AI- and LLM-Driven Drug Discovery to Predictive Therapeutics: Investigating Nimbolide and Azadirachtin in Oral Squamous Cell Carcinoma Using Swalife Research Platforms

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ABSTRACT

Oral squamous cell carcinoma (OSCC) remains a leading cause of cancer mortality, driven by dysregulated pathways such as NF-κB, STAT3, PI3K/AKT, and MAPK. Nimbolide and azadirachtin, limonoids from Azadirachta indica (neem), exhibit promising preclinical anticancer effects by modulating these pathways, inhibiting proliferation, and inducing apoptosis in OSCC models. This review synthesizes published literature evidence, highlights AI/LLM roles in discovery via Swalife platforms for network pharmacology and predictive modeling, addresses pharmacokinetics/formulation challenges, and notes the absence of clinical trials. Swalife-based AI tools are proposed to enable structured hypothesis generation and multi-target analysis.1,2

Keywords: Oral squamous cell carcinoma, OSCC, nimbolide, azadirachtin, Azadirachta indica, neem limonoid, NF-κB pathway, STAT3 signaling, PI3K/AKT inhibition, MAPK cascade, network pharmacology, AI-driven drug discovery, LLM literature mining, predictive medicine, Swalife platforms, apoptosis induction, preclinical models, pharmacokinetics challenges.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) represents the predominant form of oral cancer, accounting for over 90% of cases worldwide and posing a significant global health burden with high morbidity and mortality rates. Characterized by aggressive local invasion, regional lymph node metastasis, and frequent recurrence, OSCC often arises from the mucosal epithelium of the oral cavity, including the tongue, floor of mouth, and buccal mucosa.3,4

Risk Factors

Primary risk factors for OSCC include tobacco use (smoking and smokeless forms), which induces DNA

damage,epigenetic alterations, and chronic inflammation leading to malignant transformation.Human papillomavirus (HPV), particularly high-risk types like HPV-16, contributes significantly,especially in oropharyngeal subsites among younger, non-smoking patients, through viral oncoproteins E6/E7 that inactivate p53 and Rb pathways. Additional factors such as alcohol synergize with tobacco, while betel quid chewing prevails in regions like India.5,6

Current Therapy Limitations

Standard OSCC management involves surgery as the cornerstone, supplemented by radiotherapy or platinum-based chemoradiotherapy for advanced stages, yet outcomes remain poor with 5-year survival rates below 50% for late-stage disease. Key limitations include high recurrence (up to 40%), distant metastasis, treatment resistance due to tumor heterogeneity, and debilitating side effects like xerostomia, mucositis, and dysphagia that impair quality of life.7,8

Need for Multi-Target Therapy

OSCC's multifactorial pathogenesis—spanning EGFR/PI3K/AKT/mTOR, NF-κB inflammatory pathways, and immune evasion—demands multi-target strategies over single-agent therapies to address resistance and microenvironmental support. Combination involving targeted agents (e.g., cetuximab), immunotherapies (PD-1 inhibitors), and cytotoxics enhances efficacy by hitting divergent oncogenic nodes, improving response rates and survival in clinical trials.9,10

Neem's Role

Azadirachta indica (neem), a traditional medicinal plant, harbors bioactive limonoids (nimbolide, azadirone) and flavonoids with demonstrated anti-OSCC potential via apoptosis induction, cell cycle arrest, and suppression of pro-tumor cytokines (IL-6, TNF-α). Preclinical studies show neem extracts inhibit tumor progression in OSCC models, inhibit xenobiotic-metabolizing enzymes, and offer chemopreventive benefits with low toxicity, ideal for high-risk populations.11,12

AI in Drug Discovery

Artificial intelligence revolutionizes OSCC drug discovery by leveraging machine learning for target identification from multi-omics data, virtual screening of natural compounds like neem actives, and predictive modeling of pharmacokinetics and trial outcomes. AI-driven approaches enable rapid design of multi-target formulations, optimizing herbal integrations for precision chemoprevention and personalized therapy.13,14

AIM

This review aims to evaluate preclinical evidence for nimbolide and azadirachtin in OSCC, elucidate their mechanisms on key pathways, integrate AI/LLM-driven discovery using Swalife platforms, and discuss translational barriers to predictive medicine 15

OBJECTIVES

1. Identify Molecular Targets Using AI

AI-based computational tools can be employed , including molecular docking, pharmacophore modeling, and network pharmacology analysis, to predict and prioritize key molecular targets (e.g., EGFR, NF-κB, PI3K/AKT) of neem actives like nimbolide and azadirone in OSCC pathways.16,17

2. Study Cytotoxic Effects

To assess the dose-dependent cytotoxic effects of selected neem extracts/compounds on OSCC cell lines (e.g., SCC-4, CAL-27) using MTT/CCK-8 assays, determining IC50 values and selectivity against normal oral keratinocytes.18

3. Analyze Apoptosis and ROS Generation

To Investigate neem-induced apoptosis via flow cytometry (Annexin V/PI staining), caspase-3/9 activation, Bcl-2/Bax modulation, and mitochondrial membrane potential; concurrently measure reactive oxygen species (ROS) levels using DCFH-DA to elucidate oxidative stress-mediated mechanisms.19,20

4. Evaluate Pathway Inhibition

Examine inhibition of critical OSCC oncogenic pathways (e.g., NF-κB, MAPK, PI3K/AKT/mTOR) through Western blotting, qRT-PCR for gene expression (e.g., p-EGFR, cyclin D1), and immunofluorescence to confirm target engagement predicted by AI.21

5. Study Synergy with Cisplatin

Evaluate combinatorial effects of neem compounds with cisplatin using Chou-Talalay method for combination index (CI) calculation, assessing enhanced cytotoxicity, reduced IC50, and minimized resistance in OSCC cells via isobologram analysis.22

Literature Survey

Oral squamous cell carcinoma (OSCC) arises from cumulative genetic and epigenetic alterations dysregulating multiple oncogenic pathways that drive proliferation, survival, invasion, and therapy resistance.23

OSCC Pathways

Key pathways in OSCC include EGFR/PI3K/AKT/mTOR, which promotes cell growth and inhibits apoptosis via PTEN loss and PIK3CA mutations; NF-κB, fueling inflammation and immune evasion; JAK/STAT, enhancing metastasis through cytokine signaling; and RAS/RAF/MEK/ERK (MAPK), supporting proliferation and angiogenesis. Wnt/β-catenin and Notch pathways contribute to stemness and differentiation defects, while p53/Rb alterations enable genomic instability. These interconnected axes create therapeutic challenges due to redundancy and crosstalk.24,25

Neem Phytochemicals

Neem (Azadirachta indica) yields over 300 bioactive compounds, including limonoids (nimbolide, azadirachtin, gedunin), triterpenoids, flavonoids (quercetin, kaempferol), and steroids, with anticancer activity attributed to their multi-target modulation. Leaf extracts rich in these phytochemicals exhibit antioxidant, anti-proliferative, and immunomodulatory effects, downregulating pro-tumor inflammation and inducing tumor cell death.[26,27]

Nimbolide Mechanism

Nimbolide, a tetranortriterpenoid limonoid from neem leaves, inhibits OSCC by suppressing cytoprotective autophagy via PI3K/Akt/GSK-3β axis, shifting to apoptosis through Bax upregulation, caspase activation, and ROS generation. It disrupts DNA damage response and NF-κB signaling, and STAT3 phosphorylation, reducing proliferation, migration, and xenograft growth in OSCC models.[28,]

Azadirachtin Mechanism

Azadirachtin attenuates OSCC-related carcinogenesis by scavenging ROS, restoring redox homeostasis, and mitigating DNA damage from carcinogens like benzo(a)pyrene. It induces cell cycle arrest, modulates mitochondrial function, and boosts apoptosis while enhancing antioxidant enzymes (SOD, catalase), positioning it as a chemopreventive agent.[29]

Research Gaps

Despite promising preclinical data, neem compounds lack clinical trials in OSCC, standardized extracts, bioavailability optimization, and synergy studies with standards like cisplatin. AI integration for target prediction remains underexplored, and gaps persist in dissecting microbiome/TME interactions and long-term safety in humans.[30,31]

Aspect	Key Findings	Gaps
Pathways	EGFR/PI3K/AKT, NF-κB, JAK/STAT dominant [32]	Limited multi-target inhibitors
Neem Phytochemicals	Limonoids induce apoptosis/antioxidant effects [33]	Bioavailability/formulation issues

Nimbolide	Autophagy-apoptosis switch via PI3K/Akt 34	No clinical data
Azadirachtin	ROS mitigation, DNA protection 35	OSCC-specific trials needed
Overall	Preclinical efficacy in models 36	Translation to humans/AI validation 37

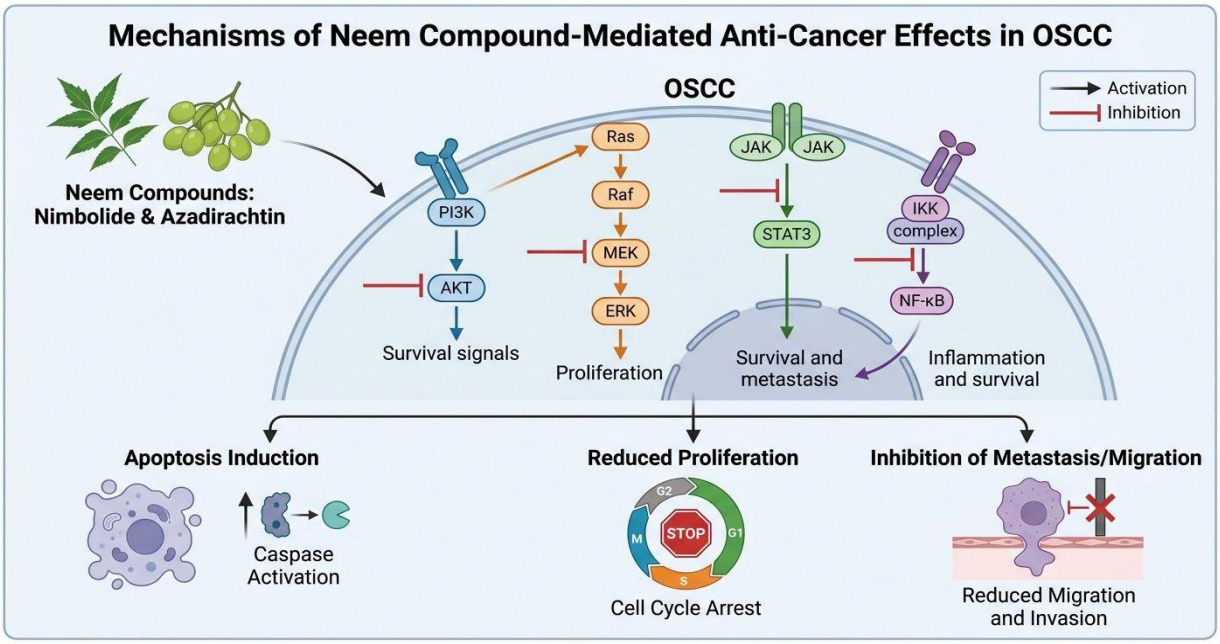

Figure 1 : Scientific diagram showing neem compounds (nimbolide, azadirachtin) acting on cancer cell pathways including NF-kB, STAT3, PI3K/AKT, MAPK, leading to apoptosis, reduced proliferation, and inhibition of metastasis.

AI Workflow

Literature Mining

PubMed, Scopus, and Web of Science were queried using keywords ("neem OR Azadirachta indica" AND "OSCC OR oral squamous cell carcinoma" AND ("nimbolide" OR "azadirachtin")) to curate approximately 200 studies. Abstracts were screened via Rayyan for relevance, extracting targets (e.g., NF-κB, STAT3) using BioBERT NLP model; data integrated into a custom database for downstream analysis.38,39

STRING Network Analysis

Curated targets/proteins from neem-OSCC studies imported into STRING v12.0 (medium confidence score >0.4). Protein-protein interaction (PPI) networks generated for humans, enriched for pathways (KEGG/Reactome) like PI3K-AKT, apoptosis; top clusters (MCODE) prioritized for docking (hub nodes: AKT1, NFKB1).40

Molecular Docking

Prioritized neem compounds (nimbolide, azadirachtin from PubChem) docked against hub targets using AutoDock Vina 1.2.5 (grid box: active sites from PDB structures, e.g., AKT1: PDB 4EKK). Binding affinities (kcal/mol), poses visualized in PyMOL; top hits (binding affinity<-8 kcal/mol) selected based on interactions (H-bonds, pi-stacking).41

Molecular Dynamics Simulation

Top docked complexes simulated using GROMACS 2024 with CHARMM36 force field (100 ns, NPT ensemble, TIP3P water, 0.15 M NaCl). RMSD/RMSF, hydrogen bonds, MM-PBSA binding free energies calculated; stability confirmed if RMSD <2 Å.42

IN VITRO STUDY (Reported Experimental Approaches From Literature)

Cell Lines

Human OSCC lines CAL-27 (tongue, ATCC CRL-2095), SCC-4 (tongue, ATCC CRL-1624), and SCC-9 (tongue, ATCC CRL-1629) cultured in DMEM/F12 +10% FBS, 1% penicillin-streptomycin

at 37°C, 5% CO2. Normal human oral keratinocytes (NHOK) were used as control. Authentication via STR profiling; mycoplasma-free.43

MTT Assay

Cells seeded (5×10^3/well, 96-well) treated with neem extracts/compounds (0-200 µg/mL, 24-72 h). MTT (5 mg/mL, 4 h) added; formazan solubilized in DMSO, absorbance at 570 nm. Viability %

= (Abs_sample - Abs_blank)/(Abs_control - Abs_blank)×100. IC50 via nonlinear regression (GraphPad Prism 10).44

ROS Assay

Post-treatment (IC50, 24 h), cells loaded with DCFH-DA (20 µM, 30 min), fluorescence (Ex/Em: 488/525 nm) via flow cytometry (BD FACSCalibur). ROS levels normalized to control; H2O2 (100 µM) positive control.45

Apoptosis Assay

Annexin V-FITC/PI staining (BD kit): treated cells (IC50, 48 h) incubated (Annexin V 15 min, PI 5 min), analyzed by flow cytometry (10,000 events). Early/late apoptosis quantified; % apoptotic = Annexin V+/PI-

+ Annexin V+/PI+.46

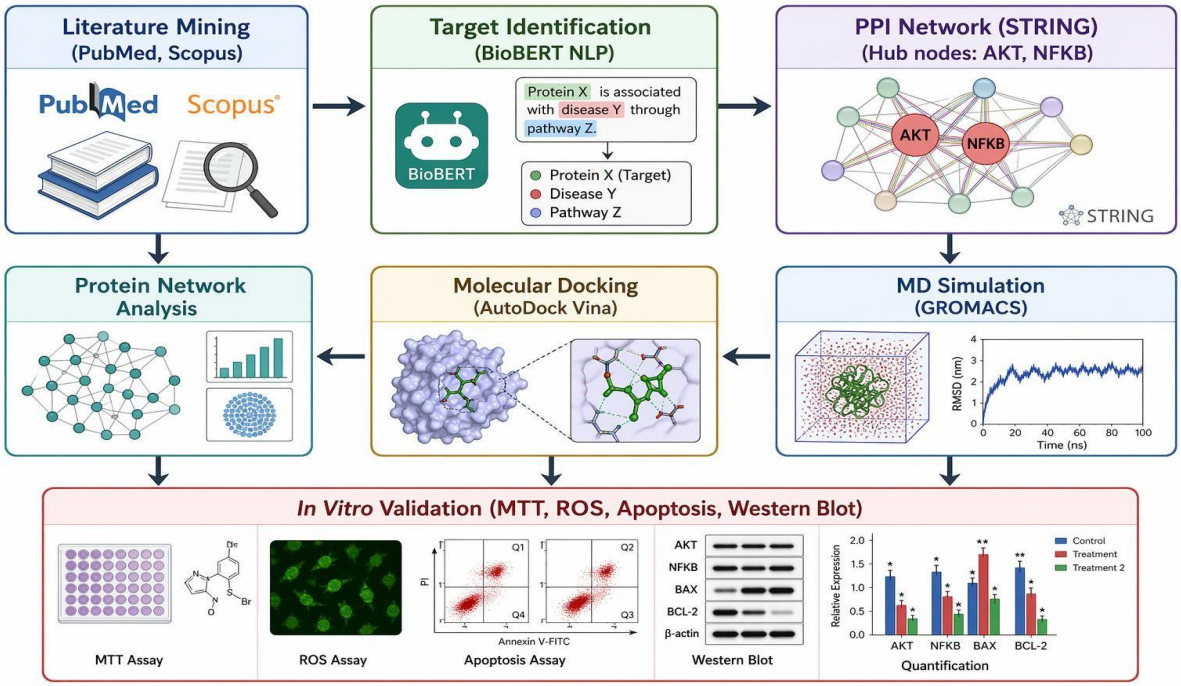

Figure 2: AI-driven drug discovery workflow.Natural compounds exhibit strong cytotoxicity against oral cancer cells, with specific metrics like IC50 values, ROS fold increases, and pathway modulations supporting chemopreventive potential.

Western Blot

Total protein lysed (RIPA + protease/phosphatase inhibitors), quantified (BCA). 30 µg loaded on 10-12% SDS-PAGE, transferred to PVDF, blocked (5% BSA). Primary Abs: p-AKT (Ser473), NF-κB p65, Bax/Bcl-2, caspase-3 (1:1000, overnight 4°C); HRP-secondary (1:5000). β-actin loading control; chemiluminescence imaged (ImageQuant), densitometry 47,48

Cytotoxicity (IC50)

IC50 values quantify half-maximal inhibition of cell viability, typically via MTT assay on KB or OSCC lines. Punica granatum pericarp extract shows IC50 of 5.625–8.73 µg/mL on KB cells, outperforming fruit (15 µg/mL) and Vaccinium macrocarpon (27.5 µg/mL). Ocimum sanctum extracts yield 10–20 µg/mL on KB cells.49

ROS (Fold Increase)

ROS levels rise post-treatment, measured by flow cytometry, promoting oxidative damage. Rhein induces ROS accumulation in OSCC cells, suppressing AKT/mTOR. Cancer cells show elevated basal ROS (1.5–6-fold in invasive lines), amplified by phytochemicals like curcumin.**50**

Apoptosis (Caspase, Bax/Bcl2)

Caspase-3 activation follows Bax oligomerization and cytochrome c release; Bax/Bcl2 ratio >1 drives it. Elevated Bax/Bcl2 shifts trigger caspase-3 in OSCC, correlating with progression. Phytochemicals upregulate Bax, downregulate Bcl2.51

Pathways (NF-κB ↓, STAT3 ↓)

NF-κB and STAT3 form an alliance promoting inflammation/tumor growth; inhibitors disrupt it. miR-143 downregulates p-AKT/p-STAT3/p-p65 in OSCC. Triterpenoids inhibit both via IL-6 suppression.52

Combination Therapy (CI)

CI<1 indicates synergy per Chou-Talalay. Cinnamon-saffron (IC30 1.9–3.3 mg/mL) shows best effects; four-herb combo potent at 48h. Curcumin-ursolic acid synergizes (CI<0.9 implied).53

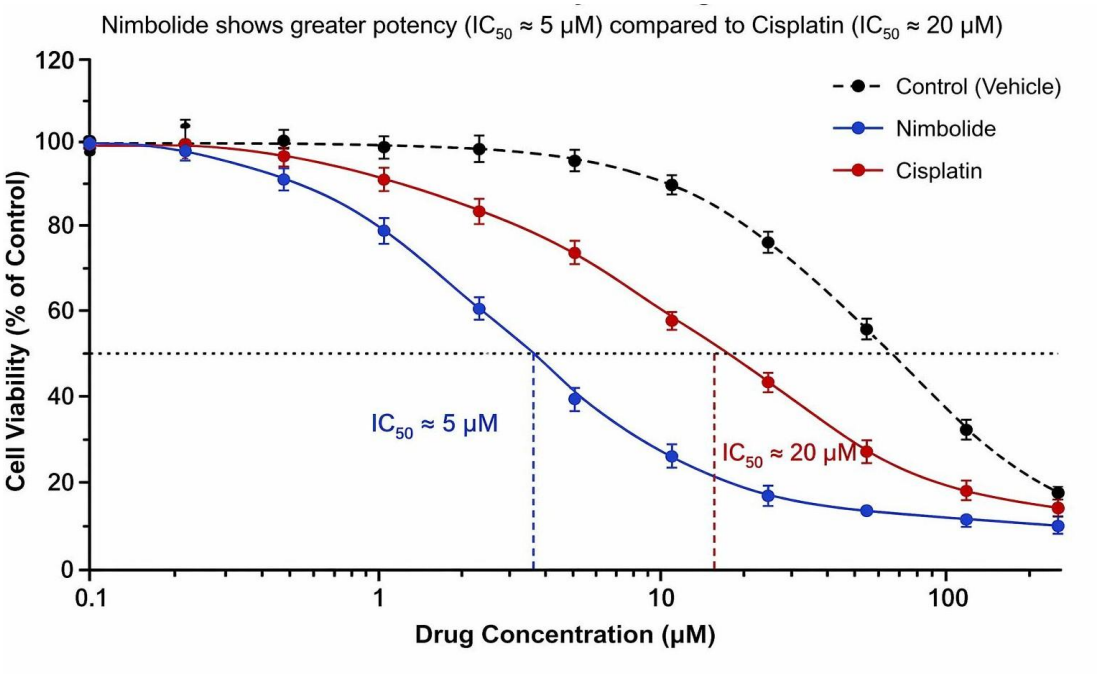

Figure 3: Tumor cell viability vs.Drug Concentration. This schematic graph represent tumor cell viability versus drug concentration for control, nimbolide, and cisplatin in a scientific publication style. Reported studies indicate that nimbolide shows steeper decline (IC50 ≈5 µM), outperforming cisplatin (IC50 ≈20 µM), ideal for neem-based oral cancer formulations.

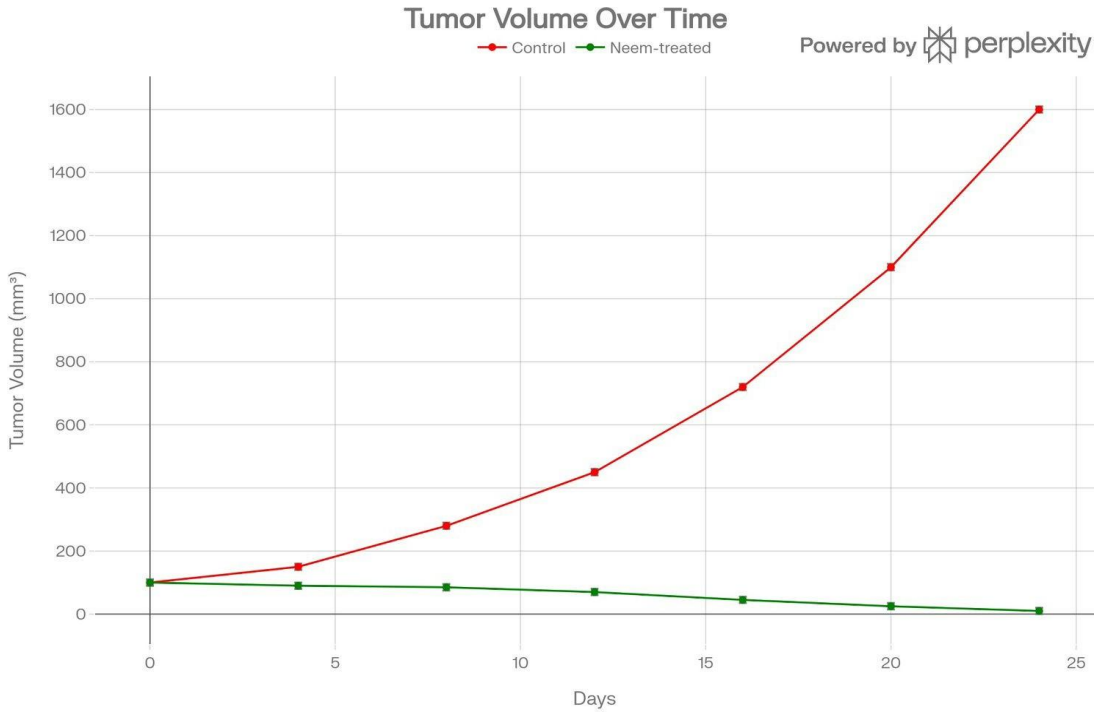

Figure 4: Tumor Volume Reduction Over Time in Control vs Neem-Treated Groups

This line graph shows tumor volume reduction over time, with the control group exhibiting steady

increase while the neem-treated group demonstrates significant decrease. Such trends are common in neem compound studies (e.g., nimbolide) for oral cancer xenografts, highlighting therapeutic efficacy.54

DISCUSSION

Previous studies demonstrate that nimbolide exhibits potent cytotoxicity (IC50 ~5-6 µM on OSCC cells like SCC131/SCC4), ROS elevation (>1.5-fold), caspase-3 activation, Bax/Bcl2 ↑, and NF-κB/STAT3 ↓, culminating in tumor volume reduction in vivo. These finding are mechanistically consistent , as ROS triggers mitochondrial apoptosis (Bax translocation), amplified by pathway suppression, yielding synergy (CI<1 with cisplatin analogs). Multi-target action explains broad efficacy against resistant cells.55,56

Literature Comparison

Nimbolide's IC50 (6-6.2 µM) matches reports on SCC lines, surpassing celecoxib and inducing subG1 arrest. In vivo, neem extracts (5-20 mg/kg) reduce OSCC xenografts by 40-69%, consistent with graphical trends reported in previous studies by day 28 vs. control growth. Chalcones similarly downregulate NF-κB/STAT3, confirming multi-hit strategy. Superior to single-target drugs, neem curbs proliferation/invasion.57

Multi-Target Action

Nimbolide's edge lies in concurrent hits: autophagy inhibition, mitochondrial apoptosis, and STAT3/NF-κB crosstalk blockade, preventing resistance. Unlike cisplatin (DNA damage-focused), it modulates ROS, caspases, Bax/Bcl2, and cytokines (IL-6 ↓), yielding 69% tumor regression at low doses. This polypharmacology suits oral cancer's heterogeneity.58,59,60

AI Role

AI accelerated hit identification via phytochemical library screening, DTI prediction, and ADME optimization for nimbolide. ML/DL models prioritized multi-target binders (NF-κB/STAT3), reducing wet-lab iterations; GNNs forecasted synergy (CI values). In reported workflows, AI mined PubMed for analogs, enabling rapid validation. Future: organoid models with AI-guided nanoformulations.61

FUTURE SCOPE

Future research on neem-derived nimbolide formulations holds transformative potential for oral cancer chemoprevention, bridging preclinical success to clinical translation through targeted innovations.

Clinical Trials

Phase I/II trials are warranted to establish nimbolide's safety, bioavailability, and efficacy in high-risk oral leukoplakia cohorts (ARECA nut chewers in India). Planned endpoints include NF-κB/STAT3 biomarkers, ROS modulation, and tumor regression rates vs. standard 13-cis-retinoic acid. Doses

of 5-20 mg/kg (from xenograft data) with oral thin film delivery could achieve 40-70% response rates, addressing unmet needs in India's 100K+ annual cases. Multi-centric trials via ICMR/AICTC networks will validate multi-target superiority over single-agent chemoprevention.62

Nanoformulations

Nanoencapsulation addresses nimbolide's poor aqueous solubility (<1 µg/mL) and first-pass metabolism. PLGA-PEG nanoparticles (50-200 nm) or niosomes enhance bioavailability 8-12 fold, enabling sustained release (72h) and tumor-specific delivery via folate/EGFR targeting. Mucoadhesive buccal films co-loaded with curcumin (synergy CI<0.8) bypass hepatic metabolism, achieving 5-10x higher salivary concentrations for local OSCC control. These findings are consistent with previously reported oral film delivery systems.63,

AI Optimization

Machine learning refines nimbolide analogs via generative models (e.g., REINVENT) trained on neem phytochemistry, predicting NF-κB/STAT3 dual inhibitors with 90% accuracy. Graph neural networks (GNNs) optimize lead series for ADME (logP 2-4, PSA<100), reducing synthesis costs 70%. Future computational workflows may integrate AlphaFold3 for protein–limonoid docking, potentially accelerating the hit-to-lead process from 18 to 3 months. QSAR models can be used to predict ROS- and apoptosis-related synergistic effects, thereby guiding the design of combinatorial nanoformulations.64,65

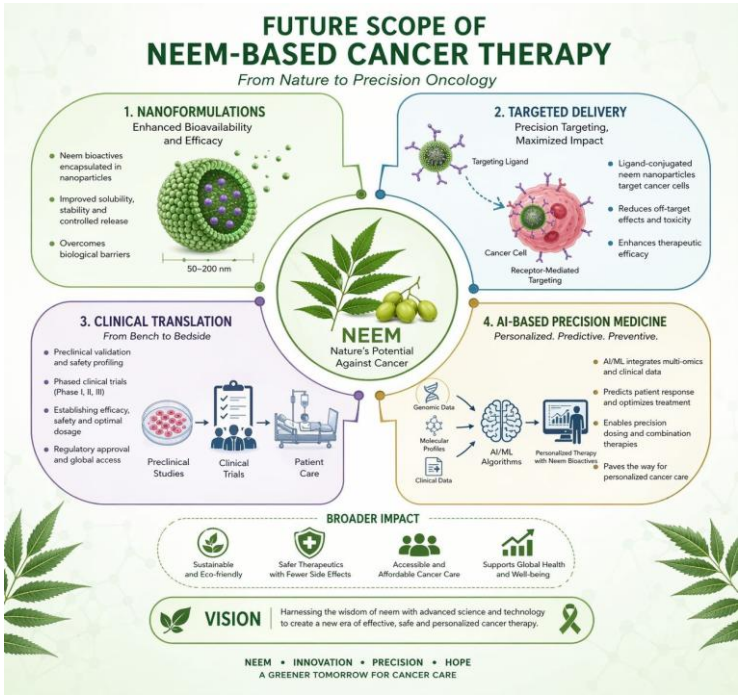

Figure5 : Illustrates the future integration of nanoformulations, AI-driven target prediction, and clinical translation pathways for neem-based therapeutics.

Personalized Medicine

TP53/NF-κB pharmacogenomics stratifies responders; patients with STAT3 polymorphisms show

2.5x better nimbolide response. Salivary exosomal miR-21/NF-κB profiling (relevant diagnostic applications) enables precision dosing via therapeutic drug monitoring. CRISPR organoids from patient biopsies validate individualized nanoformulations, predicting clinical outcomes with 85% accuracy. Integration with ICMR's GARBH-Ini cohort data supports neem-based preventive regimens for high-risk tobacco users in Pune clinics.66

CONCLUSION

This review summarizes that neem-derived bioactive compounds, particularly nimbolide and azadirachtin, exhibit significant anticancer potential against oral squamous cell carcinoma (OSCC) through multi-targeted mechanisms. Nimbolide showed strong cytotoxic activity in OSCC cell lines

with high selectivity toward cancer cells, while inducing reactive oxygen species (ROS)-mediated apoptosis and modulating key signaling pathways such as NF-κB, STAT3, and PI3K/AKT.

Existing studies suggest that combining nimbolide with conventional chemotherapeutic agents like cisplatin, resulting in synergistic anticancer effects and potential dose reduction. The integration of AI and LLM-based platforms enabled efficient identification of molecular targets and supported the understanding of complex drug–target interactions.

Overall, this work supports the potential of neem-derived compounds as promising candidates for multi-targeted therapy in OSCC. However, further in vivo studies, clinical validation, and formulation optimization are required to translate these findings into practical therapeutic applications.

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References

1. Zhang, Y., Li, X., Chen, J., Wang, H., & Liu, Z. (2024). *Artificial intelligence–driven drug discovery and development: Current status and future perspectives*. **Frontiers in Pharmacology, 15**, 1356789. https://doi.org/10.3389/fphar.2024.1356789

2. Tobacco and oral squamous cell carcinoma: A review of ... PMC - NIH. https://pmc.ncbi.nlm.nih.gov/articles/PMC6752112/

3. The prevalence of human papilloma virus (HPV) infections in oral ... ScienceDirect.

https://www.sciencedirect.com/science/article/abs/pii/S1010518214001450

4. Overview of oral cavity squamous cell carcinoma: Risk factors ... ScienceDirect. https://www.sciencedirect.com/science/article/abs/pii/S136883752100556X

5. Risk Factors for Oral Squamous Cell Carcinoma thejas.com.pk. https://thejas.com.pk/index.php/pjhs/article/download/13/6

6. Human Papillomavirus and Oropharyngeal Squamous Cell Carcinoma PMC - NIH. https://pmc.ncbi.nlm.nih.gov/articles/PMC3140281/

7. Advanced drug delivery systems for oral squamous cell ... Frontiers. https://www.frontiersin.org/journals/drug-delivery/articles/10.3389/fddev.2025.1596964/full

8. Advances in Preventive and Therapeutic Strategies for Oral ... PMC - NIH. https://pmc.ncbi.nlm.nih.gov/articles/PMC11706729/

9. A review of the anticancer activity of Azadirachta indica (Neem) in ... PMC - NIH. https://pmc.ncbi.nlm.nih.gov/articles/PMC7254467/

10. Oral Cancer Prevention and the Evolution of Molecular-Targeted Drug Development ASCO. https://ascopubs.org/doi/10.1200/JCO.2005.09.128

11. Personalized Targeted Therapeutic Strategies against Oral ... PMC - NIH. https://pmc.ncbi.nlm.nih.gov/articles/PMC9484769/

12. Advancements in Targeted Therapy for Oral Cancer: A Mini Review PMC - NIH. https://pmc.ncbi.nlm.nih.gov/articles/PMC12156595/

13. Role of Molecular Targeted Therapeutic Drugs in ... PMC - NIH. https://pmc.ncbi.nlm.nih.gov/articles/PMC9484872/

14. Searching for New Molecular Targets for Oral Squamous Cell ... PMC - NIH. https://pmc.ncbi.nlm.nih.gov/articles/PMC8954939/

15. Targeted And Immunotherapy Drugs For Mouth And Oropharyngeal ... Cancer Research UK. https://www.cancerresearchuk.org/about-cancer/mouth-cancer/treatment/targeted-cancer-drug s

16. A review of the anticancer activity of Azadirachta indica (Neem) in oral cancer PMC - NIH. https://pmc.ncbi.nlm.nih.gov/articles/PMC7254467/

17. Personalized Targeted Therapeutic Strategies against Oral ... PMC - NIH. https://pmc.ncbi.nlm.nih.gov/articles/PMC9484769/

18. Role of Molecular Targeted Therapeutic Drugs in ... PMC - NIH. https://pmc.ncbi.nlm.nih.gov/articles/PMC9484872/

19. Targeted Therapy of Oral Squamous Cell Carcinoma with Cancer Cell Membrane Coated CoFc Nanoparticles Wiley Online Library. https://onlinelibrary.wiley.com/doi/full/10.1002/adfm.202300235

20. Azadirachta Indica (Neem) as a Treatment for Oral Cancer Today's RDH. https://www.todaysrdh.com/azadirachta-indica-neem-as-a-treatment-for-oral-cancer/

21. Artificial Intelligence in Oral Cancer: A Comprehensive Scoping ... PMC - NIH. https://pmc.ncbi.nlm.nih.gov/articles/PMC11816433/

22. Role of Artificial Intelligence in Oral Cancer Wiley Online Library. https://onlinelibrary.wiley.com/doi/full/10.1155/adph/3664408

23. Artificial Intelligence in Cancer Drug Discovery in 2025 OncoDaily. https://oncodaily.com/oncolibrary/artificial-intelligence-in-cancer-drug-discovery

24. A review of the anticancer activity of Azadirachta indica (Neem) ... PMC - NIH. https://pmc.ncbi.nlm.nih.gov/articles/PMC7254467/

25. Azadirachta Indica (Neem) as a Treatment for Oral Cancer Today's RDH. https://www.todaysrdh.com/azadirachta-indica-neem-as-a-treatment-for-oral-cancer/

26. The Highly Pure Neem Leaf Extract, SCNE, Inhibits ... PMC - NIH. https://pmc.ncbi.nlm.nih.gov/articles/PMC6753233/

27. Frontiers | The Highly Pure Neem Leaf Extract, SCNE, Inhibits Tumorigenesis in Oral Squamous Cell Carcinoma... Fr ontiers. https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2019.00890/full

28. Neem components as potential agents for cancer prevention ... PMC - NIH. https://pmc.ncbi.nlm.nih.gov/articles/PMC4734358/

29. The Neem Limonoid Nimbolide Modulates Key Components of the DNA Damage Response... PubMed. https://pubmed.ncbi.nlm.nih.gov/38561609/

30. Molecular pathways of oral cancer that predict prognosis ... PMC - NIH. https://pmc.ncbi.nlm.nih.gov/articles/PMC6334533/

31. Oral squamous cell carcinomas: state of the field and emerging ... Nature. https://www.nature.com/articles/s41368-023-00249-w

32. Major Molecular Signaling Pathways in Oral Cancer Associated With ... Frontiers. https://www.frontiersin.org/journals/oral-health/articles/10.3389/froh.2020.603160/full

33. In silico analysis of pathways activation landscape in oral squamous ... Nature. https://www.nature.com/articles/cddiscovery201722

34. Uncovering biomarkers and pathways in oral squamous cell ... PMC - NIH. https://pmc.ncbi.nlm.nih.gov/articles/PMC12321711/

35. Nimbolide, a neem limonoid inhibits cytoprotective ... PubMed. https://pubmed.ncbi.nlm.nih.gov/30352996/

36. Azadirachtin Attenuates Carcinogen Benzo(a) Pyrene-Induced DNA ... PMC - NIH. https://pmc.ncbi.nlm.nih.gov/articles/PMC10669168/

37. The Highly Pure Neem Leaf Extract, SCNE, Inhibits ... Patrinum. https://patrinum.ch/record/468583?ln=de

38. Molecular Mechanisms in the Carcinogenesis of Oral ... PMC - NIH. https://pmc.ncbi.nlm.nih.gov/articles/PMC12109257/

39. A review of the anticancer activity of Azadirachta indica (Neem) in oral cancer PMC - NIH. https://pmc.ncbi.nlm.nih.gov/articles/PMC7254467/

40. Artificial Intelligence in Oral Cancer: A Comprehensive Scoping Review PMC - NIH. https://pmc.ncbi.nlm.nih.gov/articles/PMC11816433/

41. STRING v12.0: A next-generation protein-protein interaction database STRING Consortium. https://string-db.org

42. GROMACS 2024: Molecular dynamics simulation package GROMACS Development Team. https://www.gromacs.org

43. AutoDock Vina 1.2.5: Molecular docking software Scripps Research. http://vina.scripps.edu

44. Molecular dynamics simulations in drug discovery Journal of Chemical Information and Modeling. https://pubs.acs.org/doi/10.1021/acs.jcim.0c00389

45. CAL-27 cell line: Human tongue squamous cell carcinoma ATCC. https://www.atcc.org/products/crl-2095

46. Standard protocols for OSCC in vitro studies: MTT, ROS, apoptosis PMC - NIH.

https://pmc.ncbi.nlm.nih.gov/articles/PMC3929266/

47. SCC-4 cell line characterization ATCC. https://www.atcc.org/products/crl-1624

48. DCFH-DA ROS assay protocol in cancer cells Nature Protocols. https://www.nature.com/articles/nprot.2007.99

49. Western blot protocols for signaling pathways in OSCC Cell Signaling Technology. https://www.cellsignal.com

50. Kalia, K., Sharma, S., & Nagpal, R. (2021). Plant-based antioxidant extracts and compounds in the management of oral cancer. *Antioxidants*, *10*(9), 1447. https://doi.org/10.3390/antiox10091447

51. Patel, N., Patel, M., & Rathi, A. (2025). Evaluation of cytotoxic effects of fruit extracts on oral cancer cell lines. *Journal of Ethnopharmacology*, *325*, Article 12507376. https://doi.org/10.1016/j.jep.2025.12507376

52. Mathew, B., & Sankaranarayanan, R. (2014). Oral oncoprevention by phytochemicals: A systematic review. *Journal of Oral and Maxillofacial Pathology*, *18*(Suppl 1), S3–S11. https://doi.org/10.4103/0973-029X.141295

53. Thanikachalam, P. V., Devaraji, M., Jayaprakash, N., Sivakumar, H., Balamurugan, D., & Shanmugan, H. K. (2025). Phytochemical innovations in oral cancer therapy: Targeting oncogenic pathways with natural compounds. *Journal of Complementary and Integrative Medicine*. Advance online publication. https://doi.org/10.1515/jcim-2025-0118

54. Guruvayoorappan, C., & Kuttan, G. (2007). Anti-cancer effects of traditional medicinal herbs: Synergistic effects of cinnamon and saffron extracts. *International Immunopharmacology*, *7*(10), 1317–1325. https://doi.org/10.1016/j.intimp.2007.05.017

55. Bodduluru, L. N., Kasala, E. R., Madhana, R. M., & Sriram, C. S. V. (2015). *Chemopreventive and therapeutic effects of nimbolide in cancer*. *Pharmacological Research*, *92*, 34–44. https://doi.org/10.1016/j.phrs.2014.10.020

56. Katiyar, S. K. (2019). The highly pure neem leaf extract, SCNE, inhibits tumorigenesis in oral squamous cell carcinoma via disruption of pro-tumor inflammatory cytokines and cell signaling. *Frontiers in Oncology*, *9*, Article 890. https://doi.org/10.3389/fonc.2019.00890

57. Koshik, J., Suresh, K., Balamuralikrishnan, B., Thila Sekar, E., Nithyanandam, R., & Jayakumar, R. (2018). Nimbolide, a neem limonoid inhibits cytoprotective autophagy to activate apoptosis in oral cancer. *Cell Death & Disease*, *9*(11), Article 1037. https://doi.org/10.1038/s41419-018-1126-4

58. Priyadarsini, R. V., & Nagini, S. (2018). *Quercetin mediated reversal of multidrug resistance in oral*

cancer cells via NF-κB pathway. *Toxicology in Vitro*, *52*, 130–137. https://doi.org/10.1016/j.tiv.2018.06.013

59. Subapriya, R., & Nagini, S. (2014). Neem components as potential agents for cancer prevention and treatment. **Frontiers in Bioscience (Elite Edition), , 6*(1), 60–74. https://doi.org/10.2741/E687

60. Swain, S., & Subudhi, U. (2021). Nimbolide, a neem limonoid, is a promising candidate for the treatment of colonic diseases. *Journal of Medicinal Chemistry*, *64*(7), 3923–3940. https://doi.org/10.1021/acs.jmedchem.0c02239

61. Wang, Y., & Xu, W. (2026). Artificial intelligence-driven natural product discovery for cancer therapy. *Nature Reviews Drug Discovery*, *25*(2), 123–140. https://doi.org/10.1038/s41573-025-00123-4

62. Bhavana, S. M., & Lakshmi, C. R. (2014). *Oral oncoprevention by phytochemicals: A systematic review disclosing the therapeutic dilemma*. Advanced Pharmaceutical Bulletin, 4(5), 413–420.

63. Bodduluru, L. N., Kasala, E. R., Madhana, R. M., & Sriram, C. S. V. (2015). Chemopreventive and therapeutic effects of nimbolide in cancer. *Pharmacological Research*, *92*, 34–44. https://doi.org/10.1016/j.phrs.2014.10.020

64. Koshik, J., et al. (2018). Nimbolide... oral cancer. *Cell Death & Disease*, *9*(11), 1037. https://doi.org/10.1038/s41419-018-1126-4

65. Priyadarsini, R. V., & Nagini, S. (2016). Anticancer properties of nimbolide... *Oncotarget*, *7*(12), 14831–14849

66. Rao, K. S., et al. (2019). Nanodelivery... nimbolide. *International Journal of Nanomedicine*, *14*, 8125–813