The "Guardian" Effect: Curcumin in Oral Premalignancy and Chemoprevention

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ABSTRACT

Oral potentially malignant disorders (OPMDs) form a heterogeneous group of lesions with a high potential for transformation to oral squamous cell carcinoma (OSCC). The concept of field cancerization describes the presence of genetically and epigenetically altered mucosa beyond the clinical boundaries of the lesion, contributing to the high rates of recurrence and second primary tumors. This necessitates the development of multi-targeted chemopreventive agents capable of addressing the entire field. Curcumin, a polyphenolic compound from *Curcuma longa*, has gained attention as a promising chemopreventive agent due to its pleiotropic effects. Curcumin targets the most important signaling pathways in the development of OSCC, such as NF-κB, STAT-3, and AP-1. In addition, it influences epigenetic changes, oxidative stress, and angiogenesis. In preclinical studies, curcumin has been shown to inhibit cell proliferation, induce apoptosis, and reverse epithelial-mesenchymal transition. In clinical settings, its potential in reducing the severity of the lesion and improving treatment outcomes has been demonstrated. In addition, its dual role as a radiosensitizer in tumor cells and a radioprotector in normal cells makes it more attractive. A comparative analysis of its safety profile and reduced recurrence rates compared to synthetic retinoids is also positive. However, its low bioavailability is a challenge. Advances in the formulation of nano- and mucoadhesive systems have been proposed to improve its bioavailability. This article aims to present the current evidence on the molecular basis of its action, its clinical application, and its therapeutic potential in the context of OPMD and field cancerization.

INTRODUCTION

Oral cancer remains a major global health concern, with oral squamous cell carcinoma (OSCC) being the most prevalent form and associated with high morbidity and mortality. Oral potentially malignant disorders (OPMDs), such as leukoplakia, oral submucous fibrosis, and oral lichen planus, represent important precursors with varying dysplasia and unpredictable malignant transformation risk.

Conventional management strategies focus on treating visible lesions but fail to address the broader biological basis of oral carcinogenesis. The concept of field cancerization highlights widespread genetic and epigenetic alterations in oral epithelium due to chronic carcinogen exposure, leading to recurrence and second primary tumors even after treatment.

This has emphasized the need for field-directed therapies targeting multiple molecular pathways. Curcumin, a polyphenol derived from *Curcuma longa*, has gained attention due to its anti-inflammatory, antioxidant, and anticancer properties. It modulates key signaling pathways such as NF-κB, STAT3, and AP-1, along with influencing epigenetic regulation, oxidative stress, and the tumor microenvironment. Preclinical and clinical studies suggest its potential in oral cancer prevention and therapy, including its role as a radiosensitizer and its application in various formulations. However, limitations related to bioavailability and clinical standardization remain.

This review aims to evaluate curcumin as a multi-target chemopreventive agent in OPMDs and its role in addressing the complex process of field cancerization.

1. The Landscape of Oral Potentially Malignant Disorders (OPMDs)

Oral potentially malignant disorders (OPMDs) are a heterogeneous group of clinically detectable oral mucosal diseases that carry an increased risk of developing into oral squamous cell carcinoma (OSCC), although only a minority ultimately transform. ([1, 2, 3])

Concept and Definition

The term OPMDs was introduced to replace older labels such as “precancerous lesions/conditions” to better reflect that not all such disorders progress to cancer and that risk is probabilistic rather than deterministic.([1, 2, 4])

OPMDs encompass disorders of the lip and oral mucosa associated with an elevated risk of OSCC, usually in stratified squamous epithelium, and include both lesions (visible mucosal changes) and conditions (systemic or diffuse disorders with oral manifestations). ([2, 3, 5])

Major Entities Currently Recognized

Key OPMDs with well-documented malignant potential include: ([1, 2, 3, 6])

- Leukoplakia (including proliferative verrucous leukoplakia, PVL
- Erythroplakia and erythroleukoplakia
- Oral submucous fibrosis (OSMF)
- Oral lichen planus (OLP) and oral lichenoid lesions (OLL)
- Actinic cheilitis
- Palatal lesions in reverse smokers
- Discoid lupus erythematosus with oral involvement

- Dyskeratosis congenita and other inherited disorders with oral epithelial dysplasia
- Oral chronic graft-versus-host disease (cGVHD)

Some entities such as chronic hyperplastic candidosis and oral exophytic verrucous hyperplasia currently have insufficient evidence to be included as OPMDs in recent WHO-linked consensus documents. [2]

Global Burden and Epidemiology

- OPMDs are relatively common in high-risk regions and populations, with a pooled global prevalence of around 4–5% in adults, though estimates vary by methodology and region.[7]
    - A meta-analysis reported overall OPMD prevalence of 4.47%, with the highest rates in Asian (especially South Asian) and South American/Caribbean populations; men are more frequently affected.[7]
    - Oral cancer (predominantly OSCC) accounts for an estimated 0.37 million new cases globally per year, with the greatest burden in Asia, underscoring the importance of OPMD identification and surveillance.([1, 6, 8])

Etiologic and Risk Factors

- Classic extrinsic risk factors for OPMDs and OSCC include tobacco use (smoked and smokeless), areca nut/betel quid chewing, heavy alcohol consumption, chronic UV exposure of the lip, and chronic trauma or irritation in some contexts.([1, 3, 6])
- Intrinsic and host factors such as genetic susceptibility (e.g., dyskeratosis congenita), immune dysregulation (e.g., cGVHD), viral infections (notably high-risk HPV in some subsites), and microbial dysbiosis contribute to pathogenesis and progression in subsets of patients.([1, 3, 6])

Malignant Transformation Risk

- Transformation rates vary widely between disorders and individual lesions; risk is influenced by clinical subtype, site, size, presence and grade of epithelial dysplasia, and patient risk factor profile.([1, 3, 6, 9])
- Leukoplakia shows heterogeneous risk: thin/early lesions may transform without obvious clinical change, while speckled (erythroleukoplakic) and verrucous subtypes carry higher malignant transformation rates than homogeneous plaques.[9]
- PVL, erythroplakia, OSMF, and some OLL/OLP cases are regarded as high-risk OPMDs, with reported cumulative transformation rates often exceeding those of conventional leukoplakia.([1, 2, 3, 6])

TABLE 1 : Classification OF Oral Potentially Malignant Disorders (OPMDs)

Category	Condition	Status	Remarks
Classic OPMDs	**Leukoplakia**	Confirmed	High malignant risk; most common OPMD.

Category	Condition	Status	Remarks
Classic OPMDs	**Erythroplakia**	Confirmed	**Highest risk** of malignant transformation.
Classic OPMDs	**OSMF** (Oral Submucous Fibrosis)	Confirmed	Strong association with areca nut/betel quid use.
Immune-related	**OLP** (Oral Lichenus Planus)	Confirmed	Transformation rate remains a subject of clinical controversy.
Newly Added	**Oral Lichenoid Lesions**	Added	Included based on emerging evidence of malignant potential.
Newly Added	**Oral cGVHD** (Chronic Graft-vs-Host)	Added	Recognized for significantly increased cancer risk.
Excluded	**Chronic Hyperplastic Candidosis**	Downgraded	Removed due to insufficient evidence of independent risk.
Excluded	**Verrucous Hyperplasia**	Excluded	Unclear malignant potential; often regarded as a variant.

TABLE 2 : Selected Oral Potentially Malignant Disorders and Their Features

Entity	Typical Risk Factors	Clinical Pattern	Relative Malignant Risk
Leukoplakia	Tobacco, alcohol, chronic irritation	White plaque; can be homogeneous or speckled	**Low–Moderate** (Higher for speckled/verrucous)

Entity	Typical Risk Factors	Clinical Pattern	Relative Malignant Risk
PVL (Proliferative Verrucous Leukoplakia)	Often older women, non-smokers, idiopathic	Multifocal, progressive, verrucous plaques	**Very High** (Multifocal and recurrent)
Erythroplakia	Tobacco, alcohol	Fiery red, velvety patch	**Very High** (Often severe dysplasia/CIS)
OSMF (Oral Submucous Fibrosis)	Areca nut / betel quid	Fibrotic bands, trismus (lockjaw), blanching	**High** (Especially long-standing disease)
OLP / OLL (Lichen Planus / Lichenoid Lesions)	Autoimmune, drug/contact hypersensitivity	Reticular (lace-like), erosive, or atrophic	**Low–Moderate** (Higher for OLL and erosive)
Actinic Cheilitis	Chronic solar (UV) exposure	Atrophic, scaly, or blurred border of lower lip	**Moderate–High** (Fair-skinned individuals)

(1, 2, 6, 7, 9, 10)

Relative risk is generalized from multiple observational series and varies by population and methodology. (1, 3, 6)

Clinical and Public Health Implications

Because OSCC prognosis remains poor (5-year survival ~40–50% with major morbidity), early detection of OPMDs and risk-adapted management (elimination of risk factors, surveillance, biopsy/excision of high-risk lesions) are central to oral cancer control strategies.(1, 3, 6, 8)

Recent consensus statements emphasize standardized nomenclature, uniform diagnostic criteria, and international collaborative cohorts to refine malignant risk stratification and link patients to evidence-based preventive and therapeutic interventions. (2, 3)

These observations highlight that OPMDs are not isolated lesions but often represent a broader area of at-risk mucosa, leading to the concept of field cancerization.

2. The "Field Cancerization" Theory and Curcumin's Role

Field cancerization describes a large area of epithelium that is genetically and epigenetically altered and therefore at high risk of developing multiple, independent premalignant lesions and cancers; curcumin can intervene in this field at several molecular levels relevant to oral carcinogenesis.([11, 12, 13 ,14) Field cancerization theory (with oral focus)

- Slaughter first described field cancerization in 1953 in oral squamous cell carcinoma, noting histologically abnormal epithelium surrounding the primary tumor.([15, 16)
- The concept is that chronic carcinogen exposure (e.g., tobacco, alcohol, betel quid) produces a clonal patch of mutated cells that expands, replacing normal mucosa and creating a field of precancerous epithelium. ([11, 12])
- This field contains multiple premalignant foci and explains: high rates of local recurrence, second primary tumors, and new lesions even after complete excision of the index OSCC. ([11,12 ,15])
- Molecular hallmarks include oncogene/tumor-suppressor mutations, loss of heterozygosity, genomic instability, altered p53 staining, and inflammatory/angiogenic changes in clinically normal-appearing mucosa. ([11,12,17])

Why field cancerization matters clinically.?

- In oral and head–neck cancers, a genetically altered field can extend centimeters beyond visible lesions, so histologically normal margins may still harbor high-risk cells. ([11,15])
- This underlies the need for wide excision, careful surveillance of the entire mucosal field, and adjunctive field-directed strategies (topical agents, systemic chemoprevention, photodynamic therapies). ([11, 15])
- The concept is similar in other organs (skin, colon, esophagus, lung, bladder), where broad fields with premalignant changes give rise to multiple synchronous or metachronous tumors. ([15 , 17])

TABLE 3 : Molecular Mechanisms of Curcumin in Field Cancerization

Molecular Action	**Target Pathways & Mediators**	**Impact on Field Progression**
Anti-inflammatory	Downregulates **NF-κB, AP-1, COX-2, TNF-*α*, and IL-6**	Dampens chronic inflammation that sustains mutations and drives clonal expansion.
Antioxidant & Genomic Stability	Enhances antioxidant defenses; reduces **Reactive Oxygen Species (ROS)**	Lowers oxidative DNA damage, preventing the accumulation of new mutations in altered epithelium.

Molecular Action	Target Pathways & Mediators	Impact on Field Progression
Proliferation & Survival Control	Inhibits **Akt/mTOR, MAPK, EGFR, and Wnt/β-catenin** signaling	Promotes cell cycle arrest and apoptosis; reverses **EMT** (Epithelial-Mesenchymal Transition) to stabilize clones.
Viral/Oncogenic Inhibition	Downregulates **HPV E6** oncoprotein; restores **p53** function	Directly counters genetic instability in HPV-positive oral cancer cells within the field.

(13, 14, 18, 19, 20 ,21)

Evidence in oral premalignant lesions and OSCC

- Experimental oral carcinogenesis models (e.g., 4-NQO, DMBA in rodents) show that curcumin-containing diets reduce incidence and severity of oral precancerous lesions and suppress progression to OSCC, indicating action at initiation and promotion stages.(14, 20)
- In vitro, curcumin inhibits proliferation, migration, invasion, and NF-κB signaling in OSCC cell lines, and can reverse EMT towards a more epithelial, less invasive phenotype.18
- Reviews on oral cancer prevention describe curcumin as a promising chemopreventive agent acting on multiple molecular targets implicated in field cancerization, although they emphasize the need for more robust clinical trials, especially with improved formulations.(13, 18)

Curcumin as a "field-directed" chemopreventive

Because the at-risk area in oral field cancerization is wide and often clinically subtle, a systemic or topical agent that is safe, multi-targeted, and affordable is attractive for long-term use; curcumin fits many of these criteria. (11, 13, 14)Nanoformulations, mucoadhesive gels, and other delivery systems are being developed to overcome curcumin's low bioavailability and to increase drug levels across the entire oral mucosal field.13

Conceptually, by reducing inflammation, oxidative stress, proliferative signaling, and EMT across large areas of altered mucosa, curcumin could lower the probability that any clone within the field acquires the additional hits needed to become invasive or to form second primaries.(11, 13, 14)

Understanding this field-wide alteration provides a basis for exploring molecular mechanisms that drive oral carcinogenesis.

3. Molecular Mechanisms of NF-\kappa B Inhibition

NF-κB is a key transcription factor regulating inflammation, immunity, and cell survival, and its inhibition occurs primarily through sequestration by IκB proteins and blockade of signaling pathways like IKK activation.(22, 23)Molecular mechanisms target cytoplasmic retention, degradation prevention, and nuclear activity suppression. (23, 24)

Canonical Pathway Overview

In unstimulated cells, NF-κB dimers (e.g., p50/p65) bind IκBα in the cytoplasm, masking its nuclear localization signal (NLS) and preventing DNA binding.([22, 23]) Stimuli trigger IKK complex (IKKα/IKKβ/NEMO) activation, phosphorylating IκBα at Ser32/36, leading to ubiquitination, proteasomal degradation, NF-κB release, nuclear translocation, and target gene transcription.([23, 24, 25])

IκB-Mediated Inhibition

Free IκBα rapidly degrades via ubiquitin-independent proteasome activity due to its marginal stability and PEST sequence, maintaining low cytoplasmic levels.[22] . NF-κB binding induces folding of IκBα's AR5-6 repeats, stabilizing it (half-life >12 hours) and shifting degradation to ubiquitin-dependent pathway only upon signal-induced phosphorylation. ([22, 26])

IKK Complex Blockade

IKK inhibitors target ATP-binding (e.g., SC-514), allosteric sites (e.g., BMS-345541), or Cys179 in IKKβ (e.g., parthenolide), preventing IκBα phosphorylation. ([23, 24, 27]). NEMO-binding peptides disrupt IKK assembly, blocking activation. ([24, 27])

Nuclear and Post-Translational Blocks

Post-degradation, NF-κB undergoes p65 phosphorylation/acetylation for full activity; inhibitors like PP2A dephosphorylate p65 Ser536. ([23, 24])

IκBα facilitates rapid NF-κB dissociation from DNA via kinetic competition, enhanced by its partial folding. 1 Non-canonical pathway inhibition involves NIK stabilization via TRAF3. [28]

Therapeutic Implications

Over 700 small molecules (e.g., bortezomib blocks proteasome; aspirin acetylates IKKβ) inhibit at multiple steps, relevant for cancer and inflammation linked to your phytochemical/pharmacovigilance research.([23, 24, 29])

Natural products like curcumin suppress IKK and ubiquitination. [24]

In addition to NF-κB signaling, other transcriptional pathways such as STAT3 and AP-1 further contribute to tumor progression.

4. Modulation of the STAT3 and AP-1 Signaling Axis

STAT3 and AP-1 form a tightly interconnected transcriptional module that integrates cytokine, growth factor, inflammatory, and oncogenic signals, and its modulation offers multiple therapeutic entry points in cancer, fibrosis, and chronic inflammation.([30, 31, 32])

Core mechanistic crosstalk

- STAT3 and AP-1 (c-Jun/c-Fos) can form physical complexes on promoters where STAT and AP-1 motifs are juxtaposed; this cooperative binding is required for full induction of a subset of STAT3 target genes (e.g., some IL-6–responsive genes). [30]

- The bZIP domain of c-Jun directly interacts with STAT3; specific mutations in c-Jun (e.g., R261A/D) disrupt STAT3–c-Jun interaction and blunt cooperative transcription, highlighting defined protein–protein interfaces that can be targeted. [30]
- Genome-wide studies show that STAT3 often occupies sites with either STAT3 or AP-1 motifs and can be tethered indirectly through AP-1, indicating that AP-1 can recruit STAT3 to DNA in certain contexts.[33]
- In colorectal carcinoma, AP-1 drives MMP-1 expression, with STAT3 and STAT1 superimposing stimulatory and repressive influences; activated STAT3 can dampen AP-1-mediated MMP-1 upregulation, whereas STAT1 can override this repression, yielding synergistic output when all three factors act together.[34]

Network-level role in oncogenic inflammation

- STAT3, NF-κB, and AP-1 form an inflammatory regulatory network that underlies breast cellular transformation and is recurrent across many human cancers.[31]
- In an inducible inflammatory breast transformation model, STAT3, NF-κB and AP-1 co-occupy enhancers and jointly control pro-survival, pro-proliferative, and inflammatory gene programs, creating positive feedback loops that stabilize the transformed state.[31]
- STAT3 is a central node for tumor-promoting inflammation, integrating IL-6–gp130–JAK signals and cooperating with other oncogenic pathways; its persistent activation supports proliferation, survival, angiogenesis, and immune evasion.([35, 36])
- AP-1 factors (c-Jun, JunB, c-Fos) cooperate with STAT3 at these regulatory elements, while YAP/TAZ can be recruited by AP-1 and STAT3, further amplifying transcriptional output and transformation in breast cells. [33]

Examples beyond cancer

- In cervical cancer, STAT3 interacts with AP-1 (c-Fos/c-Jun) to regulate the HPV long control region, enhancing transcription of viral oncoproteins and contributing to malignant progression.[37]
- In lung fibrosis, a C/EBPβ/STAT3/AP-1 transcriptional complex has been implicated as a driver of profibrotic gene expression; disrupting this multi-factor complex is being explored as a therapeutic strategy.[32]

Modulation strategies (therapeutic and experimental)

1. Upstream receptor–JAK blockade (STAT3-centric):

Inhibition of JAK kinases (e.g., JAK1/2) reduces STAT3 Y705 phosphorylation, limiting its cooperation with AP-1 on promoters and enhancers.35 36 Clinically used tyrosine kinase inhibitors can also indirectly suppress STAT3 signaling, reducing tumor survival and promoting anti-tumor immunity.([35, 38])

2. Direct STAT3 inhibition:

Targeting the STAT3 SH2 domain, dimerization, or DNA binding using small molecules, peptides, or oligonucleotides reduces STAT3 binding at STAT/AP-1 sites and weakens AP-1-mediated transcription.([35, 36]) Specific STAT3–c-Jun interaction sites provide opportunities for selective inhibitors that disrupt STAT3–AP-1 interaction without fully blocking STAT3 function.[30]

3. AP-1 targeting:

AP-1 activity can be suppressed via inhibition of MAPK pathways (JNK/ERK/p38), interference with c-Jun/c-Fos binding, or modulation of protein stability, thereby indirectly affecting STAT3 recruitment. Since AP-1 often drives transcription (e.g., MMP-1 in CRC), STAT3 acts as a context-dependent modulator.([33, 34])

4. Targeting multi-factor complexes and co-activators:

YAP/TAZ act as co-activators of STAT3 and AP-1; their inhibition reduces combined transcriptional activity.[33]

Disruption of complexes like C/EBPβ/STAT3/AP-1 may help attenuate fibrotic and oncogenic transcription programs.[32]

5. Microenvironment and immune modulation:

STAT3 promotes immunosuppression and PD-L1 expression; its inhibition can enhance anti-tumor immunity and improve response to checkpoint inhibitors.([35, 38, 39])

Combined targeting of STAT3, AP-1, and NF-κB pathways may more effectively suppress inflammatory signaling networks. ([31 ,35])

Conceptual illustration for your writing

One way to conceptualize the STAT3/AP-1 axis for a review or grant is as a modular enhancer complex: cytokine-STAT3 signaling determines when an enhancer is competent, AP-1 defines where in the genome the module binds, and co-activators such as YAP/TAZ or C/EBPβ tune how strongly specific target genes (MMPs, cytokines, viral oncogenes, profibrotic mediators) are expressed.([30, 31, 32, 33 ,34])

This framing naturally motivates interventions that

(i) block STAT3 activation, (ii) blunt AP-1 DNA binding, or (iii) destabilize the higher-order complexes they form.

Alongside these signaling pathways, epigenetic modifications also play a critical role in regulating gene expression during oral carcinogenesis.

5. Epigenetic Re-programming: DNA Methylation and Histone Acetylation

Epigenetic re-programming involves large-scale, reversible changes to DNA methylation patterns and histone acetylation states that reset gene expression programs without altering the underlying DNA sequence. ([40, 41])

DNA methylation: basic concepts

DNA methylation is the covalent addition of a methyl group to cytosine, predominantly at CpG dinucleotides, generating 5-methylcytosine that generally stabilizes gene repression.([42, 43]) Methylation in promoter CpG islands is typically associated with transcriptional silencing, either by blocking transcription factor binding or recruiting methyl-CpG–binding proteins that assemble repressive chromatin complexes.([42, 44]) Maintenance DNMT1 copies methylation patterns during DNA replication, while de novo DNMT3A/3B establish new methylation during development and differentiation.[43] Hypomethylated regions are enriched in transcriptionally active genomic compartments, whereas hypermethylated regions correlate with inactive chromatin.[44]

Epigenetic re-programming of DNA methylation

Epigenetic re-programming in mammals refers to genome-wide erasure and re-establishment of DNA methylation marks during gametogenesis and early embryogenesis.([40,45]) In primordial germ cells and preimplantation embryos, global hypomethylation accompanied by loss of "epigenetic memory" underlies naïve pluripotency and restores developmental potential.([41, 43])

This re-programming involves active and passive demethylation, followed by de novo methylation waves that re-inscribe lineage-appropriate methylomes. Imprinted regions are a special case, as their parent-of-origin-specific methylation must be erased in germ cells, re-established in a sex-specific manner in gametes, and then protected during embryonic re-programming.([43, 45])

Histone acetylation: mechanism and function

Histone acetylation is the addition of acetyl groups to lysine residues on histone N-terminal tails, neutralizing their positive charge and weakening histone–DNA interactions.([46, 47]) This produces a more relaxed, open chromatin structure that increases DNA accessibility for transcription factors and RNA polymerase, typically promoting transcriptional activation.([46, 48])

Histone acetyltransferases (HATs/KATs) act as writers, transferring acetyl groups from acetyl-CoA to specific lysines on H3, H4, H2A, and H2B, while histone deacetylases (HDACs) act as erasers that remove acetyl groups and promote chromatin compaction and gene repression.([46, 47]) Human HDACs are grouped into four classes (I, II, III/sirtuins, IV) with distinct cofactor requirements and cellular roles in development, homeostasis, and disease.[46]

Interplay between DNA methylation and histone acetylation

There is a reciprocal relationship between DNA methylation and histone acetylation, such that deacetylated histones tend to accumulate on hypermethylated DNA, reinforcing transcriptional silencing. Methyl-CpG–binding proteins can recruit HDAC-containing complexes, linking DNA methylation to histone deacetylation and compact chromatin.([44, 49])

Conversely, histone hyperacetylation is associated with transcriptionally active or potentially active chromatin, often coinciding with hypomethylated DNA regions.[44] In epigenetic re-programming contexts (e.g., early embryos, induced pluripotent stem cells), coordinated changes in methylation and acetylation dismantle existing repressive networks and establish new gene expression landscapes.([41, 43])

Biological and translational implications

Dynamic regulation of DNA methylation and histone acetylation is crucial for cell fate decisions, memory and behavior, and long-term maintenance of gene expression patterns.([45, 48])

Dysregulation of these marks contributes to cancer, neuropsychiatric and neurodegenerative disorders, and other diseases, making DNMT and HDAC modulators important therapeutic targets.([47, 49])

These epigenetic alterations work in coordination with microenvironmental changes, including angiogenesis, to support lesion progression.

6. Inhibition of Angiogenesis in Premalignant Lesions

Angiogenesis, the formation of new blood vessels, begins in premalignant lesions and supports their progression to invasive cancer.[50] Inhibiting this process, known as angioprevention, offers potential for cancer chemoprevention, particularly relevant to oral premalignant lesions like leukoplakia given your research focus on oral cancer and phytochemicals.([50, 51])

Angiogenesis Onset

Human studies across organs show increased microvessel density (MVD) in premalignant stages, such as actinic keratoses (skin), leukoplakia (oral/larynx), Barrett's dysplasia (esophagus), and ductal carcinoma in situ (breast). VEGF expression rises early, correlating with MVD and preceding invasion; for example, in oral leukoplakia, MVD increases progressively to squamous cell carcinoma.([50, 52]) This "angiogenic switch" occurs via imbalance favoring pro-angiogenic factors over inhibitors.[50]

Key Mechanisms

Hypoxia-inducible factor-1α (HIF-1α) upregulates VEGF even non-hypoxically in lesions like breast and esophageal precursors via PI3K/Akt activation. Inflammation drives it through COX-2, macrophages releasing TNF-α/MMPs/VEGF, and NF-κB; mast cells correlate with MVD progression in oral leukoplakia to OSCC.([50, 52

) Oncogenes (RAS, MYC) and suppressors (p53/PTEN loss) directly promote it, as in cervical intraepithelial neoplasia via HPV E6/E7.[50]

Phytochemical Inhibitors

Phytochemicals like curcumin (turmeric), EGCG (green tea), resveratrol (grapes), genistein (soy), and quercetin inhibit angiogenesis in premalignant models by downregulating VEGF/HIF-1α, blocking endothelial proliferation/migration, and targeting COX-2/NF-κB. ([50, 51 ,5,3 54)] In oral cancer prevention, they reverse premalignant lesions (e.g., leukoplakia) via anti- proliferative, antioxidant, and anti-angiogenic effects; clinical doses of 500–1000 mg/m² show lesion regression.([51, 53)]Delivery systems (e.g., nanoparticles) address low bioavailability for enhanced targeting.[51]

Therapeutic Outlook

Angioprevention agents like statins, flavonoids (xanthohumol), and VEGF inhibitors (bevacizumab analogs) delay premalignant progression in models; preclinical data support phytochemical polyherbal blends for oral/breast cancers.([50, 54]) Mouse models (e.g., Kras-driven NSCLC) confirm multitargeted TKIs (sunitinib) reduce premalignant burden without altering metastasis rates.[55]

Ongoing trials explore these for high-risk lesions, emphasizing biomarkers like MVD/VEGF for monitoring.([50, 56]Collectively, these interconnected mechanisms highlight the complexity of oral carcinogenesis and provide multiple targets for therapeutic intervention.

7. Curcumin as a Natural Radiosensitizer and Radioprotector

Curcumin exhibits a unique dual role as both a radiosensitizer in cancer cells and a radioprotector in normal tissues, making it promising for enhancing radiotherapy outcomes, particularly in oral squamous cell carcinoma (OSCC). [57]

TABLE 4 : Dual Role of Curcumin in Radiotherapy: Radiosensitizer vs. Radioprotector

Function	**Mechanisms of Action**	**Key Experimental & Clinical Findings**
Radiosensitizer (Targeting Cancer)	• Elevates **Reactive Oxygen Species (ROS)** • Inhibits DNA repair enzymes (**LIG4, PNKP**)	• **OSCC (Oral Cancer):** Synergistically suppresses survivin; inhibits tumor growth without harming normal mucosa.

Function	**Mechanisms of Action**	**Key Experimental & Clinical Findings**
	• Blocks survival pathways (**NF-κB, EGFR, mTOR/HIF-1α**) • Promotes **G2/M arrest** and apoptosis	• **Glioblastoma:** Curbs EMT via Hedgehog inhibition. • **Breast, Lung, Prostate, Cervical, Colon:** ROS-mediated death under both normoxia and hypoxia.
Radioprotector (Shielding Normal Tissue)	• Scavenges ROS and upregulates antioxidants (**SOD, GSH-Px**) • Suppresses inflammation via **NF-κB/COX-2** inhibition • Mitigates fibrosis and myelosuppression	• **Mini-pigs:** Topical gels accelerate post-irradiation wound healing. • **Rat Models:** Reduced inflammatory cytokines (**TNF-α, IL-6**). • **Human Trials:** Topical use in breast cancer and nano-capsules in head/neck cases significantly reduce dermatitis and pain.
Dual Role Dynamics (Context-Dependent)	• **Pro-oxidant** in p53-mutated tumors (inhibits thioredoxin reductase) • **Antioxidant** in healthy cells (reduces micronuclei in lymphocytes)	• NF-κB inhibition acts as a "double-edged sword": driving **apoptosis in tumors** while simultaneously **controlling inflammation** in healthy tissues.

Function	Mechanisms of Action	Key Experimental & Clinical Findings
	• Timing and dosage determine the switch between roles	

(57, 58, 59, 60, 61)

Nanoformulations for Enhanced Delivery

Free curcumin's low bioavailability is overcome by liposomes, chitosan nanoparticles, mesoporous polydopamine, hyaluronic acid-silica, and DHA-microemulsions, achieving 46-fold uptake increase, targeted ROS in hypoxic tumors (COLO-205, glioma), and sustained protection.[62]

Clinical Evidence and Trials

Trials report safety up to 12g/day orally or topical; cervical cancer patients (4g/day) showed 75% survivin reduction and high response rates; head-neck/thyroid cases had lower mucositis/pneumonitis.([63,64]) NCT05947513 evaluates concomitant use in H&N cancers; OSCC preclinical synergy supports CDSCO-aligned trials with decentralized designs for phytodrug validation.[58] No major toxicity noted, positioning it as an adjuvant.[65]

Given its ability to modulate multiple molecular pathways, curcumin has also been explored in clinical settings, particularly in radiotherapy.

8. Comparative Efficacy: Curcumin vs. Synthetic Retinoids

Curcumin and synthetic retinoids like 13-cis-retinoic acid (13cRA) both exhibit chemopreventive potential in oral premalignant disorders (OPMDs) such as leukoplakia, but lack direct head-to-head clinical trials in oral squamous cell carcinoma (OSCC).([66, 67]) Curcumin shows strong preclinical anti-tumor effects with superior safety, while retinoids provide established clinical responses despite higher toxicity and recurrence rates.([68, 69])

Preclinical Mechanisms:

Curcumin inhibits OSCC proliferation, migration, invasion, and induces apoptosis via NF-κB, STAT3, EGFR suppression, EMT reversal, and ROS elevation.([70, 71]) Synthetic retinoids promote epithelial differentiation, suppress angiogenesis, and modulate RAR/RXR pathways, but show less broad multi-target activity compared to curcumin's anti-inflammatory profile.([67, 72]) Both overlap in targeting inflammation and cell growth, with curcumin potentially synergizing by restoring retinoid sensitivity in resistant cells.

Clinical Evidence:

In oral leukoplakia trials, systemic curcumin (3.6-8g/day) achieved 67.5% clinical/histological response with low relapse (7-8%), outperforming placebo.([69, 73, 74]) 13cRA (1-2 mg/kg/day) yielded 67% major lesion reduction and 54% dysplasia reversal, but with 50-64% recurrence post-treatment.([66, 67])No OSCC monotherapy RCTs exist for either; retinoids failed Phase III long-term prevention, while curcumin aids as adjunct (e.g., mucositis reduction, RR=0.38-0.48). [75]

TABLE 5 : Comparison of Curcumin and Synthetic Retinoids in OPMDs

Feature	Curcumin	Synthetic Retinoids
Response Rates (Leukoplakia)	**51–75% clinical response** with low relapse rates.	**67% reduction** in lesions, but characterized by high recurrence.
OSCC Efficacy	Strong **preclinical** evidence; currently used as a Phase II adjunct.	Effective in **premalignancy**; however, no proven survival benefit.
Toxicity & Tolerance	**Minimal toxicity**; very well-tolerated by patients.	Significant **mucocutaneous toxicity**; often leads to dose-limiting side effects.
Bioavailability	**Poor naturally**; requires nano-formulations or delivery aids to improve uptake.	**Good systemic absorption** and bioavailability.
Clinical Trial Stage	Primarily **preclinical and pilot studies** (often combined with EGCG or emodin).	**Phase III trials** have largely failed to show long-term efficacy.

(,67 69, 73, 75, 76)

Translational Outlook:

For oral cancer chemoprevention work, curcumin's safety aligns with natural product pilots, potentially superior for long-term OPMD use pending bioavailability fixes like nanoformulations.[76] Retinoids remain benchmark for early lesions but toxicity limits; combinations show preclinical promise.Biomarker-driven RCTs in OSCC premalignancy could clarify superiority.[77]

In addition to its role in radiotherapy, curcumin has been compared with established chemopreventive agents.

9. Clinical Trial Outcomes: From Lozenge to Ointment

Clinical trials for phytochemicals like curcumin in oral cancer and related conditions show promising outcomes for lozenge formulations in reducing tumor burden pre-surgery, while gels/ointments excel in managing oral mucositis during therapy. No direct trials transition the same compound from lozenge to ointment, but form-specific efficacy supports adaptation for your curcumin+EGCG+emodin pilot in oral cancer chemoprevention. [78]

Lozenge Trial Outcomes

- APG-157, a turmeric-derived (curcumin-rich) lozenge, demonstrated tumor shrinkage in phase I/II "window-of-opportunity" trials for stage I-IV oral/oropharyngeal cancer patients before standard treatments. Pilot data from VA Greater Los Angeles showed reduced tumor size, immune activation, oral microbiome modulation, and less need for extensive surgery/radiation, with high bioavailability from sublingual dissolution.([78,79])
- Phase II expansion evaluates pathological responses, salivary/blood biomarkers, and tumor changes in head/neck squamous cell carcinoma (HNSCC). Patient reports note pain relief and "miracle" tumor reduction from pea-sized lesions.([78,79])
- Curcumin lozenges (3x daily, 3 months) significantly improved mouth opening, burning pain, and tongue protrusion in oral lesions versus controls. [80]

Ointment/Gel Outcomes

- Curcumin gels/mouthwashes reduced oral mucositis (OM) severity (WHO scores), pain, and incidence (up to 37% in radiotherapy patients) in meta-analyses of cancer therapies. Forms included nanocurcumin gels and C. longa extracts, showing benefits across chemo/radiotherapy without toxicity.([81,82])
- Sinecatechins (EGCG-rich, 15% ointment) proved safe/effective in clinical trials for related mucosal conditions, suggesting topical synergy for your combo.[83]
- No emodin-specific topical trials found, but combo preclinical data support anti-proliferative effects. [84]

Formulation Transition Insights

- Lozenge suits systemic absorption/targeted delivery for premalignancy (e.g., your pilot), while ointments target localized mucositis/inflammation in OSCC therapy. Neem extracts (SCNE) showed preventive efficacy in 4NQO tongue dysplasia models, aligning with your neem/curcumin focus, but remain preclinical.[85]
- For CDSCO herbal trials, prioritize bioavailability data from lozenge pilots to justify ointment scaling.

Lozenge and ointment/gel formulations for phytochemicals like curcumin and EGCG differ significantly in application for oral cancer management.

Lozenge Aspects

Lozenge formulations, such as APG-157 or curcumin lozenges, primarily target pre-surgical tumor reduction in oral/oropharyngeal cancers. They achieve notable outcomes like tumor shrinkage in up to 69% of preclinical models and immune system boosts, supported by prior citations Bioavailability is high due to sublingual absorption, with Phase II trials ongoing.([78, 79])

Ointment/Gel Aspects

Ointment and gel forms, including curcumin gels and EGCG-rich sinecatechins ointments, focus on mucositis and pain relief during cancer therapies. They reduce oral mucositis severity by up to 37% and alleviate pain, as shown in meta-analyses of multiple RCTs, with topical sustained release.([80, 81]) Evidence comes from aggregated clinical data rather than single Phase II trials.

The therapeutic potential of curcumin is further supported by clinical studies evaluating different formulations.

10. Synergistic Potential with Piperine and Other Bio-enhancers

Piperine markedly enhances curcumin's synergistic potential in oral cancer treatment by overcoming its poor bioavailability, aligning with your OSCC chemoprevention research. This combination boosts absorption up to 2000%, amplifies apoptosis, and targets pathways like NF-κB in preclinical models.[86]

Nanoformulations further optimize delivery for clinical translation. [87]

Bioavailability Boost

Piperine inhibits intestinal glucuronidation and CYP3A4, raising curcumin serum levels from 7 ng/mL to 154 ng/mL in humans at 20 mg piperine + 2 g curcumin.([88])Clinical trials confirm 20- to 57-fold AUC increases, with emulsomes yielding superior uptake in HCT116 cells (IC50 drop to 50 μg/mL).([87, 89])

Emulsomes or micelles sustain effects longer than free curcumin.[90]

Anticancer Mechanisms in OSCC

Curcumin-piperine induces ROS-mediated apoptosis, G1 arrest, and Bax upregulation in OSCC lines like YD10B and FADU.([91, 92] Synergy suppresses migration via E-cadherin upregulation and EMT inhibition, with piperine enhancing cisplatin potency (99% viability loss).([93, 94])

Hub targets include VEGFA, AKT1, STAT3, and MMP9. [92]

Formulations and Trials

Curcumin-piperine emulsomes improve colon/OSCC efficacy; lycopene triples precancer chemoprevention.([87, 94])Ongoing trials explore adjuvant roles (e.g., NCT02598726 for inflammation). [95]

For your review articles, copper co-supplementation amplifies ROS/apoptosis 5-fold in OSCC cells. [96]

Piperine alone with curcumin:

- Boosts bioavailability by 2000% via CYP3A4/glucuronidation inhibition.
- Enhances apoptosis/NF-κB suppression in OSCC models.
- Human PK validated at 20 mg PIP + 2 g CUR.([86, 87])

Emulsomes (Curcumin + Piperine):

- Sustained release, high HCT116 uptake (IC50 ↓).
- Spherical 184-249 nm particles, 0.07-0.10 mg/ml load.
- Synergistic proliferation inhibition in colon/OSCC-relevant lines.([88, 89])

Piperine + Lycopene with Curcumin :

- Improves OSMF management, precancer chemoprevention.
- Reduces oxidative stress/lesion progression.
- Clinical efficacy in oral submucous fibrosis trials.([90, 91])

Copper + Curcumin:

- 5-fold IC50 reduction in OSCC cells (250 µM Cu).
- Induces ROS/NRF2, E-cadherin↑/vimentin↓ for EMT block.
- Early apoptosis, migration inhibition. ([92, 93])

Micelles/Nanoparticles with Curcumin :

- 57-fold bioavailability via solubility enhancement.
- Blocks MMP9/migration in FADU glioma/OSCC.
- Prolonged circulation, higher cellular uptake.([87, 94, 95])

Building upon these findings, future perspectives focus on improving delivery systems and enhancing clinical efficacy.

CONCLUSION

Oral potentially malignant disorders (OPMDs) play a key role in the development of oral squamous cell carcinoma, with field cancerization explaining the widespread molecular changes beyond visible lesions. This highlights the need for effective field-targeted therapies. Curcumin, derived from *Curcuma longa*, shows strong potential as a multi-target chemopreventive agent by modulating pathways such as NF-κB, STAT3, and AP-1,

along with influencing epigenetic and oxidative processes. Preclinical and clinical evidence supports its role in oral cancer prevention and therapy; however, challenges like poor bioavailability and lack of large-scale clinical validation remain.

Overall, curcumin is a promising and safe candidate for oral cancer chemoprevention, but further clinical studies are needed to confirm its efficacy.

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