



Naringenin in Oral Cancer Management: Molecular Targets, Antiproliferative Mechanisms, and Therapeutic Potential

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ABSTRACT

Oral cancer, of which oral squamous cell carcinoma (OSCC) accounts for the vast majority, remains a major global health burden, particularly in regions where tobacco, areca nut and alcohol use are widespread. Surgery, radiotherapy and platinum-based chemotherapy are associated with considerable morbidity, functional impairment, drug resistance and recurrence, which has stimulated interest in safer, mechanism-based adjuncts derived from natural products. Naringenin (4',5,7-trihydroxyflavanone) is a citrus flavanone, and the aglycone of naringin, with reported antioxidant, anti-inflammatory and antineoplastic activities. In oral cancer models, naringenin has been shown to reduce cell viability and induce apoptosis through reactive oxygen species (ROS) generation, modulation of the Bid/Bcl-xL axis and endoplasmic reticulum (ER) stress with associated autophagy, and to enhance anti-tumor immunity in murine OSCC models by activating lymph node CD169⁺ macrophages and promoting cytotoxic T-cell infiltration. Evidence from other malignancies further implicates cell-cycle arrest, PI3K/Akt/mTOR, MAPK, NF-κB and STAT3 signalling, as well as suppression of invasion, EMT and angiogenesis, which are plausible but incompletely validated in oral cancer. Clinical translation is limited by poor aqueous solubility, extensive first-pass conjugation and low oral bioavailability. Local delivery systems such as mucoadhesive buccal films, nanocarriers and crystal-engineering approaches (e.g., cocrystals) may allow higher mucosal exposure at the lesion site. This review summarises current knowledge on the molecular targets and antiproliferative mechanisms of naringenin in oral cancer, discusses pharmacokinetic and formulation challenges, and outlines priorities for future research.

Keywords: naringenin; oral squamous cell carcinoma; flavanone; apoptosis; ROS; ER stress; autophagy; PI3K/Akt/mTOR; buccal drug delivery; chemoprevention

1. Introduction

Cancers of the lip and oral cavity represent a substantial share of the global cancer burden, with GLOBOCAN 2022 estimating roughly 390,000 new cases and about 188,000 deaths worldwide [1]. Incidence is especially high in South and Southeast Asia, where chewing of areca nut (with or without tobacco), smoking and alcohol consumption act as dominant risk factors. Oral squamous cell carcinoma frequently arises from potentially malignant disorders, including leukoplakia, erythroplakia, oral submucous fibrosis and lichen planus [2].

Standard management combines surgical resection with radiotherapy and/or chemotherapy (cisplatin-based regimens, with or without targeted agents or immunotherapy). Despite advances, five-year survival for advanced disease remains modest, and treatment frequently causes disfigurement, dysphagia, xerostomia, mucositis and speech impairment. Intrinsic and acquired resistance to cisplatin, field cancerisation and locoregional recurrence further limit outcomes. These limitations have driven interest in plant-derived compounds that may act as chemopreventive agents, direct antiproliferative agents, or chemosensitisers with a favourable toxicity profile [3,4].

Naringenin is a flavanone abundant in grapefruit, oranges, tomatoes and other plant sources. A growing body of preclinical work suggests that it suppresses cancer cell proliferation and survival across diverse tumour types by modulating inflammation, apoptosis, autophagy, angiogenesis, invasion and metastasis [3]. A systematic review and meta-analysis of in vitro and in vivo data concluded that naringenin enhances caspase-3, caspase-8 and caspase-9 activity and Bax expression in cancer cells, supporting activation of both intrinsic and extrinsic apoptotic pathways [5]. In oral cancer

specifically, studies are fewer but increasingly mechanistic [6–8]. This review consolidates the available evidence on naringenin in oral cancer, with emphasis on molecular targets, antiproliferative mechanisms, delivery challenges and therapeutic prospects.

2. Chemistry, Sources and Pharmacokinetic Considerations

2.1 Chemical profile

Naringenin ($C_{15}H_{12}O_5$; molecular weight ≈ 272.25 g/mol) is a flavanone with a 15-carbon C6–C3–C6 skeleton, hydroxyl groups at positions 5, 7 and 4', and a saturated C2–C3 bond that distinguishes it from flavones such as apigenin. In plants it occurs mainly as glycosides, notably naringin (naringenin-7-O-neohesperidoside), which is hydrolysed by intestinal microbiota and enzymes to release the aglycone. Naringenin is lipophilic and poorly water-soluble, and is generally regarded as a BCS class II-type compound (low solubility, relatively high permeability), a property that dominates its formulation challenges.

2.2 Absorption, metabolism and bioavailability

After oral intake, naringenin undergoes extensive phase II metabolism (glucuronidation and sulfation) in enterocytes and the liver, and circulating forms are predominantly conjugates rather than the free aglycone. Its oral bioavailability has been reported at approximately 15%, with limited absorption attributed to low solubility [3]. This matters for oral cancer because the free aglycone is the species most commonly active in vitro, whereas systemic exposure after oral dosing may be dominated by conjugates and may fall short of the micromolar concentrations used in cell assays. Locally applied dosage forms that bypass first-pass metabolism are therefore conceptually attractive for lesions of the oral mucosa.

3. Molecular Targets and Antiproliferative Mechanisms

Naringenin appears to act as a pleiotropic modulator rather than a single-target inhibitor. The mechanisms below are presented with the strength of evidence in oral cancer stated explicitly; where data derive from other cancer types, they are identified as plausible, hypothesis-generating pathways for OSCC rather than established facts.

3.1 ROS generation, mitochondrial apoptosis and the Bid/Bcl-xL axis

Naringenin exhibits context-dependent redox behaviour: it is an antioxidant in normal tissues but can act as a pro-oxidant in malignant cells. In tongue squamous carcinoma CAL-27 cells, naringenin induced apoptosis in a dose-dependent manner, and the effect was linked to ROS-mediated changes in the pro-apoptotic Bid and anti-apoptotic Bcl-xL signalling pathway [7]. Elevated ROS destabilise mitochondrial membrane potential, promote Bax/Bak-dependent outer membrane permeabilisation, release cytochrome c and activate caspase-9 and caspase-3, which is consistent with meta-analytic evidence that naringenin increases caspase-9, caspase-3 and Bax in cancer cells [5]. Shifting the balance from Bcl-2 family pro-survival proteins (Bcl-2, Bcl-xL) towards pro-death members (Bax, Bid) is a recurrent theme and is relevant for OSCC, where Bcl-xL overexpression contributes to chemoresistance.

3.2 Extrinsic apoptosis

Pooled in vitro data indicate that naringenin also increases caspase-8 activity [5], suggesting engagement of death-receptor signalling. Cross-talk through Bid cleavage (tBid) may link the extrinsic and intrinsic pathways, although direct demonstration of Fas/TRAIL-receptor involvement in oral cancer models remains limited.

3.3 ER stress and autophagy

In human OSCC cells, naringenin reduced viability through intracellular ROS production, ER stress and autophagy, ultimately converging on caspase-mediated apoptosis; the authors described a shift of pro-survival responses into pro-death signalling [6]. Autophagy is a double-edged process in cancer. It can be cytoprotective under mild stress, but sustained ER stress and ROS can tilt it toward autophagy-associated cell death or facilitate apoptosis. The interplay between the unfolded protein response (e.g., PERK–eIF2 α –ATF4–CHOP) and autophagic flux is therefore a key area where naringenin may exploit the heightened proteotoxic burden of tumour cells. Inhibitor and rescue experiments (e.g., chloroquine, bafilomycin A1, 4-PBA, N-acetylcysteine) are essential to establish whether autophagy is pro-death or pro-survival in each model.

3.4 Cell-cycle arrest

Naringenin has been reported to arrest cancer cells at G0/G1 in some models (for example in breast cancer cells) and at other checkpoints in different tumour types [3]. Typical molecular correlates include down-regulation of cyclin D1, CDK4/6 and cyclin E/CDK2, and up-regulation of CDK inhibitors p21 and p27. Because cyclin D1 amplification and p16 loss are common in OSCC, G1/S control is a rational target; however, cell-cycle profiling of naringenin in oral cancer lines remains sparse and should be systematically characterised (flow cytometry with PI, cyclin/CDK immunoblots).

3.5 PI3K/Akt/mTOR signalling

The PI3K/Akt/mTOR cascade is among the most frequently deregulated pathways in head and neck cancer, driving proliferation, survival, protein synthesis and resistance to therapy. Naringenin and its glycoside have been reported to attenuate Akt phosphorylation and mTOR activity in various cancers [3,4]. Because mTOR is a negative regulator of autophagy, inhibition of this axis provides a mechanistic bridge between the autophagic and antiproliferative effects observed in OSCC. Direct validation in oral cancer cells (p-PI3K, p-Akt Ser473/Thr308, p-mTOR, p-S6K, p-4E-BP1) is still required.

3.6 MAPK pathways

ERK, JNK and p38 pathways integrate stress and growth signals. Naringenin has been reported to suppress ERK-driven proliferation and to activate stress-responsive JNK/p38 signalling, which can promote apoptosis, in several cancer models [3,4]. In the oral cavity, EGFR overexpression upstream of Ras/Raf/MEK/ERK is common, and naringenin has been described as interfering with receptor tyrosine kinase signalling (including HER2) in other tumour systems, which raises the possibility of EGFR-axis modulation that merits testing in OSCC.

3.7 NF- κ B, STAT3 and inflammation-driven carcinogenesis

Chronic inflammation (tobacco, betel quid, alcohol, microbial dysbiosis) is a hallmark of oral carcinogenesis. NF- κ B promotes survival and evasion of apoptosis, and naringin/naringenin have been shown to modulate NF- κ B signalling (for instance via p65) in other cancers such as colorectal cancer, resulting in apoptosis and cell-cycle arrest [3]. Downstream suppression of COX-2, iNOS, IL-6, IL-1 β and TNF- α reduces the pro-tumourigenic inflammatory milieu. The IL-6/JAK/STAT3 axis, strongly implicated in head and neck cancer progression and immune suppression, represents another plausible target, although direct evidence for naringenin in OSCC requires confirmation.

3.8 Wnt/ β -catenin, EMT, invasion and metastasis

Metastasis to cervical lymph nodes is the dominant determinant of prognosis in OSCC. Reported anti-invasive effects of naringenin in other cancers involve down-regulation of MMP-2/MMP-9, restoration of E-cadherin and reduction of N-cadherin, vimentin, Snail and Twist, consistent with reversal of epithelial–mesenchymal transition (EMT) [3,4]. Modulation of Wnt/ β -catenin and TGF- β /Smad signalling has also been proposed. Wound-healing, transwell migration/invasion assays and EMT marker analysis in OSCC lines (e.g., SCC-9, SCC-25, CAL-27, FaDu, KB) are needed to substantiate these effects.

3.9 Angiogenesis

Naringenin has been reported to reduce VEGF expression and HIF-1 α -associated signalling in some tumour models [3]. Given that hypoxia and angiogenesis support OSCC progression, angiogenesis assays (HUVEC tube formation, CAM assay, CD31 immunostaining in xenografts) would clarify the relevance of this mechanism.

3.10 Immune modulation and the tumour microenvironment

One of the most distinctive findings specific to oral cancer is immune-mediated. Kawaguchi et al. analysed specimens from 89 OSCC patients and showed that higher CD169⁺ macrophage counts in regional lymph nodes correlated with favourable prognosis and with CD8⁺ T-cell counts in tumours. In two murine OSCC models, naringenin suppressed tumour growth, increased lymph node mRNA levels of CD169, IL-12 and CXCL10, and increased cytotoxic T-lymphocyte infiltration, indicating that naringenin can potentiate anti-tumour immunity through lymph node sinus macrophage activation [8]. A related study with the glycoside naringin showed enhanced CTL infiltration that depended on sinus macrophages, and combination of naringin with anti-PD-L1 antibody suppressed growth of a tumour model resistant to checkpoint blockade alone [9]. These data suggest a dual mode of action in which naringenin acts directly on tumour cells and indirectly through host immunity, and they provide a rationale for testing combinations with immune checkpoint inhibitors in head and neck cancer.

3.11 Chemosensitisation

Flavonoids, including naringenin, are reported to reinforce chemosensitivity in oral carcinoma models [4]. Proposed mechanisms include reduction of Bcl-xL/Bcl-2, suppression of Akt/NF- κ B survival signalling, inhibition of drug efflux transporters (P-glycoprotein, MRP) and amplification of ROS-mediated damage. Combination studies with cisplatin, 5-fluorouracil or taxanes, with synergy quantification (combination index; Chou–Talalay), are a priority.

Table 1. Summary of molecular targets and mechanisms of naringenin relevant to oral cancer.

Target / pathway	Reported effect	Biological outcome	Evidence in oral cancer
ROS / Bid / Bcl-xL	ROS increase; modulation of Bid and Bcl-xL; caspase activation	Intrinsic apoptosis	Direct (CAL-27 tongue cancer cells) [7]
ER stress / autophagy	ROS-linked ER stress and autophagy converging on caspase-mediated apoptosis	Apoptosis, autophagy-associated death	Direct (human OSCC cells) [6]
Caspases / Bax	↑ caspase-3, -8, -9 and Bax	Intrinsic and extrinsic apoptosis	Meta-analysis across cancers [5]
CD169 ⁺ macrophages / CTLs	↑ CD169, IL-12, CXCL10 in lymph nodes; ↑ CTL infiltration	Anti-tumour immunity; reduced tumour growth	Direct (two murine OSCC models) [8]
Cyclins / CDKs / p21	G0/G1 (or other) arrest	Growth inhibition	Mainly other cancers [3]; to be confirmed
PI3K/Akt/mTOR	↓ phosphorylation of Akt and mTOR	Reduced survival; autophagy modulation	Mainly other cancers [3,4]; to be confirmed
MAPK (ERK/JNK/p38)	ERK suppression; JNK/p38 activation	Reduced proliferation; apoptosis	Mainly other cancers [3,4]; to be confirmed
NF-κB / STAT3	↓ p65 activity; ↓ inflammatory mediators	Reduced survival and inflammation	Mainly other cancers [3]; to be confirmed
MMPs / EMT markers	↓ MMP-2/9; E-cadherin restoration	Reduced invasion and metastasis	Mainly other cancers [3,4]; to be confirmed
VEGF / HIF-1α	↓ expression	Reduced angiogenesis	Mainly other cancers [3]; to be confirmed

4. Preclinical Evidence in Oral Cancer

Direct evidence in oral cancer comes from a small number of in vitro and in vivo studies (Table 2). In OSCC cells, naringenin reduced viability and triggered ROS-dependent ER stress, autophagy and apoptosis [6]; in CAL-27 cells it induced dose-dependent apoptosis through Bid/Bcl-xL modulation [7]; and in mice it suppressed tumour growth while enhancing cytotoxic T-cell infiltration [8]. Related work with naringin in KB-1 oral cancer cells reported a significant reduction in cell viability with an IC₅₀ of 125.3 (reported as μM/mL), together with nuclear morphological changes indicative of apoptosis [2], indicating that the glycoside may also contribute activity, although the aglycone is generally considered the more bioactive form in vitro. A recent integrative review of citrus flavanones in oral and gastric carcinogenesis concludes that, in oral carcinoma models, these flavonoids promote cell-cycle arrest, apoptosis and autophagy while reinforcing chemosensitivity [4].

Table 2. Selected preclinical studies relevant to naringenin/naringin in oral cancer.

Model	Compound	Main findings	Ref.
Human OSCC cell lines	Naringenin	Reduced viability; intracellular ROS, ER stress, autophagy and caspase-mediated apoptosis	[6]
CAL-27 (tongue SCC)	Naringenin	Dose-dependent apoptosis via ROS-mediated Bid and Bcl-xL signalling	[7]
Two murine OSCC models; 89 patient specimens	Naringenin	Tumour growth suppression; ↑ lymph node CD169, IL-12, CXCL10; ↑ CTL infiltration	[8]
KB-1 oral cancer cells	Naringin	Reduced viability (IC ₅₀ 125.3, as reported); apoptotic nuclear changes	[2]
Syngeneic tumour models (non-oral)	Naringin	CTL activation depends on sinus macrophages; synergy with anti-PD-L1	[9]

5. Safety and Selectivity

Flavanones from citrus are consumed as part of the normal diet, and naringenin is generally regarded as having low acute toxicity in preclinical models. Selectivity for malignant over normal cells is a frequently reported but not uniformly demonstrated feature, and should be confirmed in oral cancer studies using non-malignant oral keratinocytes or fibroblasts (e.g., HaCaT, primary gingival fibroblasts) alongside tumour lines. Two safety considerations deserve attention: (i) naringenin and grapefruit-derived flavonoids can inhibit intestinal CYP3A4 and drug transporters, creating potential for interactions with co-administered drugs, and (ii) the redox dualism of flavonoids means that antioxidant supplementation might in principle interfere with ROS-dependent chemotherapy or radiotherapy. Such interactions need to be examined before clinical combination strategies are designed.

6. Overcoming Bioavailability Limitations: Delivery Strategies

The central translational barrier is not a lack of in vitro activity but insufficient local exposure of the free aglycone at the tumour site. Several approaches are being explored for flavonoids and are relevant to naringenin.

- **Mucoadhesive buccal films and patches.** Buccal delivery avoids first-pass metabolism, permits prolonged residence on the mucosa and enables direct, sustained exposure of superficial lesions and potentially malignant disorders. Film-forming polymers such as HPMC, chitosan, PVA, sodium alginate and Carbopol can be used to tune mucoadhesion, swelling and release. Critical quality attributes include thickness, folding endurance, surface pH, mucoadhesive strength, in vitro release and ex vivo permeation across buccal mucosa.
- **Crystal engineering (cocrystals, salts, co-amorphous systems).** Pharmaceutical cocrystals of poorly soluble polyphenols with GRAS cofomers can improve dissolution rate and apparent solubility without covalent modification. Solid-state characterisation (PXRD, DSC, FTIR, Raman, SEM) and stability assessment are required to demonstrate cocrystal formation and retention in the final dosage form.
- **Nanocarriers.** Polymeric nanoparticles (PLGA, chitosan), solid lipid nanoparticles, nanostructured lipid carriers, liposomes, micelles and nanoemulsions can enhance solubility, protect against metabolism and improve cellular uptake; surface functionalisation can add tumour targeting [4].
- **Complexation and amorphous dispersions.** Cyclodextrin inclusion complexes (e.g., HP- β -CD) and polymer-based amorphous solid dispersions increase solubility and dissolution rate.
- **In situ gels, mouthwashes, lozenges and sprays.** Simple local formulations may suit chemoprevention in high-risk patients with premalignant lesions, where long-term safety is paramount.

For oral cancer, a locally delivered, mucoadhesive system is particularly appealing because the lesion is anatomically accessible. Nevertheless, deep or infiltrative tumours will not be reached by topical dosing alone, and local delivery is best viewed as a strategy for premalignant lesions, early superficial disease, post-resection field control or adjunct therapy.

7. Limitations of Current Evidence and Future Perspectives

Several limitations temper enthusiasm for naringenin as an oral cancer therapeutic:

- Direct oral cancer data are limited to a handful of cell lines and two murine models, with heterogeneity in doses, exposure times and endpoints [4,6–8].
- Many mechanistic claims (PI3K/Akt/mTOR, MAPK, NF- κ B, STAT3, EMT, angiogenesis) derive from other tumour types and have not been rigorously validated in OSCC.
- Effective in vitro concentrations are frequently in the tens to hundreds of micromolar, which may exceed concentrations attainable in plasma after oral dosing [3].
- Meta-analytic estimates of apoptotic effects show very high heterogeneity ($I^2 > 90\%$), reflecting variable experimental designs and underscoring the need for standardised protocols [5].
- No clinical trials of naringenin in oral cancer or oral potentially malignant disorders are available to date.

Future work should prioritise: (1) systematic multi-line OSCC studies (including cisplatin-resistant lines, HPV-negative and HPV-positive models) with non-malignant controls; (2) target validation using genetic knockdown and pharmacological rescue; (3) transcriptomic, proteomic and phospho-proteomic profiling to define pathway-level effects unbiasedly; (4) orthotopic and carcinogen-induced models such as 4-NQO or DMBA-induced oral carcinogenesis for chemoprevention studies; (5) pharmacokinetic/pharmacodynamic studies of local versus systemic delivery, including measurement of free aglycone in mucosal tissue; (6) combination studies with cisplatin, radiotherapy and immune checkpoint inhibitors; and (7) early-phase clinical studies of topical formulations in oral potentially malignant disorders.

8. Conclusion

Naringenin is a multi-target flavanone that, in oral cancer models, induces ROS-dependent apoptosis through the Bid/Bcl-xL axis, triggers ER stress and autophagy, and potentiates anti-tumour immunity through lymph node CD169⁺ macrophage activation and cytotoxic T-cell infiltration. Additional antiproliferative, anti-inflammatory, anti-invasive and anti-angiogenic mechanisms documented in other cancers provide a broader rationale but require direct validation in oral cancer. Poor solubility and low systemic bioavailability remain the key obstacles, and locally acting, mucoadhesive and crystal-engineered or nano-enabled formulations offer a pragmatic route to improve exposure at the oral mucosa. With rigorous mechanistic validation, improved delivery and well-designed combination and clinical studies, naringenin may serve as a safe adjunct for chemoprevention and complementary management of oral cancer.

9. References

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