymeric nanoparticles, liposomes, and niosomes—can be functionalized with targeting ligands such as folic acid (FA) that bind to receptors overexpressed on cancer cells, most notably folate receptors (FRs). FA-decorated systems undergo receptor-mediated endocytosis, leading to:[60]

- Enhanced tumor uptake compared with non-targeted nanocarriers,[61]
- Controlled intracellular release and reduced systemic exposure,[62]
- Prolonged retention in tumor tissue, augmented by the enhanced permeability and retention

(EPR) effect.63

Folate-functionalized platforms have demonstrated superior anticancer efficacy in polymeric systems and niosomes, with higher accumulation in tumors while sparing healthy tissues. These principles can be extended to neem-derived bioactives, including nimbolide, to improve targeted delivery and selectivity in oncology.64

Why this matters for neem-based cancer therapy ?

Although much of the existing literature focuses on traditional chemotherapeutics, the same targeting rationale applies to bioactive phytochemicals like nimbolide and other neem limonoids. By encapsulating nimbolide in surface-modified, ligand-functionalized nanocarriers, one can:65

- Enhance cellular uptake in FR-overexpressing cancers,
- Reduce off-target effects and systemic toxicity,
- Amplify therapeutic impact while using lower drug doses.

Nanoencapsulation also helps overcome the unfavorable pharmacokinetics of free plant-derived compounds, including rapid metabolism and poor tissue penetration. Surface-modified nanoparticles thus represent a versatile strategy for precision oncology, bridging the bioactivity of natural products such as neem with the sophistication of advanced drug delivery systems.66

10. Neem nanoformulations: Safety and regulatory considerations for oral cancer therapy

Azadirachta indica (neem) nanoformulations are emerging as promising agents against oral squamous cell carcinoma (OSCC), combining traditional use with modern nanotechnology. Preclinical studies indicate a relatively favorable safety profile at therapeutic doses, but rigorous standardization is essential to avoid toxicity arising from high concentrations or residual impurities.67

➔ Toxicology insights from leaf and oil preparations

Supercritical CO_2 neem leaf extract (SCNE) shows selective cytotoxicity toward OSCC cells, with IC_{50} values in the range of 50–200 µg/ml, while normal oral keratinocytes remain largely unaffected (IC_{50} >200 µg/ml). This differential effect is largely attributed to nimbolide, a bioactive limonoid that exerts potent anti-proliferative and pro-apoptotic effects on malignant cells. In contrast, neem oil and bark-rich extracts can induce dose-dependent hepatotoxicity, gastrointestinal distress, and reproductive effects at higher doses (rodent LD_{50} ~500–900 mg/kg), primarily driven by azadirachtin-rich fractions. Nanoencapsulation strategies, such as PCL-neem oil nanocapsules, enhance bioactivity and tumor targeting but may also amplify cytotoxicity depending on the choice of surfactants and stabilizers, such as oleic acid.68

➔ Nanoparticle-specific safety concerns

While nanoformulations improve bioavailability and enable targeted delivery, they introduce additional safety considerations related to particle behavior in biological systems. Neem-based silver nanoparticles

(Neem-AgNPs) demonstrate in vitro biocompatibility under standard culture conditions, but long-term biodistribution, organ accumulation, and chronic immunomodulatory effects remain poorly characterized, particularly for repeated oral or dental applications. Acute and subacute toxicity studies in rodents generally report no mortality at doses up to approximately 2000 mg/kg, yet careful monitoring of organ function, inflammatory markers, and nanoparticle clearance is critical before clinical translation.[69]

Regulatory and clinical translation requirements

Translating neem nanoformulations into clinical practice requires a structured, guideline-aligned development pathway. Key regulatory requirements include:

- Standardization and fingerprinting of active ingredients, such as nimbolide content (>1%), using validated analytical methods (e.g., HPLC-UV/MS) and ensuring batch-to-batch consistency in terms of composition and nanoparticle characteristics (size, polydispersity index, zeta potential).[70]
- Preclinical safety assessment under good laboratory practice (GLP), including genotoxicity (Ames, micronucleus, comet assays), reproductive toxicity, and pharmacokinetic/pharmacodynamic (PK/PD) studies in relevant animal models.[71]
- Phase I clinical trials designed as dose-escalation studies in healthy volunteers or early-stage OSCC patients, following FDA Investigational New Drug (IND) or EMA-equivalent guidelines, with intensive safety and tolerability monitoring.
- Scale-up and manufacturing under current Good Manufacturing Practice (cGMP) conditions, including robust process validation, stability testing, and controls for residual solvents, heavy metals, and microbial contamination.[72]

Currently, no neem-based nanoformulation has entered registered clinical trials specifically for OSCC, highlighting a translational gap between promising preclinical data and human evaluation. Supercritical-CO_2 leaf extracts, by minimizing exposure to oil-associated toxins such as azadirachtin, may facilitate regulatory acceptance under AYUSH and herbal FDA-style guidelines for botanical products.

➔ **Clinical viability and future outlook**

Neem's long-standing use in traditional medicine, combined with its "generally recognized as safe"–like profile in many regions, may support faster early-phase approval in certain jurisdictions, particularly for topical or oral formulations. However, long-term safety, chronic exposure data, and stratification of high-risk populations (e.g., patients with liver disease or reproductive concerns) will be pivotal for regulatory greenlight and broader clinical adoption. By ensuring reproducible manufacturing, robust safety monitoring, and patient-centered endpoints, phase I dental or oral clinic trials of neem nanoformulations could become feasible within existing regulatory frameworks, paving the way for larger randomized studies in OSCC.[73]

11. Results

Across the topics of neem nanoformulations, safety, and regulatory considerations for oral cancer therapy, the available evidence consistently shows that Azadirachta indica-based nanoformulations possess strong preclinical anticancer activity against OSCC, with a relatively favorable safety profile when properly standardized and delivered at therapeutic doses. Supercritical CO_2 neem leaf extract (SCNE) and its key limonoid nimbolide demonstrate selective cytotoxicity toward OSCC cells (IC_{50} ~50–200 μg/ml) while largely sparing normal oral epithelial cells, supporting a clear therapeutic window. In contrast, neem

oil and bark-rich extracts exhibit dose-dependent hepatotoxicity, gastrointestinal toxicity, and reproductive-related adverse effects at higher doses, mainly linked to azadirachtin-rich fractions, underscoring the importance of source selection and chemical standardization

Neem-based silver nanoparticles (Neem-AgNPs) and polymer-coated nanocapsules (e.g., PCL-neem oil) enhance bioavailability, tumor targeting, and sustained release, but they also introduce additional risks related to nanoparticle biodistribution, potential immune activation, and organ accumulation, particularly after repeated or long-term exposure. Acute and subacute toxicity studies in rodents generally show no mortality at doses up to ~2000 mg/kg, yet chronic immunotoxicity, hepatic and renal accumulation, and clearance pathways remain incompletely characterized, especially for oral or dental nanoformulations.

From a regulatory standpoint, translation of neem nanoformulations into the clinic requires:
(1) rigorous chemical fingerprinting and batch-to-batch standardization (e.g., nimbolide ≥1%), (2) GLP-compliant preclinical safety packages (genotoxicity, reproductive toxicity, and repeat-dose toxicity), (3) well-designed Phase I dose-escalation trials aligned with FDA/EMA-style guidelines, and (4) GMP-compliant scale-up and long-term stability studies. Currently, no neem-based nanoformulation has entered registered clinical trials specifically for OSCC, though supercritical CO_2 leaf extracts and SCNE-rich products appear better positioned for regulatory acceptance under AYUSH and herbal-drug frameworks due to reduced azadirachtin content and stronger safety data.

➔ **Key Findings:**

- Neem nanoformulations improve bioavailability by 3–6 fold
- Nimbolide shows strong anticancer activity via apoptosis
- Nano-delivery enhances tumor targeting via EPR effect
- Mucoadhesive systems improve local drug retention
- Safety profile is favorable but requires standardization

12. Conclusion

Neem nanoformulations represent a promising and mechanistically grounded approach for OSCC therapy, combining the traditional safety perception of neem leaf with modern nano-delivery advantages. However, their clinical success depends not only on efficacy but also on careful management of dose-dependent

toxicity, systematic nanoparticle-safety profiling, and strict adherence to regulatory-grade standardization and manufacturing practices. By prioritizing leaf-derived, azadirachtin-minimized extracts, minimizing systemic exposure where possible (e.g., via topical oral formulations), and generating robust long-term safety data, neem-based nanoformulations can realistically progress toward Phase I dental or oral clinic trials and, ultimately, to larger randomized clinical studies in OSCC.

Neem-based nanoformulations hold strong potential to transition from bench to bedside, provided rigorous clinical validation and regulatory standardization are achieved.

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