Review

Plant Bioactive Constituents and Their Therapeutic Potential in HPV-Positive Oropharyngeal Squamous Cell Carcinoma

Violeta Popovici *, Emma Adriana Ozon *, Manuela Apetrei, Rodica Boca, Cerasela Elena Gird

Posted Date: 15 May 2026

doi: 10.20944/preprints202605.1016.v1

Keywords: human papillomavirus; oropharyngeal cancer; HPV-positive oropharyngeal squamous cell carcinoma; phytochemicals; therapeutic targets; molecular interactions; mechanistic pathways; nanoformulations; clinical trials

 doi:10.20944/preprints202605.1016.v1

Review

Plant Bioactive Constituents and Their Therapeutic Potential in HPV-Positive Oropharyngeal Squamous Cell Carcinoma

Violeta Popovici [1,*], Emma Adriana Ozon [2,*], Manuela Apetrei [1], Rodica Boca [3] and Cerasela Elena Gird [2]

[1] Center for Mountain Economics, "Costin C. Kiritescu" National Institute of Economic Research (INCE-CEMONT), Romanian Academy, 725700 Vatra-Dornei, Romania

[2] Faculty of Pharmacy, "Carol Davila" University of Medicine and Pharmacy, 020945 Bucharest, Romania

[3] Clinical Laboratory, Dorna Medical Clinics, 725700 Vatra-Dornei, Romania

* Correspondence: violeta.popovici@ce-mont.ro (V.P.); emma.budura@umfcd.ro (E.A.O.)

Abstract

Human papillomavirus (HPV) has become a leading cause of oropharyngeal cancers, alongside well-known risk factors such as tobacco and alcohol use. Currently, HPV-positive oropharyngeal squamous cell carcinoma (HPV-OPSCC) has increased significantly in developed countries, with HPV-16 being the most common high-risk subtype. Clinically, HPV-OPSCC shows clear differences in prognosis compared to HPV-negative tumors, especially regarding survival rates and treatment responses. Patients with HPV-OPSCC tend to have notably better survival outcomes and a more favorable outlook. Strong evidence indicates that HPV-related oropharyngeal cancers form a distinct epidemiological, clinical, and molecular group, setting them apart from non-HPV-related cancers. As a result, treatment strategies for these subtypes should follow specific clinical protocols to achieve the best outcomes. Additionally, the viral oncoproteins E6 and E7, which systematically disrupt host tumor-suppressor networks, provide compelling reasons for targeted phytotherapeutic interventions. Therefore, there is growing interest in exploring plant bioactive compounds with promising anti-HPV and anticancer effects that target key oncogenic pathways. This review aims to compile the latest data on bioactive phytochemicals—such as polyphenols, flavonoids, carotenoids, glucosinolate derivatives, terpenoids, and alkaloids—with mechanistic evidence in HPV-OPSCC and to highlight their molecular interactions across oncogenic signaling pathways, focusing on research published from 2015 to 2025.

Keywords: human papillomavirus; oropharyngeal cancer; HPV-positive oropharyngeal squamous cell carcinoma; phytochemicals; therapeutic targets; molecular interactions; mechanistic pathways; nanoformulations; clinical trials

1. Introduction

Oral squamous cell carcinoma (OSCC) and oropharyngeal squamous cell carcinoma (OPSCC) are among the most common and deadly cancers worldwide, causing over 350,000 deaths annually [1]. Although traditionally linked to tobacco and alcohol use, recent findings have shed new light on these cancers, especially with the recognition that high-risk human papillomavirus (HPV), particularly genotype 16 (HPV16), is the main cause in a growing subset of oropharyngeal cancers [2]. In high-income countries, HPV now accounts for 60–80% of OPSCC cases [3]. HPV-positive OPSCC displays a distinct molecular profile and unique epidemiological patterns [4], mainly affecting younger, non-smoking patients, and typically results in a better prognosis than HPV-negative cases (Table 1).

 doi:10.20944/preprints202605.1016.v1

Table 1. The main differences between HPV-positive and HPV-negative OPSCC [5–17].

Feature	HPV-Positive OPSCC	HPV-Negative OPSCC
Primary risk factors	HPV (esp. HPV-16), sexual behavior	Tobacco, alcohol
Specific patient	Younger, male, non-smoker	Older, smoker/drinker
Anatomical site	Tonsil, base of tongue (oropharynx)	Oral cavity, larynx
Key oncoproteins	E6, E7 (viral)	Mutant TP53, EGFR overexpression
p16 status	Overexpressed (high)	Low/absent
Histology	Non-keratinizing, basaloid	Keratinizing SCC
AJCC staging	Separate, favorable system (8th ed.)	Conventional staging
TME	Immunogenic, T-cell rich	Immunosuppressive
Radiosensitivity	High	Lower
De-escalation therapy	Active area of investigation	Not applicable
Prognosis	Significantly better	Worse
Recurrence frequency	Lower	Higher
Prevention	Vaccination (HPV vaccine)	Tobacco/alcohol cessation

The oncogenic mechanisms of high-risk HPV mainly involve two early viral proteins, E6 and E7, which effectively disrupt the host cell cycle control and apoptosis pathways [18]. E6 binds to the tumor suppressor p53 through the cellular ubiquitin ligase E6-AP, leading to its degradation, while E7 inactivates the retinoblastoma protein (pRb). This, in turn, activates E2F transcription factors and promotes uncontrolled cell cycle progression [19]. These changes activate several downstream oncogenic pathways—including NF-κB, PI3K/AKT/mTOR, Wnt/β-catenin, MAPK/ERK, and JAK/STAT—that collectively support cancer cell growth, resistance to cell death, new blood vessel formation, and immune system evasion [20] .

HPV-positive OPSCC (HPV-OPSCC) remains a significant challenge in diagnosis and treatment, underscoring the urgent need for innovative strategies [20–22]. Despite significant advances in surgical techniques, radiotherapy, and immunotherapy—especially with agents such as pembrolizumab and nivolumab that target PD-1/PD-L1 [23,24]. The outcomes for recurrent or metastatic HPV-OPSCC remain with 5-year survival rates around 60% across all stages [25–28]. Standard treatments can cause considerable side effects, highlighting the need for new solutions [29].

In this context, plant-derived compounds [30,31] have emerged as promising multi-target agents that could effectively address various aspects of HPV-driven cancer development while reducing toxic effects compared to traditional chemotherapies [32–36]. This review provides an insightful look at bioactive phytochemicals with proven efficacy against HPV-positive oral cancer. It discusses their molecular targets, interactions with signaling pathways, supporting evidence, and potential clinical applications, highlighting the potential to incorporate these natural products into future treatment approaches [37].

2. Methods

A systematic search of PubMed, Scopus, Web of Science, and Google Scholar was performed for literature published through 2015 - 2025, combining terms relating to HPV-positive oropharyngeal cancer, OSCC/OPSCC, HPV E6/E7 oncoproteins, phytochemicals, and specific molecular pathways.

3. Molecular Oncogenesis and Conventional Therapeutic Protocol of HPV-Positive OPSCC

The molecular oncogenesis of HPV-positive oropharyngeal cancer is a multi-step process initiated by persistent HPV-16 infection. The viral E6 and E7 oncoproteins disrupt critical tumor suppressors (p53 and Rb), while simultaneously activating inflammatory pathways, particularly the

 doi:10.20944/preprints202605.1016.v1

IL-6/STAT3 axis [38,39]. Additional somatic mutations (NOTCH1, SOX2) and the presence of extrachromosomal DNA further drive malignant transformation [38,40]. The tumor microenvironment, including immune cell populations and hypoxic conditions, plays a crucial modulatory role in disease progression and treatment response [40–43] This complex interplay of viral, genetic, and microenvironmental factors distinguishes HPV-OPSCC from other head and neck cancers and explains its unique clinical characteristics, including improved initial prognosis but heterogeneous treatment responses (Figure 1).

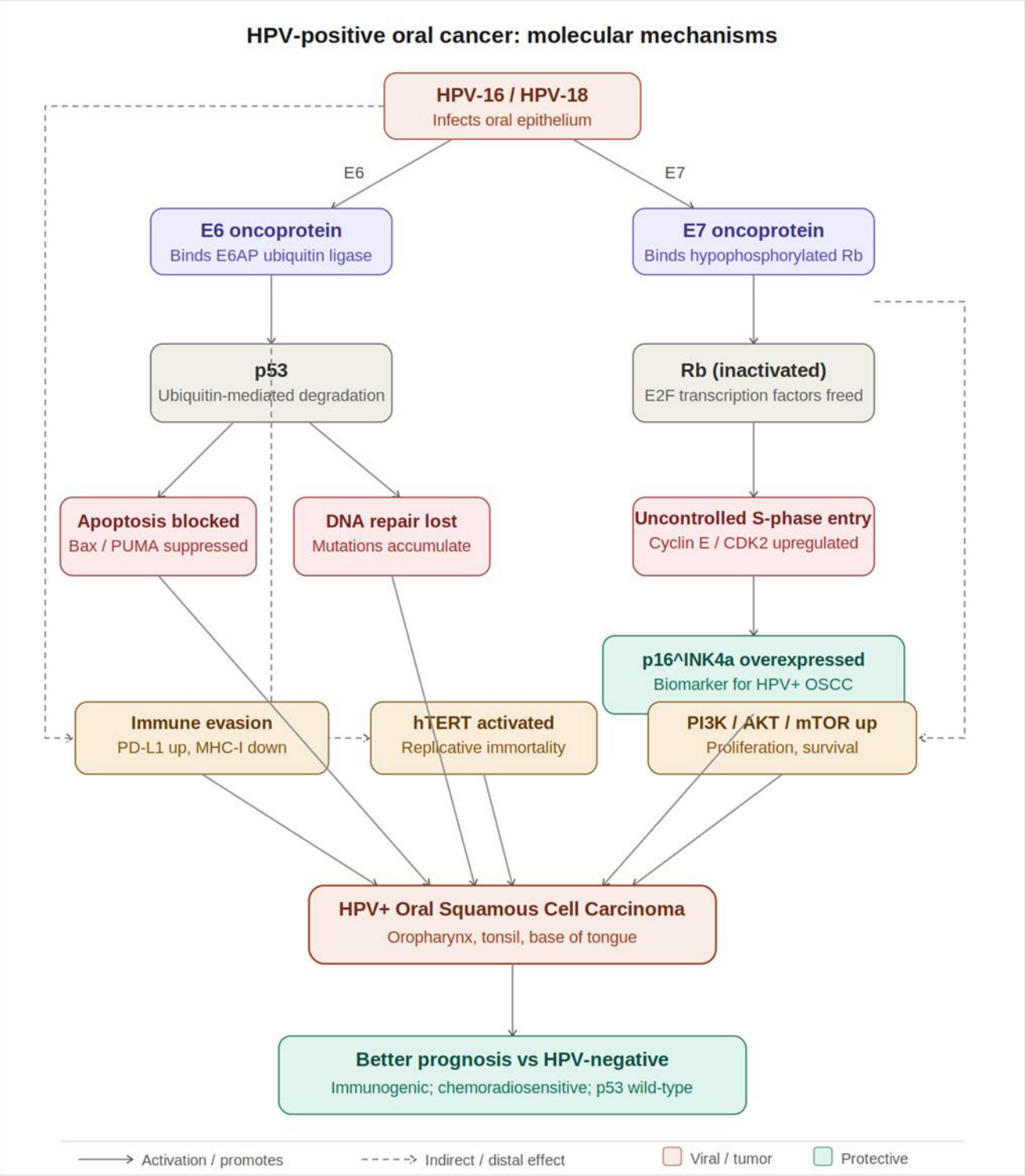


Figure 1. HPV-induced oropharyngeal carcinogenesis. E6 binds the ubiquitin ligase E6AP to target p53 for proteasomal degradation. Without p53, cells cannot arrest the cell cycle at DNA damage checkpoints or trigger

 doi:10.20944/preprints202605.1016.v1

apoptosis, leading to the accumulation of oncogenic mutations. E6 also directly transactivates the hTERT promoter, conferring replicative immortality on cells. E7 binds hypophosphorylated Rb and displaces it from the E2F family of transcription factors, forcing continuous S-phase entry. The resulting loss of Rb feedback paradoxically leads to strong overexpression of the CDK inhibitor p16^INK4a, which is why p16 immunohistochemistry serves as the standard surrogate biomarker for HPV-driven tumors, despite p16 normally functioning as a tumor suppressor. Secondary effects include upregulation of the PI3K / AKT / mTOR pathway (amplified in approximately 50–80% of HPV-positive OPSCC) and immune evasion through PD-L1 upregulation and MHC-I downregulation — the latter being an important therapeutic target given the high immunogenicity of these tumors. Despite their aggressive molecular profile, HPV-positive OPSCC has a significantly better prognosis than HPV-negative ones, largely because p53 remains wild-type at the genomic level (only suppressed by E6) and because the tumor-infiltrating lymphocyte response to viral antigens makes them highly sensitive to chemoradiation. Solid arrows: direct activation or promotion of downstream targets. Dashed arrows: indirect or distal molecular effects. Orange/coral boxes: viral oncoproteins and tumor nodes. Green boxes: clinically favorable outcomes and biomarkers. OPSCC – oropharyngeal squamous cell carcinoma; HPV+ Oral Squamous Cell Carcinoma – HPV-positive Oral Squamous Cell Carcinoma.

3.1. The E6/p53 Axis

HPV16 E6, approximately 150 amino acids long, contains two zinc-binding domains that create a surface for binding p53. When E6, E6-AP (an E3 ubiquitin ligase), and p53 form a ternary complex, p53 is rapidly ubiquitylated and degraded by the proteasome—a process that has recently been understood at atomic detail [44]. This has significant consequences: loss of p53-controlled G1/S and G2/M checkpoints, weakened DNA damage response, reduced apoptosis due to lower BAX levels, and less p21 (CDKN1A) induction [45,46]. Additionally, E6 interferes with the p53-p300-CBP transcriptional activator complex, decreasing p53 acetylation and limiting its activity even when protein levels remain relatively stable [47]. From a phytotherapeutic perspective, the E6/p53 pathway is a particularly promising target [48]. Compounds that can inhibit E6 gene transcription, destabilize E6 protein, or competitively bind to E6 interaction sites could, in theory, restore proper p53 signaling and reactivate the cell's innate apoptotic pathways—similar to how MDM2 inhibitors have been effectively used in HPV-negative p53 wild-type cancers [49,50].

3.2. The E7/pRb Axis and Cell-Cycle Dysregulation

The HPV16 E7 protein binds to pRb via a conserved LXCXE motif, preventing pRb from sequestering E2F transcription factors. Consequently, E2F1-3 can activate genes essential for S-phase entry, such as Cyclin E, Cyclin A, and CDK2. Furthermore, E7 encourages the ubiquitination and proteasomal degradation of pRb [51]. A recently discovered additional mechanism involves E7 disrupting the DREAM complex, a repressive complex involving E2F4/5, leading to widespread activation of cell-cycle genes independent of E6's influence on p53 [51,52]. The overexpression of p16INK4A—used clinically as a surrogate marker for HPV—serves as a compensatory feedback loop within the pRb pathway, rather than indicating effective tumor suppression [53].

3.3. Downstream Oncogenic Signaling Networks

The loss of p53 and pRb function triggers multiple oncogenic pathways that are further enhanced in HPV-positive OHSCC:

- NF-κB pathway, activated by viral proteins and inflammatory stimuli, promotes transcription of anti-apoptotic genes (Bcl-2, cIAP-2, Bcl-xL), pro-angiogenic factors (VEGF, IL-8), and invasion-related genes (MMP-2, MMP-9, E-selectin) [54–57].
- PI3K/AKT/mTOR pathway is often activated through EGFR overexpression (seen in about 90% of OPSCC), PTEN loss, or direct viral influence; it promotes proliferation, metabolic reprogramming, and resistance to apoptosis [58–62].

 doi:10.20944/preprints202605.1016.v1

- Wnt/β-catenin pathway supports cancer stem cell maintenance, epithelial-mesenchymal transition (EMT), and resistance to treatment; β-catenin accumulation in the nucleus has been observed in HPV-positive OPSCC [63–66].
- In the JAK/STAT pathway, STAT3 is constantly active in OPSCC, aiding immune evasion by upregulating PD-L1 and inhibiting dendritic cell maturation [67–72].
- MAPK/ERK pathway with downstream EGFR and RAS, encourages cell proliferation and survival; RAS mutations that activate this pathway are less common in HPV-positive than in HPV-negative OPSCC [73,74].

3.4. Immune Evasion in HPV-Positive OPSCC

Despite the immunogenic nature of HPV infection, tumors effectively evade immune surveillance through multiple mechanisms: E6-mediated repression of E-cadherin disrupts antigen presentation; E7 promotes immune exclusion via MARCHF8-dependent degradation of FAS and TRAIL death receptors; HIF-1α-driven PD-L1 upregulation inactivates tumor-infiltrating T cells; and myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) accumulate in the tumor microenvironment (TME) [75,76].

3.5. Conventional Therapeutic Protocol for HPV-OPSCC

The conventional therapeutic protocol for HPV-positive oral cancer is shown in Figure 2. The figure outlines the standard-of-care pathway for HPV-positive OPSCC using the AJCC 8th edition staging system, which specifically reclassified p16+/HPV+ tumors as a separate, more favorable category [77]. The improved prognosis of HPV-OPSCC compared to HPV-negative oral cancers has driven extensive research into treatment de-escalation to reduce long-term toxicity without affecting oncological outcomes [78].

3.5.1. Low-Risk Status (Stage I–II)

These patients are candidates for de-escalation strategies to reduce treatment intensity, such as less invasive surgery, lower radiation doses, or reduced chemotherapy [79–81]. This approach decreases long-term side effects and improves patients' quality of life without compromising high survival rates [82]. When surgical access allows, transoral robotic surgery (TORS) or transoral laser microsurgery (TLM) is preferred [83–85], with reduced-dose adjuvant therapy if pathological risk factors like positive margins or extracapsular extension are absent. Radiation alone at a lower dose (60–66 Gy) is an alternative. [81,86] Several clinical trials (e.g., ECOG-ACRIN 3311, PATHOS) are actively refining these thresholds [82,87–91] (Figure 2).

3.5.2. Locally Advanced (Stage III–IV)

Concurrent chemoradiation remains the standard, typically IMRT to 70 Gy with cisplatin (100 mg/m² q3w) [89]. Post-CRT PET-CT at 12 weeks guides the decision for salvage neck dissection [92–95]. Surveillance is intensive during the first two years, then tapers off, with focus on thyroid function (if the neck was irradiated) [96–103], swallowing therapy [82,104–107], and smoking cessation (since smoking worsens prognosis even in HPV+ disease) [108–110] (Figure 2).

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 15 May 2026 doi:10.20944/preprints202605.1016.v1

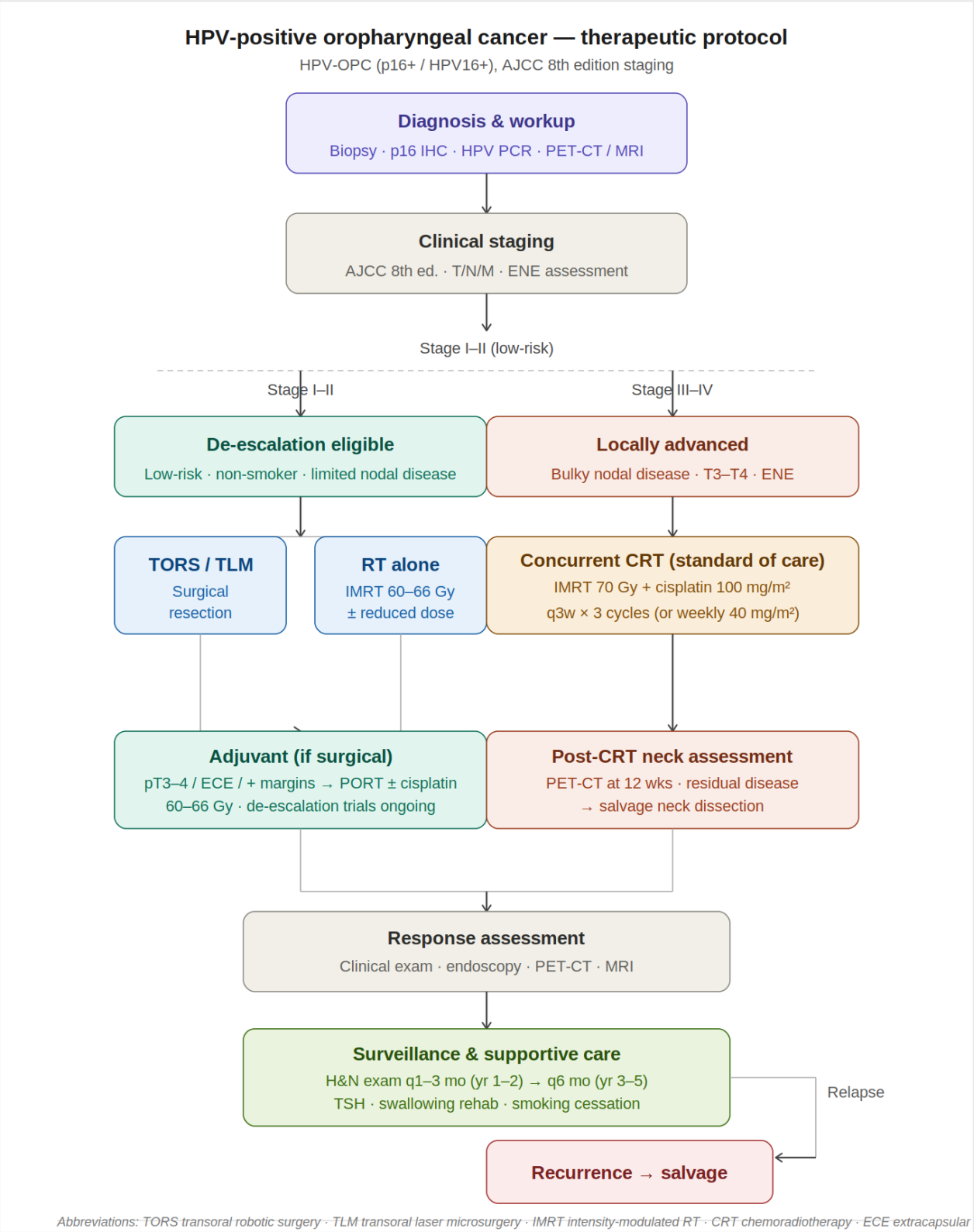
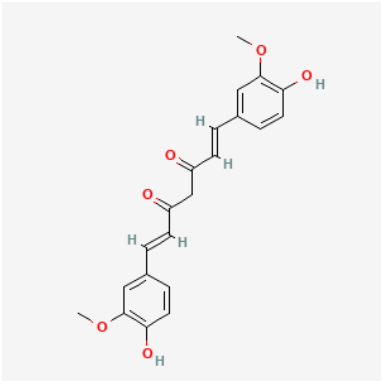


Figure 2. Conventional therapeutic protocol for HPV-positive oropharyngeal squamous cell carcinoma. HPV-OPC - HPV-positive oropharyngeal cancer; AJCC - American Joint Committee on Cancer; TORS - transoral robotic surgery; TLM - transoral laser microsurgery; IMRT - intensity-modulated radiotherapy; CRT - chemoradiotherapy; ENE - extranodal extension; ECE - extracapsular extension; PORT - postoperative radiotherapy.

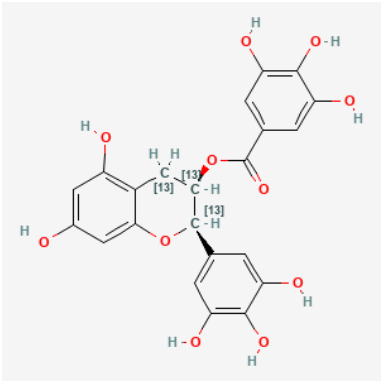
 doi:10.20944/preprints202605.1016.v1

4. Plant-Derived Compounds: Mechanisms and Evidence

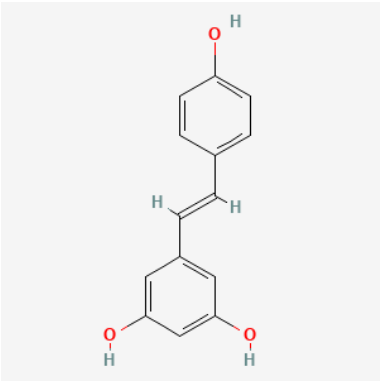
Fifteen phytochemicals directly target these immune evasion mechanisms, as explained below. The bioactive compounds belong to various chemical categories: polyphenols (curcumin, EGCG, resveratrol, their triple combination (TriCurin), quercetin, apigenin, kaempferol, luteolin), flavonoglicans (silibinin), lactones (withaferin A), carotenoids (lycopene), glucosinolate derivatives (Indole-3-carbinol, sulforaphane), terpenoids (artemisinin), xantones (alpha-Mangostin), and alkaloids (berberine) (Figure 3).



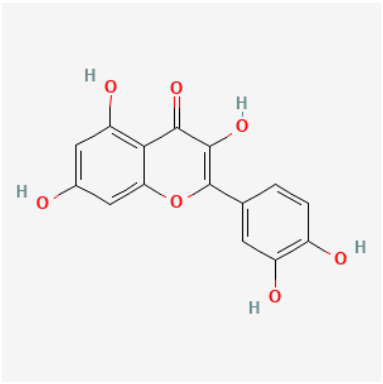
Curcumin (CID: 969516)



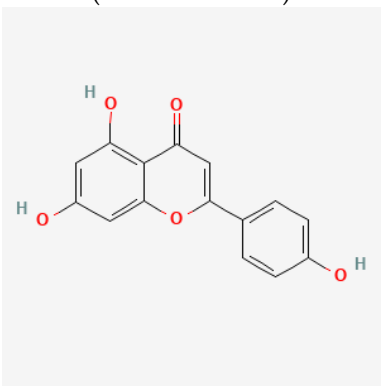
(+/-)-Epigallocatechin Gallate-13C3 (CID: 162642698)



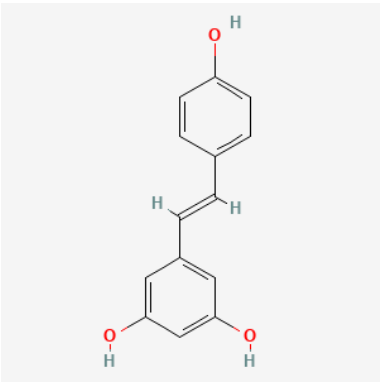
Resveratrol (CID: 445154)



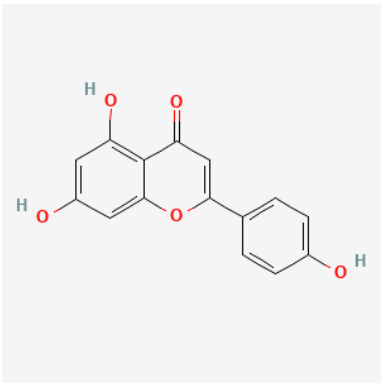
Quercetin (CID: 5280343)



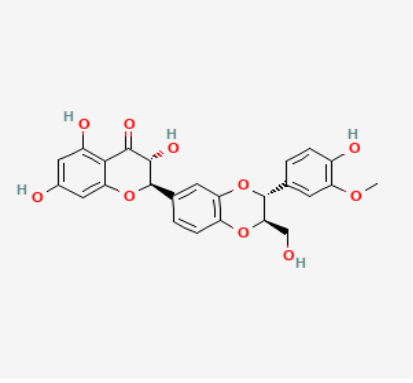
Apigenin (CID: 5280443)



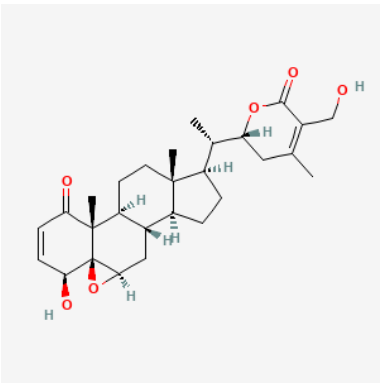
Kaempferol (CID: 5280863)



Luteolin (CID: 5280445)

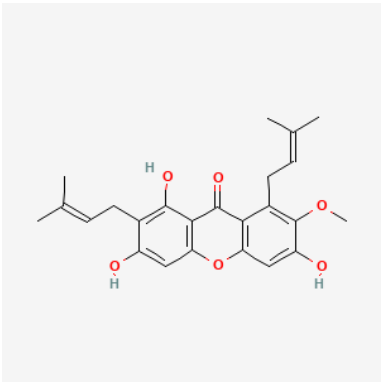


Silibinin (CID: 31553)

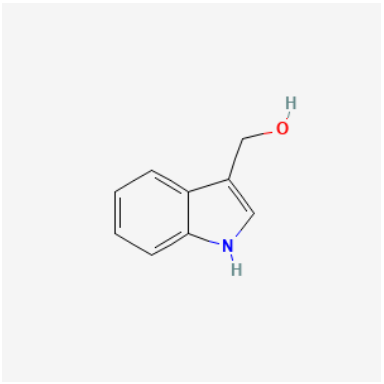


Withaferin A (CID: 265237)

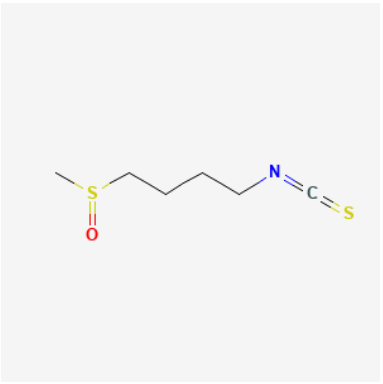
 doi:10.20944/preprints202605.1016.v1



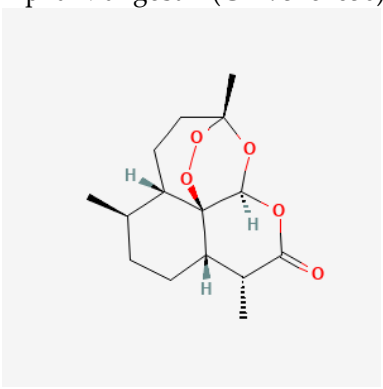
Alpha-Mangostin (CID: 5281650)



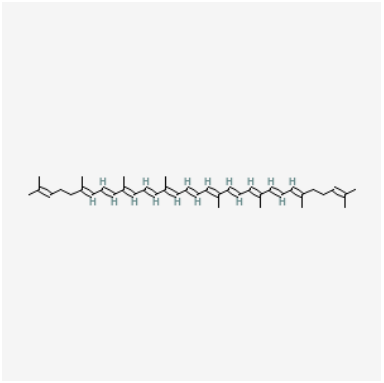
Indole-3-carbinol (CID: 3712)



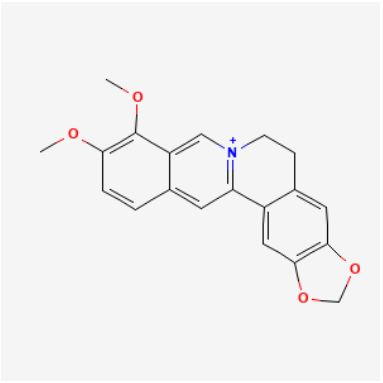
Sulphoraphane (CID: 5350)



Artemisinin (CID: 68827)



Lycopene (CID: 446925)



Berberine (CID: 2353)

Figure 3. Bioactive phytochemicals (2-D structures, as depicted in https://pubchem.ncbi.nlm.nih.gov/compound).

4.1. Curcumin

Curcumin, (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione), is the principal bioactive polyphenol extracted from the rhizome of turmeric (Curcuma longa), a member of the Zingiberaceae family. It belongs to the curcuminoid class and has been investigated in over 150 human clinical trials across oncological and inflammatory conditions

Mishra et al. [111] demonstrates that curcumin is a powerful and highly selective inhibitor of HPV16 E6 oncogene transcription in the HPV16-positive oral carcinoma cell line 93VU147T. It works by blocking the transcriptional activators AP-1 and NF-κB, which normally bind to the HPV upstream regulatory region (URR) to promote E6 and E7 gene expression. Immunoblot analyses show an encouraging inverse relationship: as curcumin levels increase, E6 protein decreases, and p53 protein is restored. At the same time, the levels of anti-apoptotic proteins Bcl-2 and cIAP-2 decline, while pro-apoptotic BAX increases—highlighting the reactivation of p53-dependent apoptosis.

Other authors offered a thorough review of curcumin's mechanisms of action across multiple pathways in head and neck cancer [112]. They confirm that its cell-killing effects in HPV+ cell lines are mainly due to E6 suppression and the subsequent restoration of p53. The review covers curcumin's effects on:

- Wnt/β-catenin: It inhibits Wnt ligand-receptor interaction and promotes GSK3β-mediated phosphorylation and degradation of β-catenin, which helps reduce cancer stem cell renewal [113].

- PI3K/AKT/mTOR: It suppresses PI3K activity and AKT phosphorylation. This downregulation decreases mTOR activity, which in turn reduces the translation of oncoproteins, as shown in oral cancer cells by blocking EGFR phosphorylation and ERK1/2 [112,113].

 doi:10.20944/preprints202605.1016.v1

- JAK/STAT3: Curcumin reduces STAT3 phosphorylation at Y705, leading to lower transcription of genes like Cyclin D1, c-Myc, and PD-L1 [113].

- Notch signaling: It decreases Notch-1 and its downstream targets HES1/HEY1, thereby reducing invasion and EMT in OSCC cell lines [113].

- miR-31 regulation: Curcumin lowers the levels of miR-31 (an oncomiR that is overexpressed in OSCC), which reduces AKT activation and C/EBPβ-driven transcription [113].

- Epigenetic reprogramming: It inhibits DNMT1 and HDAC activities, reactivating silenced tumor suppressor genes [113].

- Ferroptosis induction: Recent research has identified this as an additional mechanism, involving GPX4 modulation and lipid peroxide accumulation, that contributes to cancer cell death [113].

It was also reported that copper supplementation enhances the cytotoxicity of curcumin in oral cancer cell lines [114].

4.2. (+/-)-. Epigallocatechin Gallate-13C3

(+/-)-Epigallocatechin Gallate-13C3 (EGCG, [2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromen-3-yl] 3,4,5-trihydroxybenzoate) is the most abundant and biologically active catechin in green tea (Camellia sinensis, Theaceae). It makes up about 40–60% of the total catechin content in fresh tea leaves and is classified as a flavan-3-ol polyphenol.[115].

Tsouh et al. [116] demonstrated that EGCG: (1) helps slow the growth of HNSCC cell lines and promotes cell death; (2) decreases pEGFR, a key factor in promoting cancer in OSCC; (3) lowers Cox-2 levels, which helps reduce immunosuppression caused by prostaglandin E2; (4) suppresses activated STAT3 (pSTAT3), leading to less PD-L1 production; and (5) reduces Cyclin D1, supporting G1 cell-cycle arrest [116]. EGCG also binds to the proteins Bcl-2 and Bcl-xL, preventing their inhibition of cell death and thus promoting apoptosis. Furthermore, EGCG can disrupt lipid rafts in HNSCC cells, displacing EGFR from its signaling hubs and reducing downstream cancer-promoting signals [117].

EGCG targets HPV at multiple points: it blocks the virus from entering cells by binding to HPV L1 capsid protein, preventing attachment to epithelial cells—beneficial for both prevention and treatment. It also lowers E6 and E7 levels by inhibiting NF-κB and AP-1, reducing their gene activity [118,119]. Additionally, recent research shows that EGCG can inhibit PD-L1 expression by suppressing NF-κB, helping to restore CD8+ T cell activity in tumors—an important finding for HPV-positive OPSCC, where PD-L1/PD-1 inhibitors are already approved treatments [120,121]. Recent reviews confirm that EGCG has anticancer activity, especially against HPV16-related cancers, and that this promising effect is dose-dependent [116,118–124].

Interestingly, a standardized green tea extract called Polyphenon E, marketed as Veregen®, is FDA-approved for treating external genital warts caused by HPV [118].

4.3. Resveratrol

Resveratrol, 5-[E)-2-(4-hydroxyphenyl) ethenyl] benzene-1,3-diol, is a naturally occurring compound classified as a stilbene polyphenol. It is produced as a defensive response, called a phytoalexin, mainly in grapes (*Vitis vinifera*), blueberries, mulberries, peanuts, and most abundantly in *Polygonum cuspidatum*. This compound has two isomeric forms, cis and trans, with the "trans" form being biologically active.

Resveratrol can decrease HPV E6 and E7 mRNA and protein levels in HPV16-positive (CaSki) and HPV18-positive (HeLa) cervical cancer cells [125]. These findings are especially relevant for HPV-positive OPSCC because they involve similar viral cancer mechanisms. The proposed idea is that resveratrol interrupts the splicing of the E6 intron from the E6E7 pre-mRNA, a crucial step after transcription. This leads to several benefits: (1) restoring the expression of tumor suppressors p53 and p16INK4A; (2) raising BAX levels and lowering Bcl-2, thereby encouraging apoptosis; (3) causing

 doi:10.20944/preprints202605.1016.v1

G1/S cell cycle arrest through p21 activation; and (4) reducing phospho-pRb1, counteracting the effects of E7 on cell cycle control [125].

Chatterjee et al. expanded on these findings by showing that resveratrol and its more bioavailable form, pterostilbene, also decrease HPV E6 levels and inhibit NF-κB activity in HPV-positive cancer cells [126,127]. Researchers also found that combining resveratrol with other polyphenols produces a synergistic effect, leading to the development of TriCurin [128]. In addition to targeting viral proteins, resveratrol helps shut down persistent NF-κB activation in head and neck cancers, reducing the secretion of inflammatory factors such as TNF-α, IL-6, and VEGF [129]. It also inhibits STAT3 phosphorylation and lowers MMP-2 and MMP-9 levels, helping to prevent cancer invasion [130]. Its ability to stop metastasis is partly due to its suppression of EMT, as indicated by lower levels of vimentin, E-cadherin, and Snail [131].

4.4. TriCurin: A Synergistic Polyphenol Combination

TriCurin is a rationally designed combination of three food-derived polyphenols: curcumin (from *Curcuma longa*), epicatechin gallate (ECG, from green tea), and resveratrol (from grapes), combined at the specific molar ratio of 4:1:12.5. [132,133]

A detailed analysis of various two- and three-way combinations of polyphenols against HPV-positive cervical cancer cells (HeLa) and HPV16+ head and neck cancer cells (TC-1) [132,133]. Using combination index (CI) analysis, they identified a particularly effective mix, TriCurin. This combination showed the strongest synergy (CI < 1). In HPV16+ TC-1 cells, which produce c-Ha-ras and HPV16 E6/E7, TriCurin significantly increased HPV E6 protein suppression by 4.7 times, doubled p53 induction, raised activated p53 (acetyl-p53) sixfold, and elevated activated caspase-3 levels by 1.7 times compared to curcumin alone [134]. When tested in live animals, intralesional injections of TriCurin into subcutaneous TC-1 tumors in C57BL/6 mice resulted in an impressive 80–90% reduction in tumor growth during treatment, all without harmful effects on healthy control mice. The treatment works by the three compounds acting together to interfere with the E6–p300/CBP interaction: curcumin and resveratrol first reduce E6 transcription by suppressing NF-κB and AP-1 pathways, while ECG enhances p300 acetyltransferase activity, shifting the balance toward p53 acetylation and activation [135]. Piao et al. further explored TriCurin's effects specifically on HPV-positive HNSCC, confirming that it can effectively target HPV+ HNSCC cell lines without harming normal keratinocytes—highlighting its promising potential as a safe and effective treatment option in the oropharyngeal area [132].

4.5. Quercetin

Quercetin, 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one, is common in plants and is found in high amounts in onions (*Allium cepa*), elderberries, capers, kale, and tea. It is believed to be the most widely consumed dietary flavonoid worldwide.

Quercetin's anticancer effects on various OSCC cell lines were investigated using various methods (MTT assay, flow cytometry, wound-healing assay, invasion assay, and gelatin zymography). Key findings include: (1) inducing a selective G2/M cell-cycle arrest—by suppressing Cyclin B1/CDK1—without affecting normal human oral keratinocytes (HaCaT, nHOK); (2) blocking TGF-β1-induced EMT by targeting the Slug transcription factor, which decreases fibronectin and vimentin levels; (3) reducing MMP-2 and MMP-9 activity, thereby limiting basement membrane invasion [136–139].

A scoping review and molecular docking study [140] confirmed quercetin's strong binding affinity for BCl-2 protein outperforming the reference ligand doxorubicin and providing a structural basis for its pro-apoptotic activity. The review of nine eligible studies reaffirmed its effects on cancer invasion, migration, proliferation, and induction of apoptosis across multiple OSCC model systems [141–145].

Regarding HPV-specific activity, quercetin suppresses NF-κB activity, similar to curcumin and EGCG. In vitro studies of HPV+ cancer cells show decreased E-cadherin repression and increased T-

 doi:10.20944/preprints202605.1016.v1

cell-mediated killing compared to untreated HPV+ controls, indicating potential indirect immune-boosting effects in the HPV-positive environment [146,147]. Moreover, the combination of quercetin and cisplatin increases apoptosis of OSCC cells by downregulating XIAP through the NF-kB pathway [148]. Quercetin also augments the oral cancer cells' sensitivity to Vincristine [149].

4.6. Apigenin

Apigenin (5,7-dihydroxy-2-(4-hydroxyphenyl)chromen-4-one) is a flavone subclass flavonoid found in high amounts in *Petroselinum crispum* and *Matricaria chamomilla*. It has attracted researchers' attention for its ability to slow cell growth and its gentle effect on normal cells.

A recent study examined curcumin, EGCG, and apigenin together in the context of HPV-related cancer [117]. They noted that apigenin interacts with the PI3K/AKT, NF-κB, MAPK/ERK, and Wnt/β-catenin pathways, which are often disrupted in HPV-positive OSCC [117]. Its anti-HPV effects are more indirect, by (1) reducing NF-κB activity, which leads to less E6/E7 expression driven by HPV URR, (2) lowering STAT3 phosphorylation, which decreases PD-L1 and helps the immune system, (3) cutting down Cox-2 and prostaglandin E2, which helps reduce inflammation that can promote tumors, (4) directly encouraging cancer cell death through caspase-3/7 activation and PARP cleavage in OSCC cells and (5) working together with EGCG to boost cancer cell death even more, with the combination showing stronger effects at doses that are safe on their own [117,150–155].

The therapeutic targets of the main polyphenols in HPV-positive oral cancer are illustrated in Figure 4.

 doi:10.20944/preprints202605.1016.v1

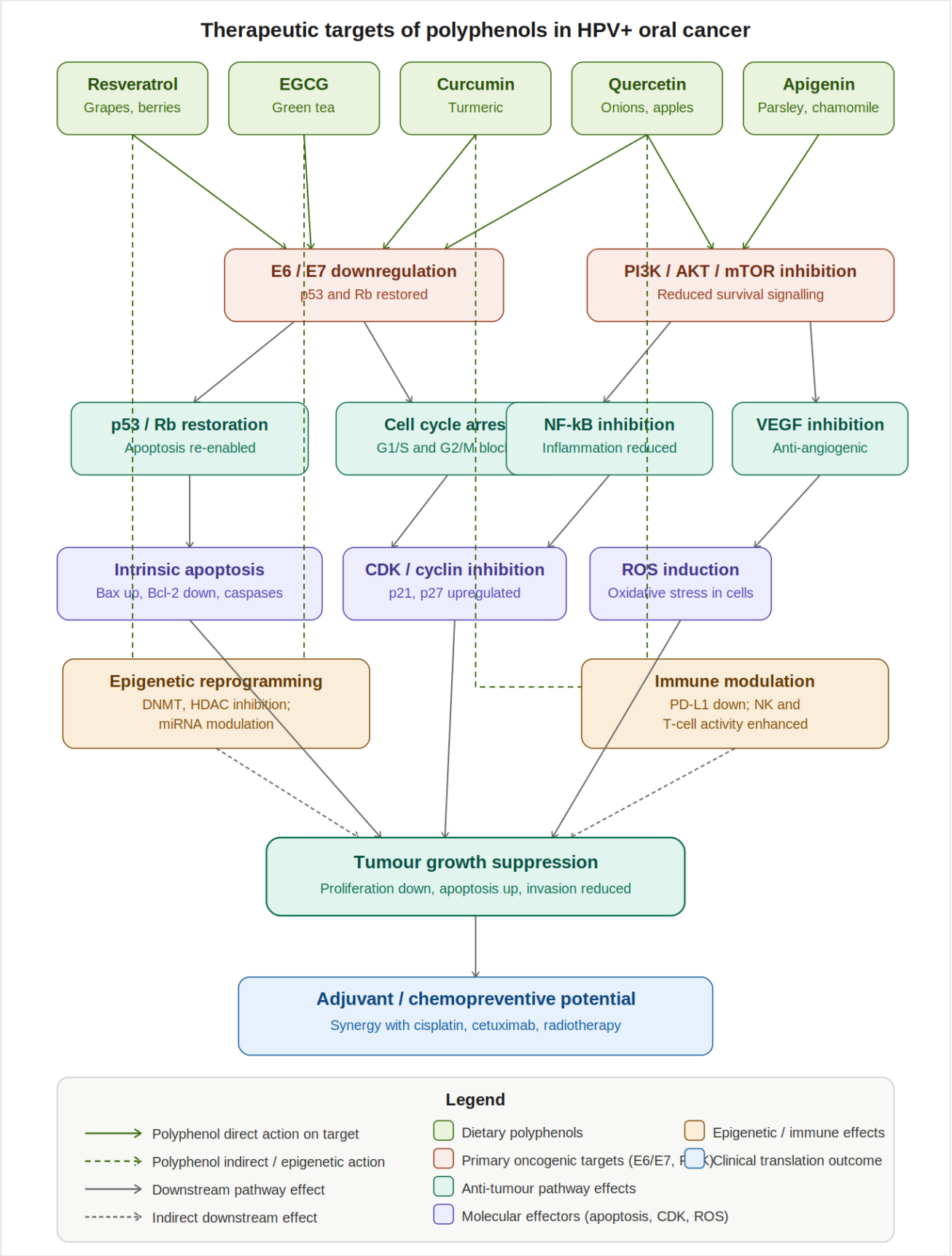


Figure 4. Therapeutic targets of the main polyphenols in HPV-positive oral cancer. Five well-characterized polyphenols — resveratrol, EGCG, curcumin, quercetin, and apigenin — converge on multiple oncogenic pathways. Direct actions include downregulation of E6/E7 (restoring p53 and Rb), inhibition of PI3K/AKT/mTOR, NF-kB suppression, and VEGF blockade. Downstream effects include intrinsic apoptosis,

 doi:10.20944/preprints202605.1016.v1

CDK/cyclin inhibition, and ROS induction. Epigenetic and immune effects include DNMT/HDAC inhibition, miRNA modulation, PD-L1 downregulation, and T-cell/NK enhancement. Collectively, these mechanisms support adjuvant and chemopreventive use, with synergy reported with cisplatin, cetuximab, and radiotherapy. Arrow types: Solid green arrow: Direct action of a polyphenol on a molecular target (e.g., E6/E7 suppression, PI3K inhibition); Dashed green arrow: Indirect or epigenetic action of a polyphenol (e.g., DNMT/HDAC inhibition, immune modulation); Solid grey arrow: Downstream pathway consequence — activation or inhibition of secondary targets; Dashed grey arrow: Indirect downstream effect converging on tumor suppression. Color coding: Green: Dietary polyphenols and their natural food sources. Coral / red: Primary oncogenic targets (HPV E6/E7 oncoprotein activity; PI3K/AKT/mTOR survival signaling). Teal: Anti-tumor pathway effects (p53/Rb restoration, cell cycle arrest, NF-kB and VEGF inhibition, overall tumor suppression). Purple: Molecular effectors of cell death (intrinsic apoptosis via Bax/Bcl-2/caspase cascade, CDK/cyclin inhibition via p21/p27 upregulation, ROS induction). Amber: Epigenetic and immune effects (DNMT/HDAC inhibition, tumor-suppressive miRNA modulation, PD-L1 downregulation, NK cell and cytotoxic T-cell enhancement). Blue: Clinical translation — adjuvant and chemopreventive potential, including demonstrated synergy with cisplatin, cetuximab, and radiotherapy. EGCG: epigallocatechin-3-gallate; E6/E7: HPV early proteins 6 and 7; PI3K: phosphoinositide 3-kinase; AKT: protein kinase B; mTOR: mechanistic target of rapamycin; NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cells; VEGF: vascular endothelial growth factor; CDK: cyclin-dependent kinase; ROS: reactive oxygen species; DNMT: DNA methyltransferase; HDAC: histone deacetylase; miRNA: microRNA; PD-L1: programmed death-ligand 1; NK: natural killer; Bcl-2: B-cell lymphoma 2; Bax: Bcl-2-associated X protein; p53: tumor protein p53; Rb: retinoblastoma protein.

4.7. Kaempferol

Kaempferol, 3,5,7-trihydroxy-2-(4-hydroxyphenyl) chromen-4-one, is found in many plant species (*Spinacia oleracea, Brassica oleracea, Capparis spinosa, Rosmarinus officinalis*).

Molecular docking analysis of five natural flavonoid glycosides (fisetin, kaempferol, morin, myricetin, and quercetin) against HPV-18 E6 and E7 oncoproteins showed that kaempferol had the highest binding affinity to both E6 and E7. All compounds adhered to Lipinski's rules of drug-likeness [156].

A study examining flavonoids (kaempferol, galangin, luteolin, chrysin, quercetin, and apigenin) in HPV-transformed cell lines found that each compound at 50 μM almost entirely suppressed clones in cells transformed by HPV16, HPV18, or HPV68. The compounds caused cell cycle alterations, leading to a notable increase in p53 and p21 levels, which aligns with the disruption of the E6–E6AP interaction, a process essential for both the induction and maintenance of the virus-induced cancer phenotype [157].

4.8. Luteolin

Luteolin, 2-(3,4-dihydroxyphenyl)-5,7-dihydroxychromen-4-one, is commonly found in plants from the Asteraceae, Lamiaceae, Poaceae, Leguminosae, and Scrophulariaceae families. It has been the most extensively studied flavonoid for directly inhibiting HPV oncoproteins. Luteolin showed a significant, dose-dependent cytotoxic effect only in HPV-positive cancer cells, not in HPV-negative cells. It suppressed the expression of HPV E6 and E7 oncogenes, restored levels of pRb and p53, and increased E2F5 levels. Additionally, luteolin enhanced the expression of death receptors (Fas/FasL, DR5/TRAIL, FADD), activated caspase cascades—specifically caspase-3 and -8—induced mitochondrial membrane potential collapse, caused cytochrome c release, and inhibited Bcl-2 and Bcl-xL [158–161].

Using structure-based virtual screening of the HPV-16 E6–E6AP interface, luteolin emerged as the most potent inhibitor of the E6–E6AP interaction, which is essential for p53 degradation — providing a direct mechanistic rationale for its HPV-selective activity [158–160].

 doi:10.20944/preprints202605.1016.v1

4.9. Indole-3-Carbinol

Indole-3-carbinol (I3C, 1H-indol-3-ylmethanol) is a product of glucosinolate hydrolysis found in cruciferous vegetables (such as broccoli, cabbage, cauliflower, kale, and mustard) [161]. In the acidic environment of the stomach, I3C further condenses to form diindolylmethane (DIM), which contributes to many of I3C's bioactivities [162].

I3C-specific anti-HPV mechanisms consist of the following: (1) I3C counteracts HPV16 immune evasion by antagonizing E6 protein-mediated repression of E-cadherin, restoring cell-surface adhesion molecule expression and enhancing antigen presentation to cytotoxic T lymphocytes; (2) I3C functions as a class I HDAC inhibitor, derepressing tumor suppressor genes silenced by E7-driven epigenetic modifications; (3) I3C decreases proinflammatory cytokines (TNF-α, IL-1β, IL-6) and T-cell activation by disrupting HDAC-dependent transcriptional programs [163–165] .

Indole-3-carbinol inhibits nasopharyngeal carcinoma cell growth in vivo and in vitro through apoptosis based on the PI3K/Akt pathway [166]

I3C and sulforaphane are some of the most scientifically supported cruciferous-derived agents for preventing oral cancer, noting their combined anti-proliferative and immune-modulating effects [161,167–170].

4.10. Alpha-Mangostin

Alpha-Mangostin (α-MG, 1,3,6-trihydroxy-7-methoxy-2,8-bis(3-methylbut-2-enyl) xanthen-9-one) is a xanthone derivative extracted from the pericarp (peel) of the tropical mangosteen fruit (*Garcinia mangostana*, Clusiaceae). It is a polyhydroxylated compound with strong antioxidant, anti-inflammatory, and antineoplastic effects.

Díaz et al. [171]provided direct molecular evidence that α-Mangostin inhibits cervical cancer cell proliferation and tumor growth by downregulating E6/E7 HPV oncogenes and the KCNH1 potassium channel gene, which is an E6/E7-regulated driver of proliferation. The inhibitory effects were proportional to the HPV copy number—the cell line with the highest HPV load (CaSki with HPV16) showed the greatest sensitivity—directly implicating the E6/E7 suppression mechanism [171].

Majdalawieh et al. [172] reviewed the anti-OSCC evidence for α-MG, highlighting the following mechanistic pathways: (1) G1-phase cell cycle arrest through downregulation of CDK4/CDK6 and Cyclin D1; (2) activation of the intrinsic (mitochondrial) apoptosis pathway via collapse of mitochondrial membrane potential, cytochrome c release, and caspase-9/caspase-3 activation; upregulation of pro-apoptotic BAX and downregulation of anti-apoptotic Bcl-2**.**

Critically, a recent clinical-stage development study tested a 1% α-Mangostin orabase gel formulation directly against OSCC cells [173]. Additionally, mucoadhesive films loaded with α-MG [174] demonstrated anti-HPV16 activity at both attachment and post-attachment stages, establishing dual antiviral and anticancer activities within a single mucosal delivery format.

4.11. Silibinin

Silymarin is the standardized extract derived from the seeds of milk thistle (*Silybum marianum, Asteraceae*), comprising approximately 65–80% silibinin, along with silydianin and silychristin. Silibinin is the most pharmacologically active constituent.

Silibinin, (2R,3R)-3,5,7-trihydroxy-2-[(2R,3R)-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]-2,3-dihydrochromen-4-one, has been shown to inhibit STAT3 and NF-κB signaling pathways in head and neck squamous cell carcinoma (HNSCC) cell lines, thereby decreasing the expression of genes related to survival and inflammation [175]. In the tumor microenvironment of oral squamous cell carcinoma (OSCC), STAT3 activation increases PD-L1 levels and hinders dendritic cell maturation. The inhibition of STAT3 by silybin offers both direct anti-proliferative effects and indirect immunity-enhancing benefits [176].

 doi:10.20944/preprints202605.1016.v1

Silymarin was also shown to have anti-HPV activity, as confirmed by molecular docking in a study of Fazeli et al. [177].

4.12. Withaferin A (WFA)

Withaferin A, (1S,2R,6S,7R,9R,11S,12S,15R,16S)-6-hydroxy-15-[(1S)-1-[(2R)-5-(hydroxymethyl)-4-methyl-6-oxo-2,3-dihydropyran-2-yl]ethyl]-2,16-dimethyl-8-oxapentacyclo [9.7.0.02,7.07,9.012,16]octadec-4-en-3-one, is the main bioactive compound from *Withania somnifera* (Ashwagandha) [178].

WFA shows promising therapeutic potential for oral cancer by decreasing cell viability and blocking cell migration. It decreases viability in oral cancer cell lines like HSC-3, HSC-4, and Ca9-22 through apoptosis, evidenced by nuclear fragmentation, ROS production, and activation of caspases 3, 8, and 9. WFA promotes apoptosis by increasing Bax and Bim proteins and can also induce G2/M phase cell cycle arrest along with mitochondrial membrane depolarization. Even at low, non-toxic doses, WFA can hinder migration and invasion of oral cancer cells by suppressing MMP-2 and MMP-9. Studies also suggest WFA acts as an anti-tumor agent in chemically induced oral cancer models, reducing tumor size and growth [179–186].

4.13. Sulforaphane

Sulforaphane, 1-isothiocyanato-4-methylsulfinylbutane, and related isothiocyanates (ITCs) are produced enzymatically when myrosinase in cruciferous vegetables (Brassica oleracea) hydrolyzes glucosinolate precursors upon disruption [186]. Sulforaphane's primary anticancer mechanism in OSCC involves the Nrf2/ARE (antioxidant response element) pathway: it alkylates and inactivates KEAP1, releasing NRF2, which translocates to the nucleus and activates transcription of phase II detoxification enzymes such as glutathione S-transferases, NQO1, and HO-1. This process reduces carcinogen-induced DNA damage and oxidative stress. This chemopreventive action is significant for both HPV-negative OSCC (caused by tobacco) and HPV-positive OSCC (where increased oxidative DNA damage leads to viral integration instability). A chemopreventive review shows that sulforaphane induces caspase-3-dependent apoptosis in oral cancer cell lines, as confirmed by caspase-3 activity assays. Furthermore, sulforaphane's inhibition of HDAC reactivates silenced tumor suppressor genes in OSCC, supporting the epigenetic effects of I3C/DIM [187–190].

4.14. Lycopene

Lycopene, (6E,8E,10E,12E,14E,16E,18E,20E,22E,24E,26E)-2,6,10,14,19,23,27,31-Octamethyl-2,6,8,10,12,14,16,18,20,22,24,26,30-dotriacontatridecaen, is a straight-chain, acyclic carotenoid abundant in tomatoes (*Solanum lycopersicum)* [187]. Unlike β-carotene, it cannot be converted into vitamin A, but it has strong antioxidant properties—around twice as potent as β-carotene.

Lycopene's mechanisms in OSCC include: (1) potent ROS scavenging, which decreases oxidative DNA damage that promotes HPV genome integration; (2) modulation of connexin-43-mediated gap junctional intercellular communication (GJIC)—enhanced GJIC is anti-tumorigenic, and lycopene restores GJIC in cells exposed to carcinogens; (3) direct anti-proliferative effects in OSCC cell lines through apoptosis induction and CDK/cyclin modulation, as reviewed by Ullah et al. (Antioxidants, 2021). Epidemiological data from multiple case-control studies link higher lycopene intake with a lower risk of oral cancer, with a meta-analysis showing an odds ratio of 0.69 (95% CI: 0.55–0.87) for the highest versus the lowest lycopene quartile [188–192].

4.15. Artemisinin

Artemisinin, (3R,5aS,6R,8aS,9R,12S,12aR)-octahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin-10(3H)-one, is a sesquiterpene lactone endoperoxide derived from sweet wormwood (*Artemisia annua, Asteraceae*), originally developed as an antimalarial drug.

 doi:10.20944/preprints202605.1016.v1

Semisynthetic derivatives (artesunate, artemether, dihydroartemisinin) are used clinically as antimalarials and are currently being investigated for cancer treatment.

Artemisinin's anticancer mechanism is fundamentally different from that of other phytochemicals discussed here. In cancer cells—which accumulate iron through transferrin receptor overexpression—artemisinin's endoperoxide bridge reacts with intracellular ferrous iron (Fe2+) via a Fenton-type reaction, producing carbon-centered and oxygen-derived free radicals that lead to membrane lipid peroxidation and trigger ferroptosis, a regulated form of cell death distinct from apoptosis. This iron-dependent selectivity makes cancer cells, which generally have higher iron levels than normal cells, more susceptible to killing.

Artemisinin and its derivatives inhibit VEGF expression and angiogenesis in OSCC tumor models through NF-κB suppression, and induce caspase-mediated apoptosis across multiple OSCC cell lines. Artesunate has demonstrated radio-sensitizing effects in vitro in HNSCC, suggesting a potential role in combination therapies .

4.16. Berberine

Berberine, 16,17-dimethoxy-5,7-dioxa-13-azoniapentacyclo[11.8.0.02,10.04,8.015,20]henicosa-1(13),2,4(8),9,14,16,18,20-octaene, is an isoquinoline alkaloid found in *Berberis vulgaris* (barberry), *Hydrastis canadensis* (goldenseal), *Coptis chinensis* (Chinese goldthread), and *Berberis aristata*. It has a long history of use in traditional Chinese and Ayurvedic medicine.

Berberine has dual actions—tumor growth inhibition and immune restoration—especially relevant in HPV-positive OSCC, where immunosuppression is caused by both the virus and the tumor. Berberine specifically: (1) disrupts the IL-6/STAT3 axis in cancer-associated fibroblasts, lowering VEGF and PD-L1 levels; (2) stabilizes endothelial tight junctions and reduces oxidative damage, normalizing tumor blood vessels and enhancing T-cell infiltration; (3) reduces immunosuppressive MDSCs in the tumor environment, allowing more effective activation of cytotoxic T-cells; (4) destabilizes PD-L1 protein via STUB1-mediated ubiquitylation, decreasing immune checkpoint engagement [193].

Berberine also suppresses telomerase activity in cancer cells—a mechanism especially important in HPV-positive cancers, where E6 increases hTERT (human telomerase reverse transcriptase), leading to cellular immortalization [193].

5. Convergent Signaling Pathway Analysis

Analysis of molecular targets across all 15 compounds shows clear convergence on a core set of oncogenic nodes that are amplified or derepressed by HPV E6/E7 activity. This convergence has significant implications for the design of combination therapies.

5.1. The E6/p53 Restoration Axis

Curcumin, resveratrol, TriCurin, and α-Mangostin all restore p53 function through complementary mechanisms: curcumin and resveratrol suppress HPV URR transcriptional activity; resveratrol also interferes with E6/E7 mRNA splicing; α-Mangostin suppresses E6/E7 at the transcriptional level. TriCurin's synergy results from simultaneously blocking E6 transcription and increasing p53 acetylation (activation), thereby restoring p53-dependent apoptosis in a feed-forward manner.

5.2. NF-κB Pathway Suppression

NF-κB serves as a convergence point for at least eight reviewed compounds (curcumin, EGCG, resveratrol, quercetin, apigenin, silymarin, artemisinin, and berberine). In HPV-positive OSCC, persistent NF-κB activation encourages both viral E6/E7 transcription and host oncogenic processes. The variety of compounds targeting this pathway explains why combining polyphenols often yields synergistic effects at doses below their individual effective levels.

 doi:10.20944/preprints202605.1016.v1

5.3. PI3K/AKT/mTOR Axis

EGFR overexpression in approximately 90% of OPSCC cases activates the PI3K/AKT/mTOR pathway. Curcumin (by inhibiting EGFR and PI3K), EGCG (by disrupting EGFR lipid rafts), quercetin (by targeting BCl-2/BCl-xL), resveratrol (by inhibiting Akt phosphorylation), and apigenin (by suppressing PI3K) all engage this pathway. Importantly, mTOR inhibition by curcumin and resveratrol decreases cap-dependent translation of oncoproteins, including Cyclin D1 and c-Myc, thereby increasing G1 arrest.

5.4. Tumor Microenvironment and Immune Remodeling

HPV-positive OPSCC has a relatively high tumor mutational burden and an immunologically 'hot' microenvironment, yet it systematically evades immune killing through PD-L1 upregulation (STAT3-dependent), MDSC accumulation, and loss of death receptor expression. EGCG (PD-L1 suppression via NF-κB), berberine (PD-L1 destabilization; MDSC reduction), curcumin (anti-PD-L1 through STAT3 inhibition; TME reversal), and I3C (E-cadherin restoration; HDAC inhibition) form a multi-compound immunological toolkit that could effectively improve the efficacy of anti-PD-1 checkpoint inhibitors.

6. Bioavailability Challenges and Nanoformulation Strategies

The main obstacle to using phytochemicals in clinical settings is their poor pharmacokinetics: most polyphenols have low water solubility, undergo extensive first-pass metabolism (glucuronidation, sulphation), are quickly cleared from the body, and therefore reach low plasma levels after oral intake. For example, the oral bioavailability of curcumin in humans is estimated to be less than 1% when administered as a free compound.

6.1. Nanoparticle Delivery Systems

Nanoparticle-based delivery systems for phytochemicals offer an extensive platform for oral cancer applications [194–196].

PLGA (poly-lactic-co-glycolic acid) nanoparticles are biodegradable and biocompatible [197]. Advances in curcumin nanoformulations for oral cancer have been reported, showing that PLGA-encapsulated nanocurcumin can be up to 9 times more effective than free curcumin due to enhanced cellular uptake, prolonged release, and protection against degradation [115,116].

Researchers are also exploring other promising options, such as lipid nanoparticles, polymeric micelles, and cyclodextrin complexes [116–118].

Lipid nanoparticles (LNPs) are self-emulsifying drug delivery systems and nanostructured lipid carriers significantly enhance the bioavailability of hydrophobic compounds such as EGCG, resveratrol, and curcumin [198,199].

Polymeric micelles: amphiphilic block copolymers form hydrophobic cores for loading phytochemicals; pH-responsive micelles enable targeted release in the acidic tumor microenvironment [200]. Literature data report curcumin and quercetin-loaded polymeric micelles [201–207].

Chitosan nanoparticles: mucoadhesive, positively charged nanocarriers, especially useful for oral mucosal delivery; chitosan coating improves retention at oral tumor sites and prolongs drug exposure [208–210].

Exosome-based carriers: naturally secreted nanovesicles with high biocompatibility and innate tumor-targeting properties [211–214]

Additionally, encouraging findings from several curcumin-based treatments currently in phase I/II trials for HNSCC demonstrate that they are safe and effective when combined with standard chemo/radiotherapy [113,115,116]. Recent studies have also examined the improved suppression of oral cancer cells by combining curcumin with conventional anticancer drugs (paclitaxel and cisplatin)

 doi:10.20944/preprints202605.1016.v1

[119,120]. Furthermore, topical curcumin formulations have been shown to be effective for transdermal delivery to treat accessible mucosal lesions [121–123].

6.2. Local Delivery Strategies for Oral Cancer

Oral cancer's anatomical accessibility provides a distinct advantage: local delivery systems can reach therapeutic mucosal concentrations without systemic administration. Current approaches include:

Mucoadhesive films containing α-mangostin adhere to the oral mucosa and provide sustained local exposure, while also showing anti-HPV16 and anti-OSCC activity [173,174]. Oral gel formulations allow controlled release at specific intraoral sites; notably, α-mangostin in an orabase gel showed anticancer activity against SCC25 cells in vitro [173].

6.3. Rational Combination Strategies

The documented synergies between polyphenols (EGCG + resveratrol; curcumin + EGCG; TriCurin) demonstrate that carefully designed multi-compound formulas can achieve therapeutic drug levels even at doses too low to produce clinical effects alone. This approach could broaden the therapeutic window. Moreover, computational methods—including molecular docking, network pharmacology, and machine-learning-based predictions of the combination index—are making the development of next-generation phytochemical combinations faster and more efficient.

7. Clinical Translation Status

The main challenges to completing clinical trials include: (1) regulatory classification issues for natural products with multiple compounds; (2) variability in bioavailability that requires standardized formulations; (3) absence of validated HPV-specific molecular biomarkers for response monitoring; (4) funding challenges for compounds that cannot be patented.

Therefore, despite the depth of preclinical evidence, clinical trial data specifically for HPV-positive oral cancer remain limited. The following represent the most advanced translational positions.

7.1. Curcumin in HNSCC

Multiple Phase I/II trials with curcumin as an adjunct to chemo/radiotherapy: principal safety and tolerability findings are positive, while efficacy endpoints are mixed, largely limited by bioavailability (Curcumin Biomarker Trial in Head and Neck Cancer, available at https://clinicaltrials.gov/study/NCT01160302, accessed on 13 May 2026).

7.2. Polyphenon E (EGCG) for Oral Leukoplakia

Phase I/II trial at MD Anderson shows acceptable safety and signs of efficacy in reducing premalignant lesions [215].

7.3. Veregen (Sinecatechins/EGCG):

FDA-approved for HPV-related external genital warts—representing the most important regulatory achievement for a phytochemical in HPV-associated diseases [187]. Recent clinical trials showed that Veregen®, a topical ointment containing 55–72 mg of EGCG, is a safe and effective treatment for vulval warts, benign lesions caused by low-risk HPV strains [216–218].

A phase II randomized controlled trial (RCT) was conducted to assess whether Veregen® is also effective against usual-type vulvar intraepithelial neoplasia (uVIN), a premalignant lesion associated with high-risk HPV infection. Patients eligible for the study were randomized to receive either Veregen® or a placebo ointment (applied three times daily for 16 weeks), with follow-ups at 2, 4, 8, 16, 32, and 52 weeks. Twenty-six patients participated; all 13 treated with Veregen® exhibited either

 doi:10.20944/preprints202605.1016.v1

a complete (n=5) or partial (n=8) clinical response (CR). The Veregen® group showed a significant improvement in CR compared to the placebo group (p = 0.0026). No differences were observed in histological response or toxicity between the groups [219].

7.4. Silymarin for Radiotherapy-Induced Mucositis

Clinical observations (420 mg/day or 70mg/5mL oral nano Silymarin solution) showed a significant reduction in the onset and severity of grade 3–4 mucositis [220,221].

Clinical evidence supports the mechanistic insights; silymarin at 420 mg per day decreased the severity and delayed the onset of radiotherapy-induced oral mucositis in patients with head and neck cancer—an aspect that is highly relevant, as mucositis is the most debilitating acute toxicity associated with radiotherapy for OPSCC [220,221].

Additionally, systemic administration of 140 mg three times daily showed a trend toward reducing chemotherapy-induced hepatotoxicity, further endorsing silybin's role as a protective adjunct during standard treatments [222].

7.5. I3C for Recurrent Respiratory Papillomatosis

It is clinically used in adult patients as an adjunct to surgical resection; 200 mg/day for 3-4 years provides direct antiviral evidence against HPV in mucosal tissue [223].

Furthermore, the drug Epigalin® (a combination of 400 mg I3C and 90 mg EGCG) is an effective oncoprotective, normalizing the balance of estrogen and contributing to the elimination of HPV [224].

The combination of 200 mg of indole-3-carbinol and 60 mg of trans-resveratrol for preventing persistent HPV infection and treating cervical intraepithelial neoplasia shows significant promise [225]. However, further research is needed to determine the most effective application methods.

In summary, the key molecular targets and evidence level of the main bioactive plant-derived products are shown in Table 2.

Table 2. The main bioactive phytochemicals, key molecular targets, and evidence level.

Phytochemicals	Key Molecular Targets / Mechanistic Pathways	Evidence Level	References
Curcumin	↓HPV16 E6/AP-1/NF-κB; ↑p53; Wnt/PI3K/AKT/STAT3 inhibition	In vitro (HPV16+ 93VU147T); mouse xenograft; clinical studies	[111–113,226–229]
EGCG	↓EGFR/pEGFR/Cox-2/STAT3/Cyclin D1; ↓PD-L1 (NF-κB); apoptosis induction	In vitro HNSCC; FDA-approved Veregen® clinical studies	[216–219,230–240]
Resveratrol	↓HPV E6/E7 mRNA & protein; ↑p53/p16/BAX; G1/S arrest; NF-κB inhibition	In vitro HPV16/18 cervical & HNSCC lines; mouse model; clinical studies	[241–253]
TriCurin	4.7× ↑E6 inhibition vs curcumin alone; ↑p53/acetyl-p53/caspase-3; 80–90% tumor reduction in vivo	Mouse HPV16+ TC-1 tumor model; HeLa cells	[128,132–134,254]

 doi:10.20944/preprints202605.1016.v1

Quercetin	G2/M arrest; ↓EMT (Slug); ↓MMP-2/9; BCl-2 binding; caspase-3 apoptosis	In vitro OSCC cell lines; mouse model	[137,142,143,149,255–260]
Apigenin	↓PI3K/AKT/NF-κB; ↑apoptosis; ↓Cox-2; synergy with EGCG vs HPV cancers	In vitro cervical/HNSCC; limited OSCC-specific data	[128,133,134]
Indole-3-Carbinol (I3C)	Antagonizes E6 repression of E-cadherin; HDAC class I inhibition; ↓proinflammatory cytokines	In vitro HPV16+ cells; clinical use in recurrent respiratory papillomatosis	[161,164,167,170,223,225,261–265]
α-Mangostin	↓HPV E6/E7 & KCNH1; G1 arrest; intrinsic apoptosis (cytochrome c/Bcl-2 family); ↓CDK/cyclin	In vitro OSCC (HSC-2,3,4, SCC25); mouse xenograft; mucoadhesive films and oral gel formulations tested	[171–174,266–268]
Silymarin / Silibinin	↓STAT3/NF-κB; anti-inflammatory; hepatoprotection; radiomucositis reduction (clinical: 420 mg/day)	In vitro HNSCC; Phase II-like clinical observation (oral mucositis and protective hepatorenal effects)	[175,221,222,269–271]
Sulforaphane	Nrf2 pathway; HDAC inhibition; ↑phase-II enzymes; caspase-3 apoptosis; ROS-mediated death	In vitro cancer cell lines; nutritional considerations for oral cancer risk reduction	[272–274]
Lycopene	ROS scavenging; ↓connexin-43; ↑apoptosis; ↓cell proliferation OSCC; gap junction modulation	In vitro HNSCC; nutritional considerations for oral cancer risk reduction	[187,188,191]
Artemisinin	Iron-dependent ROS generation; ferroptosis; ↓NF-κB/VEGF/angiogenesis; caspase activation OSCC	In vitro OSCC; limited in vivo oral data	[275–283]
Berberine	↓IL-6/STAT3; ↓VEGF/PD-L1; stabilises endothelial junctions; immune TME remodelling	In vitro, various cancers; preclinical HNSCC data	[284–293]

 doi:10.20944/preprints202605.1016.v1

8. Current Key Findings and Future Directions

Plant-derived compounds provide a scientifically supported, mechanistically consistent, and toxicologically safe adjuvant approach for HPV-positive oral cancer. Thirteen plant-derived compounds—including curcumin, EGCG, resveratrol, quercetin, indole-3-carbinol, alpha-mangostin, apigenin, silymarin, sulforaphane, lycopene, artemisinin, and berberine—demonstrate significant preclinical activity against HPV-positive oral cancer.

Direct targeting of HPV oncoproteins is the most clinically significant mechanism. The phytochemicals also affect NF-κB, PI3K/AKT/mTOR, Wnt/β-catenin, STAT3, and PD-L1 pathways, creating a multi-target pharmacological profile ideally suited for the complex, network-based development of HPV-positive OSCC.

Curcumin, resveratrol, and their combination (TriCurin) all work to suppress the E6 oncoprotein, which normally hijacks and degrades p53. By restoring p53 function, these phytochemicals reactivate the cell's own apoptotic processes. Studies on the HPV16-positive oral carcinoma cell line 93VU147T showed that curcumin selectively inhibits HPV16/E6 oncogene transcription while also blocking the host transcription factors AP-1 and NF-κB that promote viral gene expression. Synergistic combinations offer a promising strategy. The TriCurin formulation (curcumin + epicatechin gallate + resveratrol at a molar ratio of 4:1:12.5) produced 4.7-fold greater HPV E6 inhibition than curcumin alone in HPV16+ TC-1 cells and caused an 80–90% reduction in tumor growth in the mouse model.

EGCG has the most translational data among green tea compounds. EGCG inhibits the growth of head and neck squamous cell carcinoma cell lines, induces apoptosis, and favorably alters the expression of pEGFR, COX-2, activated STAT3, and Cyclin D1. A standardized catechin preparation (Polyphenon E / Veregen®) is FDA-approved for HPV-related genital warts, providing a regulatory precedent. Quercetin shows selective toxicity that is particularly valuable: it suppresses the viability of OSCC cell lines by inducing G2/M cell cycle arrest and inhibiting migration via EMT and MMP pathways, while having no effect on normal keratinocytes. Indole-3-carbinol directly counteracts HPV immune evasion: I3C counteracts HPV16 immune evasion by antagonizing E6 repression of E-cadherin and decreases proinflammatory cytokine production via histone deacetylase class I inhibition.

The primary challenge across all compounds is bioavailability — poor oral absorption and rapid metabolism limit in vivo concentrations. Current research is actively exploring nanoencapsulation, mucoadhesive films, and combination strategies to address this problem. Key priorities for advancing research include developing standardized, bioavailability-enhanced formulations (such as PLGA nanoparticles, LNPs, and mucoadhesive films) as essential steps before conducting efficacy trials.

Future research on the design of rational combination regimens should be validated using both computational methods and HPV-positive HNSCC-specific in vivo models, with orthotopic tumor models preferred over subcutaneous xenografts for oropharyngeal disease. Additionally, prospective biomarker-enriched clinical trials in HPV-positive OPCs—using HPV E6/E7 suppression, p16 restoration, and PD-L1 modulation as pharmacodynamic endpoints—could be vital for further investigation. Future studies might analyze combinations with pembrolizumab or nivolumab, given that EGCG, berberine, and curcumin all reduce PD-L1 expression and could serve as chemosensitizers for checkpoint immunotherapy. Moreover, advanced research could examine epigenetic interactions between phytochemicals and HPV integration sites, especially regarding HDAC inhibitors (I3C, sulforaphane), which may derepress integration-silenced viral genomes.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflict of interest.

 doi:10.20944/preprints202605.1016.v1

References

1. Wu, J.; Chen, H.; Liu, Y.; Yang, R.; An, N. The Global, Regional, and National Burden of Oral Cancer, 1990–2021: A Systematic Analysis for the Global Burden of Disease Study 2021. *J. Cancer Res. Clin. Oncol.* **2025**, *151*, doi:10.1007/s00432-025-06098-w.
2. Zumsteg, Z.S.; Luu, M.; Rosenberg, P.S.; Elrod, J.K.; Bray, F.; Vaccarella, S.; Gay, C.; Lu, D.J.; Chen, M.M.; Chaturvedi, A.K.; et al. Global Epidemiologic Patterns of Oropharyngeal Cancer Incidence Trends. *JNCI: Journal of the National Cancer Institute* **2023**, *115*, 1544–1554, doi:10.1093/jnci/djad169.
3. KOKKINIS, E.; BASTAS, N.S.; MEGA, I.; TSIRONIS, C.; LIANOU, A.D. Association of HPV with Oral and Oropharyngeal Cancer: Current Evidence. *Maedica - A Journal of Clinical Medicine* **2024**, *19*, doi:10.26574/maedica.2024.19.4.801.
4. Deutsch, F.; Regina Bullen, I.; Nguyen, K.; Tran, N.-H.; Elliott, M.; Tran, N. Current State of Play for HPV-Positive Oropharyngeal Cancers. *Cancer Treat. Rev.* **2022**, *110*, 102439, doi:10.1016/j.ctrv.2022.102439.
5. Vivani, M.C.; María, V.S.; Carrizo, G.; Lermer, D.; Calderón, J.G.; Rubino, A.; Aguilar, O.G. Prognosis of HPV Positive and HPV Negative Oropharyngeal Cancer. A First Retrospective Observational Cohort Study in Argentina. *Revista Argentina de Cirugia (Argentina)* **2025**, *117*, doi:10.25132/raac.v117.n2.1827.
6. Maxwell, J.H.; Kumar, B.; Feng, F.Y.; Worden, F.P.; Lee, J.S.; Eisbruch, A.; Wolf, G.T.; Prince, M.E.; Moyer, J.S.; Teknos, T.N.; et al. Tobacco Use in Human Papillomavirus–Positive Advanced Oropharynx Cancer Patients Related to Increased Risk of Distant Metastases and Tumor Recurrence. *Clinical Cancer Research* **2010**, *16*, 1226–1235, doi:10.1158/1078-0432.CCR-09-2350.
7. Mores, A.L.; Bonfim-Alves, C.G.; López, R.V.M.; Rodrigues-Oliveira, L.; Palmier, N.R.; Mariz, B.A.L.A.; Migliorati, C.A.; Kowalski, L.P.; Santos-Silva, A.R.; Brandão, T.B.; et al. Prognostic Factors in Head and Neck Cancer: A Retrospective Cohort Study of 3052 Patients in Brazil. *Oral Dis.* **2025**, *31*, 1133–1139, doi:10.1111/odi.15196.
8. Zou, Z.; Li, B.; Wen, S.; Lin, D.; Hu, Q.; Wang, Z.; Fang, J. The Current Landscape of Oral Squamous Cell Carcinoma: A Comprehensive Analysis from ClinicalTrials.Gov. *Cancer Control* **2022**, *29*, doi:10.1177/10732748221080348.
9. Dong, L.; Xue, L.; Cheng, W.; Tang, J.; Ran, J.; Li, Y. Comprehensive Survival Analysis of Oral Squamous Cell Carcinoma Patients Undergoing Initial Radical Surgery. *BMC Oral Health* **2024**, *24*, 919, doi:10.1186/s12903-024-04690-z.
10. Fatima, J.; Fatima, E.; Mehmood, F.; Ishtiaq, I.; Khan, M.A.; Khurshid, H.M.S.; Kashif, M. Comprehensive Analysis of Oral Squamous Cell Carcinomas: Clinical, Epidemiological, and Histopathological Insights With a Focus on Prognostic Factors and Survival Time. *Cureus* **2024**, doi:10.7759/cureus.54394.
11. Rushiti, A.; Castellani, C.; Cerrato, A.; Fedrigo, M.; Sbricoli, L.; Bressan, E.; Angelini, A.; Bacci, C. The Follow-Up Necessity in Human Papilloma Virus-Positive vs. Human Papilloma Virus-Negative Oral Mucosal Lesions: A Retrospective Study. *J. Clin. Med.* **2023**, *13*, 58, doi:10.3390/jcm13010058.
12. Khanna, S.; Palackdharry, S.; Roof, L.; Wicker, C.A.; Mark, J.; Zhu, Z.; Jandorav, R.; Molinolo, A.; Takiar, V.; Wise-Draper, T.M. Determining the Molecular Landscape and Impact on Prognosis in HPV-Associated Head and Neck Cancer. *Cancers Head Neck* **2020**, *5*, 11, doi:10.1186/s41199-020-00058-2.
13. Chang, P.-H.; Wang, H.-M.; Kuo, Y.-C.; Lee, L.-Y.; Liao, C.-J.; Kuo, H.-C.; Hsu, C.-L.; Liao, C.-T.; Lin, S.H.-C.; Huang, P.-W.; et al. Circulating P16-Positive and P16-Negative Tumor Cells Serve as Independent Prognostic Indicators of Survival in Patients with Head and Neck Squamous Cell Carcinomas. *J. Pers. Med.* **2021**, *11*, 1156, doi:10.3390/jpm11111156.
14. Sharkey Ochoa, I.; O'Regan, E.; Toner, M.; Kay, E.; Faul, P.; O'Keane, C.; O'Connor, R.; Mullen, D.; Nur, M.; O'Murchu, E.; et al. The Role of HPV in Determining Treatment, Survival, and Prognosis of Head and Neck Squamous Cell Carcinoma. *Cancers (Basel).* **2022**, *14*, 4321, doi:10.3390/cancers14174321.
15. Lopez-Pousa, A.; Lopez V, M.; Garcia, J.; Farre, N.; Gallego Rubio, O.; Majercakova, K.; Camacho, D.; Borrell, M.; Molto, C.; Riudavets, M.; et al. Risk of Second Primary Neoplasia in Patients with Oropharyngeal Carcinoma: Role of HPV Status in the Outcome. *Journal of Clinical Oncology* **2019**, *37*, e17544–e17544, doi:10.1200/JCO.2019.37.15_suppl.e17544.

 doi:10.20944/preprints202605.1016.v1

16. Lechner, M.; Liu, J.; Masterson, L.; Fenton, T.R. HPV-Associated Oropharyngeal Cancer: Epidemiology, Molecular Biology and Clinical Management. *Nat. Rev. Clin. Oncol.* **2022**, *19*, 306–327, doi:10.1038/s41571-022-00603-7.
17. Powell, S.F.; Vu, L.; Spanos, W.C.; Pyeon, D. The Key Differences between Human Papillomavirus-Positive and -Negative Head and Neck Cancers: Biological and Clinical Implications. *Cancers (Basel).* **2021**, *13*, 5206, doi:10.3390/cancers13205206.
18. Pan, C.; Issaeva, N.; Yarbrough, W.G. HPV-Driven Oropharyngeal Cancer: Current Knowledge of Molecular Biology and Mechanisms of Carcinogenesis. *Cancers Head Neck* **2018**, *3*, 12, doi:10.1186/s41199-018-0039-3.
19. Yeo-Teh, N.S.L.; Ito, Y.; Jha, S. High-Risk Human Papillomaviral Oncogenes E6 and E7 Target Key Cellular Pathways to Achieve Oncogenesis. *Int. J. Mol. Sci.* **2018**, *19*, 1706, doi:10.3390/ijms19061706.
20. Hassan, A.; Aubel, C. The PI3K/Akt/MTOR Signaling Pathway in Triple-Negative Breast Cancer: A Resistance Pathway and a Prime Target for Targeted Therapies. *Cancers (Basel).* **2025**, *17*, 2232, doi:10.3390/cancers17132232.
21. Perry, A.; Lee, S.H.; Cotton, S.; Kennedy, C. Therapeutic Exercises for Affecting Post-Treatment Swallowing in People Treated for Advanced-Stage Head and Neck Cancers. *Cochrane Database of Systematic Reviews* 2016, *2016*.
22. Hughes, R.T.; Levine, B.J.; May, N.; Shenker, R.F.; Yang, J.H.; Lanier, C.M.; Frizzell, B.A.; Greven, K.M.; Waltonen, J.D. Survival and Swallowing Function after Primary Radiotherapy versus Transoral Robotic Surgery for Human Papillomavirus-Associated Oropharyngeal Squamous Cell Carcinoma. *ORL* **2023**, *85*, doi:10.1159/000531995.
23. Saba, N.F.; Pamulapati, S.; Patel, B.; Mody, M.; Strojan, P.; Takes, R.; Mäkitie, A.A.; Cohen, O.; Pace-Asciak, P.; Vermorken, J.B.; et al. Novel Immunotherapeutic Approaches to Treating HPV-Related Head and Neck Cancer. *Cancers (Basel).* **2023**, *15*, 1959, doi:10.3390/cancers15071959.
24. Roof, L.; Yilmaz, E. Immunotherapy in HPV-Related Oropharyngeal Cancers. *Curr. Treat. Options Oncol.* **2023**, *24*, 170–183, doi:10.1007/s11864-023-01050-x.
25. Costantino, A.; Haughey, B.H.; Alamoudi, U.; Magnuson, J.S. Prognostic Significance of Distant Metastasis Site at Diagnosis in HPV-Related Oropharyngeal Cancer. *Oral Oncol.* **2025**, *165*, 107361, doi:10.1016/j.oraloncology.2025.107361.
26. Koskenniemi, A.R.; Huusko, T.; Routila, J.; Jalkanen, S.; Hollmén, M.; Vainio, P.; Ventelä, S. Histological Tumor Necrosis Predicts Decreased Survival after Neoadjuvant Chemotherapy in Head and Neck Squamous Cell Carcinoma. *Oral Oncol.* **2025**, *165*, 107287, doi:10.1016/j.oraloncology.2025.107287.
27. Zhang, S.; Xiao, H.D.; Cai, Z.; Covinsky, M.; Saluja, K.; Patino, M.O.; Liu, X.; Zhu, H. P16-Positive Cystic Squamous Cell Carcinoma in Midline Neck: Metastasis from Oropharynx or Primary Carcinoma Arising from Thyroglossal Duct Cyst? *Hum. Pathol.* **2018**, *81*, 291–297, doi:10.1016/j.humpath.2018.03.002.
28. Vermeer, D.W.; Coppock, J.D.; Zeng, E.; Lee, K.M.; Spanos, W.C.; Onken, M.D.; Uppaluri, R.; Lee, J.H.; Vermeer, P.D. Metastatic Model of HPV+ Oropharyngeal Squamous Cell Carcinoma Demonstrates Heterogeneity in Tumor Metastasis. *Oncotarget* **2016**, *7*, 24194–24207, doi:10.18632/oncotarget.8254.
29. Parvathaneni, U.; Lavertu, P.; Gibson, M.K.; Glastonbury, C.M. Advances in Diagnosis and Multidisciplinary Management of Oropharyngeal Squamous Cell Carcinoma: State of the Art. *RadioGraphics* **2019**, *39*, 2055–2068, doi:10.1148/rg.2019190007.
30. Ratha, K.K.; Misra, S.R.; Das, R. Traditional Ayurvedic Medicine as a Therapeutic Option in Oral Cancer: An Alternative Medicine Perspective. *Oral Oncology Reports* **2024**, *9*, 100207, doi:10.1016/j.oor.2024.100207.
31. Gunasekaran, V.; Sathishkumar, P. Why Natural Drugs Being Attracted to Treat Oral Cancer? – Highlights from "Oral Oncology Reports." *Oral Oncology Reports* **2024**, *10*, 100395, doi:10.1016/j.oor.2024.100395.
32. Clark, J.M.; Holmes, E.M.; O'Connell, D.A.; Harris, J.; Seikaly, H.; Biron, V.L. Long-Term Survival and Swallowing Outcomes in Advanced Stage Oropharyngeal Squamous Cell Carcinomas. *Papillomavirus Research* **2019**, *7*, doi:10.1016/j.pvr.2018.09.002.
33. Haddad, R.; Fayette, J.; Teixeira, M.; Prabhash, K.; Mesia, R.; Kawecki, A.; Dechaphunkul, A.; Dinis, J.; Guo, Y.; Masuda, M.; et al. Atezolizumab in High-Risk Locally Advanced Squamous Cell Carcinoma of the Head and Neck. *JAMA* **2025**, *333*, 1599, doi:10.1001/jama.2025.1483.

 doi:10.20944/preprints202605.1016.v1

34. Zenga, J.; Wilson, M.; Adkins, D.R.; Gay, H.A.; Haughey, B.H.; Kallogjeri, D.; Michel, L.S.; Paniello, R.C.; Rich, J.T.; Thorstad, W.L.; et al. Treatment Outcomes for T4 Oropharyngeal Squamous Cell Carcinoma. *JAMA Otolaryngology–Head & Neck Surgery* **2015**, *141*, 1118, doi:10.1001/jamaoto.2015.0764.
35. Perri, F.; Longo, F.; Caponigro, F.; Sandomenico, F.; Guida, A.; Della Vittoria Scarpati, G.; Ottaiano, A.; Muto, P.; Ionna, F. Management of HPV-Related Squamous Cell Carcinoma of the Head and Neck: Pitfalls and Caveat. *Cancers (Basel).* **2020**, *12*, 975, doi:10.3390/cancers12040975.
36. O'Sullivan, B.; Huang, S.; Perez-Ordonez, B.; Liu, F.; Massey, C.; Weinreb, I.; Chen, E.; Cummings, B.; Kim, J.; Waldron, J. Outcome of Radiotherapy Alone in HPV Associated Oropharyngeal Cancer. *International Journal of Radiation Oncology*Biology*Physics* **2010**, *78*, S62–S63, doi:10.1016/j.ijrobp.2010.07.178.
37. Dey, P.; Kundu, A.; Chakraborty, H.J.; Kar, B.; Choi, W.S.; Lee, B.M.; Bhakta, T.; Atanasov, A.G.; Kim, H.S. Therapeutic Value of Steroidal Alkaloids in Cancer: Current Trends and Future Perspectives. *Int. J. Cancer* **2019**, *145*, 1731–1744, doi:10.1002/ijc.31965.
38. Terkimbi, S.D.; Paul-Chima, U.O.; Mujinya, R.; Joan, C.; Mounmbegna, P.E.P.; Okon, M. Ben; Emeka, A.G.; Mbina, S.A.; Nkemjika, A.C.; Aja, P.M. Molecular, Immunological and Oncogenic Mechanisms of Cervical Cancer Mediated by HPV/HIV Co-Infection, Clinical Implication and Management. *Infect. Agent. Cancer* **2025**, *21*, 12, doi:10.1186/s13027-025-00729-0.
39. Liang, L.; Wang, W. The Impact of P53 Mutation on Tumor Immune Evasion: Mechanistic Insights and Clinical Implications. *Front. Immunol.* **2026**, *17*, doi:10.3389/fimmu.2026.1753215.
40. Cui, H.; Zhou, Y.; Wang, F.; Cheng, C.; Zhang, W.; Sun, R.; Zhang, L.; Bi, Y.; Guo, M.; Zhou, Y.; et al. Characterization of Somatic Structural Variations in 528 Chinese Individuals with Esophageal Squamous Cell Carcinoma. *Nat. Commun.* **2022**, *13*, 6296, doi:10.1038/s41467-022-33994-3.
41. Yuan, W.; Qiu, Y.; Tang, Q.; Li, M.; Tang, X.; Yang, T. Identification of IGF2BP2 and Long Non-Coding RNA TUG1 for the Prognosis and Tumour Microenvironment in Head and Neck Squamous Cell Carcinoma. *Acta Otorhinolaryngologica Italica* **2025**, *45*, 84–93, doi:10.14639/0392-100X-N3024.
42. Zhao, X.; Zhu, Y.; He, Y.; Gu, W.; Zhou, Q.; Jin, B.; Chen, S.; Lin, H. Unraveling the Immune Evasion Mechanisms in the Tumor Microenvironment of Head and Neck Squamous Cell Carcinoma. *Front. Immunol.* **2025**, *16*, doi:10.3389/fimmu.2025.1597202.
43. Wang, G.; Zhang, M.; Cheng, M.; Wang, X.; Li, K.; Chen, J.; Chen, Z.; Chen, S.; Chen, J.; Xiong, G.; et al. Tumor Microenvironment in Head and Neck Squamous Cell Carcinoma: Functions and Regulatory Mechanisms. *Cancer Lett.* **2021**, *507*, 55–69, doi:10.1016/j.canlet.2021.03.009.
44. Đukić, A.; Lulić, L.; Thomas, M.; Skelin, J.; Saidu, N.E.B.; Grce, M.; Banks, L.; Tomaić, V. HPV Oncoproteins and the Ubiquitin Proteasome System: A Signature of Malignancy? *Pathogens* 2020, *9*.
45. Ozdogan, M.; Tutkun, G.; Cakir, M.O.; Ashrafi, G.H. Molecular Insights into HPV-Driven Head and Neck Cancers: From Viral Oncoproteins to Precision Therapeutics. *Viruses* **2025**, *17*, 1276, doi:10.3390/v17091276.
46. Wang, J.C.K.; Baddock, H.T.; Mafi, A.; Foe, I.T.; Bratkowski, M.; Lin, T.Y.; Jensvold, Z.D.; Preciado López, M.; Stokoe, D.; Eaton, D.; et al. Structure of the P53 Degradation Complex from HPV16. *Nat. Commun.* **2024**, *15*, doi:10.1038/s41467-024-45920-w.
47. Li, L.; Dong, X.; Tang, Y.; Lao, Z.; Li, X.; Lei, J.; Wei, G. Deciphering the Mechanisms of HPV E6 Mutations in the Destabilization of E6/E6AP/P53 Complex. *Biophys. J.* **2022**, *121*, 1704–1714, doi:10.1016/j.bpj.2022.03.030.
48. Kenny, S.; Iyer, S.; Gabel, C.A.; Tegenfeldt, N.; DeMarco, A.G.; Hall, M.C.; Chang, L.; Davisson, V.J.; Pol, S. Vande; Das, C. Structure of E6AP in Complex with HPV16-E6 and P53 Reveals a Novel Ordered Domain Important for E3 Ligase Activation. *Structure* **2025**, *33*, 504-516.e4, doi:10.1016/j.str.2024.12.013.
49. Rietz, A.; Kumari, L.; Koirala, A.; Pelletier, S.; Lu, Z.; Androphy, E.J. Covalent Inhibition of the Human Papillomavirus Type 16 E6 Protein Restores P53 and Suppresses HPV-Driven Tumorigenesis. *bioRxiv* **2025**.
50. Heer, A.; Alonso, L.G.; De Prat-Gay, G. E6*, the 50 Amino Acid Product of the Most Abundant Spliced Transcript of the E6 Oncoprotein in High-Risk Human Papillomavirus, Is a Promiscuous Folder and Binder. *Biochemistry* **2011**, *50*, doi:10.1021/bi101941c.
51. Hwang, S.G.; Lee, D.; Kim, J.; Seo, T.; Choe, J. Human Papillomavirus Type 16 E7 Binds to E2F1 and Activates E2F1-Driven Transcription in a Retinoblastoma Protein-Independent Manner. *Journal of Biological Chemistry* **2002**, *277*, doi:10.1074/jbc.M109113200.

 doi:10.20944/preprints202605.1016.v1

52. Wang, H.; Sun, R.; Lin, H.; Hu, W. P16 ^{INK4A} as a Surrogate Biomarker for Human Papillomavirus-associated Oropharyngeal Carcinoma: Consideration of Some Aspects. *Cancer Sci.* **2013**, *104*, 1553–1559, doi:10.1111/cas.12287.
53. Deschoolmeester, V.; Van Marck, V.; Baay, M.; Weyn, C.; Vermeulen, P.; Van Marck, E.; Lardon, F.; Fontaine, V.; Vermorken, J.B. Detection of HPV and the Role of P16INK4Aoverexpression as a Surrogate Marker for the Presence of Functional HPV Oncoprotein E7 in Colorectal Cancer. *BMC Cancer* **2010**, *10*, 117, doi:10.1186/1471-2407-10-117.
54. Kalimuthu, S.; Se-Kwon, K. Cell Survival and Apoptosis Signaling as Therapeutic Target for Cancer: Marine Bioactive Compounds. *Int. J. Mol. Sci.* **2013**, *14*, 2334–2354, doi:10.3390/ijms14022334.
55. Li, X.; Chen, Y.; Qi, H.; Liu, L.; Shuai, J. Synonymous Mutations in Oncogenesis and Apoptosis versus Survival Unveiled by Network Modeling. *Oncotarget* **2016**, *7*, 34599–34616, doi:10.18632/oncotarget.8963.
56. Shiau, M.-Y.; Fan, L.-C.; Yang, S.-C.; Tsao, C.-H.; Lee, H.; Cheng, Y.-W.; Lai, L.-C.; Chang, Y.-H. Human Papillomavirus Up-Regulates MMP-2 and MMP-9 Expression and Activity by Inducing Interleukin-8 in Lung Adenocarcinomas. *PLoS One* **2013**, *8*, e54423, doi:10.1371/journal.pone.0054423.
57. James, M.A.; Lee, J.H.; Klingelhutz, A.J. Human Papillomavirus Type 16 E6 Activates NF-KB, Induces CIAP-2 Expression, and Protects against Apoptosis in a PDZ Binding Motif-Dependent Manner. *J. Virol.* **2006**, *80*, 5301–5307, doi:10.1128/JVI.01942-05.
58. Deng, R.; Zhu, Y.; Liu, K.; Zhang, Q.; Hu, S.; Wang, M.; Zhang, Y. Genetic Loss of Nrf1 and Nrf2 Leads to Distinct Metabolism Reprogramming of HepG2 Cells by Opposing Regulation of the PI3K-AKT-MTOR Signalling Pathway. *Bioorg. Chem.* **2024**, *145*, 107212, doi:10.1016/j.bioorg.2024.107212.
59. Martelli, A.M.; Chiarini, F.; Evangelisti, C.; Cappellini, A.; Buontempo, F.; Bressanin, D.; Fini, M.; McCubrey, J.A. Two Hits Are Better than One: Targeting Both Phosphatidylinositol 3-Kinase and Mammalian Target of Rapamycin as a Therapeutic Strategy for Acute Leukemia Treatment. *Oncotarget* **2012**, *3*, 371–394, doi:10.18632/oncotarget.477.
60. Morgan, T.; Koreckij, T.; Corey, E. Targeted Therapy for Advanced Prostate Cancer: Inhibition of the PI3K/Akt/MTOR Pathway. *Curr. Cancer Drug Targets* **2009**, *9*, 237–249, doi:10.2174/156800909787580999.
61. Evangelisti, C.; Chiarini, F.; Cappellini, A.; Paganelli, F.; Fini, M.; Santi, S.; Martelli, A.M.; Neri, L.M.; Evangelisti, C. Targeting Wnt/B-catenin and PI3K/Akt/MTOR Pathways in T-cell Acute Lymphoblastic Leukemia. *J. Cell. Physiol.* **2020**, *235*, 5413–5428, doi:10.1002/jcp.29429.
62. Jiang, M.; Zhang, K.; Zhang, Z.; Zeng, X.; Huang, Z.; Qin, P.; Xie, Z.; Cai, X.; Ashrafizadeh, M.; Tian, Y.; et al. PI3K/AKT/MTOR Axis in Cancer: From Pathogenesis to Treatment. *MedComm (Beijing).* **2025**, *6*, doi:10.1002/mco2.70295.
63. Brkic, F.F.; Stoiber, S.; Maier, T.; Gurnhofer, E.; Kenner, L.; Heiduschka, G.; Kadletz-Wanke, L. Targeting Wnt/Beta-Catenin Signaling in HPV-Positive Head and Neck Squamous Cell Carcinoma. *Pharmaceuticals* **2022**, *15*, 378, doi:10.3390/ph15030378.
64. Shan, S.; Lv, Q.; Zhao, Y.; Liu, C.; Sun, Y.; Xi, K.; Xiao, J.; Li, C. Wnt/β-Catenin Pathway Is Required for Epithelial to Mesenchymal Transition in CXCL12 over Expressed Breast Cancer Cells. *Int. J. Clin. Exp. Pathol.* **2015**, *8*.
65. Saloura, V.; Izumchenko, E.; Zuo, Z.; Bao, R.; Korzinkin, M.; Ozerov, I.; Zhavoronkov, A.; Sidransky, D.; Bedi, A.; Hoque, M.O.; et al. Immune Profiles in Primary Squamous Cell Carcinoma of the Head and Neck. *Oral Oncol.* **2019**, *96*, 77–88, doi:10.1016/j.oraloncology.2019.06.032.
66. Guerra, E.; Trerotola, M.; Relli, V.; Lattanzio, R.; Tripaldi, R.; Vacca, G.; Ceci, M.; Boujnah, K.; Garbo, V.; Moschella, A.; et al. Trop-2 Induces ADAM10-Mediated Cleavage of E-Cadherin and Drives EMT-Less Metastasis in Colon Cancer. *Neoplasia* **2021**, *23*, 898–911, doi:10.1016/j.neo.2021.07.002.
67. Wang, W.; Lopez McDonald, M.C.; Kim, C.; Ma, M.; Pan, Z. (Tommy); Kaufmann, C.; Frank, D.A. The Complementary Roles of STAT3 and STAT1 in Cancer Biology: Insights into Tumor Pathogenesis and Therapeutic Strategies. *Front. Immunol.* **2023**, *14*, doi:10.3389/fimmu.2023.1265818.
68. Li, X. The Impact of STAT3/PD-L1 Signaling in the Tumor Environment to Improve HNSCC Therapy. In Proceedings of the Abstract- und Posterband – 90. Jahresversammlung der Deutschen Gesellschaft für HNO-Heilkunde, Kopf- und Hals-Chirurgie e.V., Bonn – Digitalisierung in der HNO-Heilkunde; April 23 2019; Vol. 98.

 doi:10.20944/preprints202605.1016.v1

69. Lim, S.T.; Song, T.; Lim, J.Q.; Laurensia, Y.; Pang, J.W.L.; Nagarajan, S.; Claresta, G.; Jing, T.; Tang, T.P.L.; Nairismagi, M.-L.; et al. Oncogenic Activation of STAT3 Pathway Drives PD-L1 Expression in Natural Killer/T Cell Lymphoma. *Journal of Clinical Oncology* **2017**, *35*, 7549–7549, doi:10.1200/JCO.2017.35.15_suppl.7549.
70. Zhang, J.-P.; Song, Z.; Wang, H.-B.; Lang, L.; Yang, Y.-Z.; Xiao, W.; Webster, D.E.; Wei, W.; Barta, S.K.; Kadin, M.E.; et al. A Novel Model of Controlling PD-L1 Expression in ALK+ Anaplastic Large Cell Lymphoma Revealed by CRISPR Screening. *Blood* **2019**, *134*, 171–185, doi:10.1182/blood.2019001043.
71. Song, T.L.; Nairismägi, M.-L.; Laurensia, Y.; Lim, J.-Q.; Tan, J.; Li, Z.-M.; Pang, W.-L.; Kizhakeyil, A.; Wijaya, G.-C.; Huang, D.-C.; et al. Oncogenic Activation of the STAT3 Pathway Drives PD-L1 Expression in Natural Killer/T-Cell Lymphoma. *Blood* **2018**, *132*, 1146–1158, doi:10.1182/blood-2018-01-829424.
72. Bu, L.L.; Yu, G.T.; Wu, L.; Mao, L.; Deng, W.W.; Liu, J.F.; Kulkarni, A.B.; Zhang, W.F.; Zhang, L.; Sun, Z.J. STAT3 Induces Immunosuppression by Upregulating PD-1/PD-L1 in HNSCC. *J. Dent. Res.* **2017**, *96*, 1027–1034, doi:10.1177/0022034517712435.
73. Deng, J.; Liu, Y.; Ma, X.; Li, D.; Li, Z.; Pan, Y.; Zeng, X. NK Cells in HPV-Related Tumorigenesis: Mechanisms and Clinical Applications. *Front. Cell. Infect. Microbiol.* **2026**, *15*, doi:10.3389/fcimb.2025.1723091.
74. Rong, C.; Muller, M.; Flechtenmacher, C.; Holzinger, D.; Dyckhoff, G.; Bulut, O.C.; Horn, D.; Plinkert, P.; Hess, J.; Affolter, A. Differential Activation of ERK Signaling in HPV-Related Oropharyngeal Squamous Cell Carcinoma. *Cancers (Basel).* **2019**, *11*, 584, doi:10.3390/cancers11040584.
75. Khalil, M.I.; Yang, C.; Vu, L.; Chadha, S.; Nabors, H.; James, C.D.; Morgan, I.M.; Pyeon, D. The Membrane-Associated Ubiquitin Ligase MARCHF8 Stabilizes the Human Papillomavirus Oncoprotein E7 by Degrading CUL1 and UBE2L3 in Head and Neck Cancer. *J. Virol.* **2024**, *98*, doi:10.1128/jvi.01726-23.
76. Khalil, M.I.; Yang, C.; Vu, L.; Chadha, S.; Nabors, H.; Welbon, C.; James, C.D.; Morgan, I.M.; Spanos, W.C.; Pyeon, D. HPV Upregulates MARCHF8 Ubiquitin Ligase and Inhibits Apoptosis by Degrading the Death Receptors in Head and Neck Cancer. *PLoS Pathog.* **2023**, *19*, e1011171, doi:10.1371/journal.ppat.1011171.
77. Amin, M.B.; Greene, F.L.; Edge, S.B.; Compton, C.C.; Gershenwald, J.E.; Brookland, R.K.; Meyer, L.; Gress, D.M.; Byrd, D.R.; Winchester, D.P. The Eighth Edition <scp>AJCC</Scp> Cancer Staging Manual: Continuing to Build a Bridge from a Population-based to a More "Personalized" Approach to Cancer Staging. *CA Cancer J. Clin.* **2017**, *67*, 93–99, doi:10.3322/caac.21388.
78. Cakir, M.O.; Kayhan, G.; Yilmaz, B.; Ozdogan, M.; Ashrafi, G.H. Emerging Therapeutic Strategies for HPV-Related Cancers: From Gene Editing to Precision Oncology. *Curr. Issues Mol. Biol.* **2025**, *47*, 759, doi:10.3390/cimb47090759.
79. Golubev, P.; Bolotina, L.; Gevorkov, A.; Deshkina, T.; Kuzmina, E.; Pokataev, I.; Galkin, V. De-Escalation Treatment of Patients with HPV-Positive Oropharyngeal Squamous Cell Carcinoma. *Journal of Clinical Oncology* **2024**, *42*, e18052–e18052, doi:10.1200/JCO.2024.42.16_suppl.e18052.
80. Chen, A.M. De-Escalation for Human Papillomavirus-Positive Oropharyngeal Cancer: A Look at the Prospective Evidence. *Curr. Oncol. Rep.* **2025**, *27*, 355–361, doi:10.1007/s11912-025-01652-8.
81. Chen, A.M. De-Escalated Radiation for Human Papillomavirus Virus-Related Oropharyngeal Cancer: Who, Why, What, Where, When, How, How Much…and What Next? *Radiotherapy and Oncology* **2024**, *200*, 110373, doi:10.1016/j.radonc.2024.110373.
82. Hutcheson, K.A.; Patterson, J.; Hurt, C.; Barbon, C.E.; Watson, L.J.; Valencia, D.; Alvarez, C.; Heiberg, C.; Jones, T.; Evans, M. Aspiration Rates and Clinician-Graded Dysphagia after Transoral Surgery (TOS): An Interim Analysis of Modified Barium Swallow (MBS) Studies (Videofluoroscopy) from the PATHOS Trial. *International Journal of Radiation Oncology*Biology*Physics* **2024**, *118*, e47–e48, doi:10.1016/j.ijrobp.2024.01.106.
83. Carnevale, C.; Ortiz-González, I.; Ortiz-González, A.; Bodi-Blanes, L.; Til-Pérez, G. Early T1-T2 Stage P16+ Oropharyngeal Tumours. Role of Upfront Transoral Robotic Surgery in de-Escalation Treatment Strategies. A Review of the Current Literature. *Oral Oncol.* **2021**, *113*, 105111, doi:10.1016/j.oraloncology.2020.105111.
84. Mulcahy, C.F.; Gross, N.D. Advances in Surgical Therapy for HPV-Associated Squamous Cell Carcinoma. *Curr. Otorhinolaryngol. Rep.* **2022**, *10*, 475–482, doi:10.1007/s40136-022-00421-6.

 doi:10.20944/preprints202605.1016.v1

85. Molteni, G.; Bassani, S.; Arsie, A.E.; Zampieri, E.; Mannelli, G.; Orlandi, E.; Bossi, P.; De Virgilio, A. Role of TORS as De-Escalation Strategy in HPV-Related Oropharyngeal Cancer, What We Need to Know. *Healthcare* **2024**, *12*, 1014, doi:10.3390/healthcare12101014.
86. Ma, D.; Routman, D.M. De-Escalation of Adjuvant Therapy in Operatively Managed HPV Associated Oropharyngeal Carcinoma: Current Status and Future Directions. *Semin. Radiat. Oncol.* **2025**, *35*, 166–172, doi:10.1016/j.semradonc.2025.02.002.
87. Higgins, E.; Webster, R.; Palaniappan, N.; Hurt, C.; Nabi, Z.; Rizos, K.; Elliott, K.; Miles, E.; Patterson, J.; Hutcheson, K.; et al. 49 Development of a Normal Tissue Complication Probability Model for Dysphagia in PATHOS Trial Patients. *Radiotherapy and Oncology* **2024**, *192*, S17–S20, doi:10.1016/S0167-8140(24)00435-3.
88. O'Hara, J.T.; Hurt, C.N.; Ingarfield, K.; Patterson, J.M.; Hutcheson, K.; Canham, J.E.; Nixon, L.S.; Heiberg, C.D.; Johson, S.; Evans, M.; et al. Transoral Laser or Robotic Surgery Outcomes for Oropharyngeal Carcinoma. *JAMA Otolaryngology–Head & Neck Surgery* **2024**, *150*, 1002, doi:10.1001/jamaoto.2024.3371.
89. Ferris, R.L.; Flamand, Y.; Weinstein, G.S.; Li, S.; Quon, H.; Mehra, R.; Garcia, J.J.; Chung, C.H.; Gillison, M.L.; Duvvuri, U.; et al. Transoral Robotic Surgical Resection Followed by Randomization to Low- or Standard-Dose IMRT in Resectable P16+ Locally Advanced Oropharynx Cancer: A Trial of the ECOG-ACRIN Cancer Research Group (E3311). *Journal of Clinical Oncology* **2020**, *38*, 6500–6500, doi:10.1200/JCO.2020.38.15_suppl.6500.
90. Kang, J.J.; Yu, Y.; Chen, L.; Zakeri, K.; Gelblum, D.Y.; McBride, S.M.; Riaz, N.; Tsai, C.J.; Kriplani, A.; Hung, T.K.W.; et al. Consensuses, Controversies, and Future Directions in Treatment Deintensification for Human Papillomavirus-associated Oropharyngeal Cancer. *CA Cancer J. Clin.* **2023**, *73*, doi:10.3322/caac.21758.
91. Higgins, E.; Palaniappan, N.; Webster, R.; Nabi, Z.; Lad, R.; Elliott, K.; Miles, E.; Canham, J.; Nixon, L.; Hurt, C.; et al. MO-0712 Compliance to the PATHOS Swallowing OAR Atlas and Impact on Predicted Dysphagia for Trial Patients. *Radiotherapy and Oncology* **2023**, *182*, S581–S582, doi:10.1016/S0167-8140(23)08437-2.
92. Elsholtz, F.H.J.; Ro, S.R.; Shnayien, S.; Erxleben, C.; Bauknecht, H.C.; Lenk, J.; Schaafs, L.A.; Hamm, B.; Niehues, S.M. Inter- And Intrareader Agreement of NI-RADS in the Interpretation of Surveillance Contrast-Enhanced CT after Treatment of Oral Cavity and Oropharyngeal Squamous Cell Carcinoma. *American Journal of Neuroradiology* **2020**, *41*, doi:10.3174/AJNR.A6529.
93. Elsholtz, F.H.J.; Ro, S.R.; Shnayien, S.; Dinkelborg, P.; Hamm, B.; Schaafs, L.A. Impact of Double Reading on NI-RADS Diagnostic Accuracy in Reporting Oral Squamous Cell Carcinoma Surveillance Imaging - a Single-Center Study. *Dentomaxillofacial Radiology* **2022**, *51*, doi:10.1259/DMFR.20210168.
94. Chen, A.M.; Harris, J.P.; Gan, M.; Nabar, R.; Tjoa, T.; Haidar, Y.M.; Truong, A.; Chow, D.S.; Armstrong, W.B. Posttreatment Surveillance Imaging After Radiation for Head and Neck Cancer. *JAMA Netw. Open* **2023**, *6*, e2342825, doi:10.1001/jamanetworkopen.2023.42825.
95. Mukherjee, S.; Fischbein, N.J.; Baugnon, K.L.; Policeni, B.A.; Raghavan, P. Contemporary Imaging and Reporting Strategies for Head and Neck Cancer: MRI, FDG PET/MRI, NI-RADS, and Carcinoma of Unknown Primary?AJR Expert Panel Narrative Review. *American Journal of Roentgenology* 2023, *220*.
96. Liao, Y.H.; Chen, Y.F.; Hsieh, M.S.; Lin, M.C.; Wang, C.W.; Wang, C.P.; Lou, P.J.; Chen, T.C. The Prognostic Importance of Radiologic Extranodal Extension in Hypopharyngeal Carcinoma. *Head Neck* **2025**, *47*, doi:10.1002/hed.27978.
97. Beltz, A.; Zimmer, S.; Michaelides, I.; Evert, K.; Psychogios, G.; Bohr, C.; Künzel, J. Significance of Extranodal Extension in Surgically Treated HPV-Positive Oropharyngeal Carcinomas. *Front. Oncol.* 2020, *10*.
98. Li, X.; Yao, X.; Liu, S.; Mei, F.; Yu, B.; Wang, B.; Song, S.; Tan, S. Gross Recurrent Laryngeal Nerve Invasion by Extranodal Extension in Thyroid Carcinoma. *BMC Cancer* **2025**, *25*, 109, doi:10.1186/s12885-025-13500-w.
99. Kijima, N.; Uzawa, Y.; Hirai, Y.; Nojima, Y.; Aoyama, J.; Takahashi, H.; Arai, Y.; Sano, D.; Nishimura, G.; Oridate, N.; et al. Clinicopathological Significance of Extranodal Extension in Hypopharyngeal and Laryngeal Squamous Cell Carcinoma. *Head Neck* **2025**, *47*, 1769–1778, doi:10.1002/hed.28090.
100. King, A.D.; Tsang, Y.M.; Leung, H.S.; Yoon, R.G.; Vlantis, A.C.; Wong, K.C.W.; Lee, J.H.; Ai, Q.Y.H. Imaging of Extranodal Extension: Why Is It Important in Head and Neck Cancer? *ESMO Open* 2025, *10*.

 doi:10.20944/preprints202605.1016.v1

101. Gomes, M.A.; de Souza, M.C.; Araújo Júnior, M.L.C.; Vaisman, F.; de Araújo, S.R.C.; Fernandes, P.V.; Dias, F.L. The Extent of Extranodal Extension as a Prognostic Indicator in Papillary Thyroid Cancer. *Arch. Endocrinol. Metab.* **2025**, *69*, 1–10, doi:10.20945/2359-4292-2025-0094.
102. Sahin, O.; Kamel, S.; Wahid, K.A.; Dede, C.; Taku, N.; He, R.; Naser, M.A.; Sharafi, C.S.; Mäkitie, A.; Kann, B.H.; et al. International Multispecialty Expert Physician Preoperative Identification of Extranodal Extension in Patients with Oropharyngeal Cancer Using Computed Tomography: Prospective Blinded Human Inter-Observer Performance Evaluation. *Cancer* **2025**, *131*, doi:10.1002/cncr.35815.
103. Jiang, W.; Wang, G.-Y.; Qin, G.-J.; Zhang, W.-Q.; Zhu, X.-D.; Han, Y.-Q.; Lei, F.; Shen, L.-F.; Yang, K.-Y.; Cui, C.-Y.; et al. Advanced Image-Identified Extranodal Extension of Retropharyngeal Lymph Nodes in the Refinement of N Classification for Nasopharyngeal Carcinoma. *Cell Rep. Med.* **2025**, *6*, 101942, doi:10.1016/j.xcrm.2025.101942.
104. Jaison Varghese, J.; Aithal, V.U.; Sharan, K.; Maiya, A.G.; Rajashekhar, B. Profiling of Swallowing Function in Head and Neck Cancer Patients Prior to Radiation Therapy-Findings from a Tertiary Hospital in South India. *Prev. Med. Rep.* **2024**, *41*, doi:10.1016/j.pmedr.2024.102713.
105. Parsons, A.; Dewan, K. Dysphagia and Dysphonia After Head and Neck Cancer. *Oral Dis.* **2025**, *31*, 2753–2760, doi:10.1111/odi.15152.
106. Costa, D.R.; Santos, P.S. da S.; Fischer Rubira, C.M.; Berretin-Felix, G. Immediate Effect of Neuromuscular Electrical Stimulation on Swallowing Function in Individuals after Oral and Oropharyngeal Cancer Therapy. *SAGE Open Med.* **2020**, *8*, doi:10.1177/2050312120974152.
107. Tseng, W.-H.; Li, T.-H.; Chiu, H.-L.; Yang, T.-L.; Wang, C.-P.; Chen, T.-C.; Chen, C.-N.; Ko, J.-Y.; Hsiao, T.-Y.; Lou, P.-J. Long-Term Swallowing-Related Outcomes in Oral Cancer Patients Receiving Proactive Swallowing Therapy. *Oral Oncol.* **2021**, *122*, 105569, doi:10.1016/j.oraloncology.2021.105569.
108. Mohebbi, E.; Guthrie, G.; Patil, S.; Benjamin, W.; Tan, M.; Giurintano, J.P.; Witek, M.E.; Ahn, P.H.; Taylor, K.; Wolf, G.; et al. Postdiagnosis Smoking Cessation and Survival Outcomes of Head and Neck Cancer Patients. *Head Neck* **2025**, *47*, doi:10.1002/hed.28182.
109. Rzepakowska, A.; Marcinkiewicz, B.; Żurek, M.; Wiśniewska, D.; Niemczyk, K. Motivation to Smoking Cessation in Head and Neck Cancer and Dysplasia Patients in Confrontation with the Attitudes of Otorhinolaryngologists in Delivering Anti-Smoking Therapies. *European Archives of Oto-Rhino-Laryngology* **2022**, *279*, 3645–3655, doi:10.1007/s00405-021-07209-2.
110. Steffenssen, M.C.W.; Klemp, I.; Nielsen, M.; Bakholdt, V.; Thomsen, J.-B.; Sørensen, J.A. Nurse-Led Counselling and Replacement Therapy Is Effective for Smoking Cessation in Oral Cancer Patients. *Eur. J. Plast. Surg.* **2017**, *40*, 593–596, doi:10.1007/s00238-017-1314-y.
111. Mishra, A. Curcumin Modulates Cellular AP-1, NF-KB, and HPV16 E6 Proteins in Oral Cancer. *Ecancermedicalscience* **2015**, *9*, doi:10.3332/ecancer.2015.525.
112. Veselá, K.; Kejík, Z.; Masařík, M.; Babula, P.; Dytrych, P.; Martásek, P.; Jakubek, M. Curcumin: A Potential Weapon in the Prevention and Treatment of Head and Neck Cancer. *ACS Pharmacol. Transl. Sci.* **2024**, *7*, 3394–3418, doi:10.1021/acsptsci.4c00518.
113. Akter, K.; Gul, K.; Mumtaz, S. Revisiting Curcumin in Cancer Therapy: Recent Insights into Molecular Mechanisms, Nanoformulations, and Synergistic Combinations. *Curr. Issues Mol. Biol.* **2025**, *47*, 716, doi:10.3390/cimb47090716.
114. Lee, H.-M.; Patel, V.; Shyur, L.-F.; Lee, W.-L. Copper Supplementation Amplifies the Anti-Tumor Effect of Curcumin in Oral Cancer Cells. *Phytomedicine* **2016**, *23*, 1535–1544, doi:10.1016/j.phymed.2016.09.005.
115. Farhan, M. Green Tea Catechins: Nature's Way of Preventing and Treating Cancer. *Int. J. Mol. Sci.* **2022**, *23*, 10713, doi:10.3390/ijms231810713.
116. Tsouh Fokou, P.V.; Kamdem Pone, B.; Appiah-Oppong, R.; Ngouana, V.; Bakarnga-Via, I.; Ntieche Woutouoba, D.; Flore Donfack Donkeng, V.; Tchokouaha Yamthe, L.R.; Fekam Boyom, F.; Arslan Ateşşahin, D.; et al. An Update on Antitumor Efficacy of Catechins: From Molecular Mechanisms to Clinical Applications. *Food Sci. Nutr.* **2025**, *13*, doi:10.1002/fsn3.70169.
117. Asiri, A.; Bokahri, B.T.; Sadaf; Eisa, A.A.; Aljohani, H.M.; Nofal, W.; Kausar, T.; Najm, M.Z. Curcumin, EGCG and Apigenin in Cervical Cancer: Mechanistic Insights and Therapeutic Potential. *Front. Pharmacol.* **2025**, *16*, doi:10.3389/fphar.2025.1592395.

 doi:10.20944/preprints202605.1016.v1

118. Miyoshi, N.; Tanabe, H.; Suzuki, T.; Saeki, K.; Hara, Y. Applications of a Standardized Green Tea Catechin Preparation for Viral Warts and Human Papilloma Virus-Related and Unrelated Cancers. *Molecules* **2020**, *25*, 2588, doi:10.3390/molecules25112588.
119. Oh, J.-W.; Muthu, M.; Pushparaj, S.S.C.; Gopal, J. Anticancer Therapeutic Effects of Green Tea Catechins (GTCs) When Integrated with Antioxidant Natural Components. *Molecules* **2023**, *28*, 2151, doi:10.3390/molecules28052151.
120. Cheng, Z.; Zhang, Z.; Han, Y.; Wang, J.; Wang, Y.; Chen, X.; Shao, Y.; Cheng, Y.; Zhou, W.; Lu, X.; et al. A Review on Anti-Cancer Effect of Green Tea Catechins. *J. Funct. Foods* **2020**, *74*, 104172, doi:10.1016/j.jff.2020.104172.
121. Xu, J.; Xu, Z.; Zheng, W. A Review of the Antiviral Role of Green Tea Catechins. *Molecules* **2017**, *22*, 1337, doi:10.3390/molecules22081337.
122. Yiannakopoulou, E.C. Targeting DNA Methylation with Green Tea Catechins. *Pharmacology* **2015**, *95*, 111–116, doi:10.1159/000375503.
123. Younes, M.; Aggett, P.; Aguilar, F.; Crebelli, R.; Dusemund, B.; Filipič, M.; Frutos, M.J.; Galtier, P.; Gott, D.; Gundert-Remy, U.; et al. Scientific Opinion on the Safety of Green Tea Catechins. *EFSA Journal* **2018**, *16*, doi:10.2903/j.efsa.2018.5239.
124. Andrade, E.D.S.; Santos, R.A.; Guillermo, L.V.C.; Miyoshi, N.; Ferraz da Costa, D.C. Immunomodulatory Effects of Green Tea Catechins and Their Ring Fission Metabolites in a Tumor Microenvironment Perspective. *Molecules* **2024**, *29*, 4575, doi:10.3390/molecules29194575.
125. Sun, X.; Fu, P.; Xie, L.; Chai, S.; Xu, Q.; Zeng, L.; Wang, X.; Jiang, N.; Sang, M. Resveratrol Inhibits the Progression of Cervical Cancer by Suppressing the Transcription and Expression of HPV E6 and E7 Genes. *Int. J. Mol. Med.* **2020**, *47*, 335–345, doi:10.3892/ijmm.2020.4789.
126. Chatterjee, K.; AlSharif, D.; Mazza, C.; Syar, P.; Al Sharif, M.; Fata, J.E. Resveratrol and Pterostilbene Exhibit Anticancer Properties Involving the Downregulation of HPV Oncoprotein E6 in Cervical Cancer Cells. *Nutrients* **2018**, *10*, 243, doi:10.3390/nu10020243.
127. Chatterjee, K.; Mukherjee, S.; Vanmanen, J.; Banerjee, P.; Fata, J.E. Dietary Polyphenols, Resveratrol and Pterostilbene Exhibit Antitumor Activity on an HPV E6-Positive Cervical Cancer Model: An in Vitro and in Vivo Analysis. *Front. Oncol.* **2019**, *9*, doi:10.3389/fonc.2019.00352.
128. Mukherjee, S.; Hussaini, R.; White, R.; Atwi, D.; Fried, A.; Sampat, S.; Piao, L.; Pan, Q.; Banerjee, P. TriCurin, a Synergistic Formulation of Curcumin, Resveratrol, and Epicatechin Gallate, Repolarizes Tumor-Associated Macrophages and Triggers an Immune Response to Cause Suppression of HPV+ Tumors. *Cancer Immunology, Immunotherapy* **2018**, *67*, 761–774, doi:10.1007/s00262-018-2130-3.
129. Ren, Z.; Zheng, S.; Sun, Z.; Luo, Y.; Wang, Y.; Yi, P.; Li, Y.; Huang, C.; Xiao, W. Resveratrol: Molecular Mechanisms, Health Benefits, and Potential Adverse Effects. *MedComm (Beijing).* **2025**, *6*, doi:10.1002/mco2.70252.
130. Kohandel, Z.; Farkhondeh, T.; Aschner, M.; Pourbagher-Shahri, A.M.; Samarghandian, S. STAT3 Pathway as a Molecular Target for Resveratrol in Breast Cancer Treatment. *Cancer Cell Int.* **2021**, *21*, 468, doi:10.1186/s12935-021-02179-1.
131. Bhuia, Md.S.; Chowdhury, R.; Akter, Mst.A.; Ali, Md.A.; Afroz, M.; Akbor, Md.S.; Sonia, F.A.; Mubarak, M.S.; Islam, M.T. A Mechanistic Insight into the Anticancer Potentials of Resveratrol: Current Perspectives. *Phytotherapy Research* **2024**, *38*, 3877–3898, doi:10.1002/ptr.8239.
132. Piao, L.; Mukherjee, S.; Chang, Q.; Xie, X.; Li, H.; Castellanos, M.R.; Banerjee, P.; Iqbal, H.; Ivancic, R.; Wang, X.; et al. TriCurin, a Novel Formulation of Curcumin, Epicatechin Gallate, and Resveratrol, Inhibits the Tumorigenicity of Human Papillomaviruspositive Head and Neck Squamous Cell Carcinoma. *Oncotarget* **2017**, *8*, doi:10.18632/oncotarget.10620.
133. Mukherjee, S.; Debata, P.R.; Hussaini, R.; Chatterjee, K.; Baidoo, J.N.E.; Sampat, S.; Szerszen, A.; Navarra, J.P.; Fata, J.; Severinova, E.; et al. Unique Synergistic Formulation of Curcumin, Epicatechin Gallate and Resveratrol, Tricurin, Suppresses HPV E6, Eliminates HPV+ Cancer Cells, and Inhibits Tumor Progression. *Oncotarget* **2017**, *8*, doi:10.18632/oncotarget.16648.
134. Einbond, L.S.; Zhou, J.; Wu, H.; Mbazor, E.; Song, G.; Balick, M.; DeVoti, J.A.; Redenti, S.; Castellanos, M.R. A Novel Cancer Preventative Botanical Mixture, TriCurin, Inhibits Viral Transcripts and the Growth of

 doi:10.20944/preprints202605.1016.v1

W12 Cervical Cells Harbouring Extrachromosomal or Integrated HPV16 DNA. *Br. J. Cancer* **2021**, *124*, 901–913, doi:10.1038/s41416-020-01170-3.

135. Pandey, P.; Verma, M.; Lakhanpal, S.; Pandey, S.; Kumar, M.R.; Bhat, M.; Sharma, S.; Alam, M.W.; Khan, F. An Updated Review Summarizing the Anticancer Potential of Poly(Lactic- *Co* -Glycolic Acid) (<scp>PLGA</Scp>) Based Curcumin, <scp>Epigallocatechin Gallate</Scp> , and Resveratrol Nanocarriers. *Biopolymers* **2025**, *116*, doi:10.1002/bip.23637.
136. Son, H.-K.; Kim, D. Quercetin Induces Cell Cycle Arrest and Apoptosis in YD10B and YD38 Oral Squamous Cell Carcinoma Cells. *Asian Pacific Journal of Cancer Prevention* **2023**, *24*, 283–289, doi:10.31557/APJCP.2023.24.1.283.
137. Haghiac, M.; Walle, T. Quercetin Induces Necrosis and Apoptosis in SCC-9 Oral Cancer Cells. *Nutr. Cancer* **2005**, *53*, 220–231, doi:10.1207/s15327914nc5302_11.
138. Guo, X.; Sun, Z.; Chen, H.; Li, C.; Chang, A.; Zhao, H.; Ling, J.; Zhuo, X. Exploring Molecular Targets of Quercetin for the Treatment of Nicotine-Related Oral Carcinoma: A Network Pharmacology Analysis and In Vitro Study. *Food Sci. Nutr.* **2025**, *13*, doi:10.1002/fsn3.71241.
139. Sun, H.; Wang, H.; Guo, S. Quercetin as a Therapeutic Agent for Oral Cancer: Current Evidence and Future Directions. *Asia. Pac. J. Clin. Oncol.* **2025**, doi:10.1111/ajco.70046.
140. Afriza, D.; Arma, U.; Faslah, R.; Suriyah, W.H. Anticancer Potential of Quercetin on Oral Squamous Cell Carcinoma: A Scoping Review and Molecular Docking. *Eur. J. Dent.* **2025**, *19*, 015–023, doi:10.1055/s-0044-1789016.
141. Clemente-Soto, A.; Salas-Vidal, E.; Milan-Pacheco, C.; S**&#65533;**nchez-Carranza, J.; Peralta-Zaragoza, O.; Gonz**&#65533;**lez-Maya, L. Quercetin Induces G2 Phase Arrest and Apoptosis with the Activation of P53 in an E6 Expression-independent Manner in HPV-positive Human Cervical Cancer-derived Cells. *Mol. Med. Rep.* **2019**, *19*, doi:10.3892/mmr.2019.9850.
142. Zhuang, Y.; Coppock, J.D.; Haugrud, A.B.; Lee, J.H.; Messerli, S.M.; Miskimins, W.K. Dichloroacetate and Quercetin Prevent Cell Proliferation, Induce Cell Death and Slow Tumor Growth in a Mouse Model of HPV-Positive Head and Neck Cancer. *Cancers (Basel).* **2024**, *16*, 1525, doi:10.3390/cancers16081525.
143. Chen, S.-F.; Nien, S.; Wu, C.-H.; Liu, C.-L.; Chang, Y.-C.; Lin, Y.-S. Reappraisal of the Anticancer Efficacy of Quercetin in Oral Cancer Cells. *Journal of the Chinese Medical Association* **2013**, *76*, 146–152, doi:10.1016/j.jcma.2012.11.008.
144. Ma, Y.; Yao, C.; Liu, H.; Yu, F.; Lin, J.; Lu, K.; Liao, C.; Chueh, F.; Chung, J. Quercetin Induced Apoptosis of Human Oral Cancer SAS Cells through Mitochondria and Endoplasmic Reticulum Mediated Signaling Pathways. *Oncol. Lett.* **2018**, *15*, doi:10.3892/ol.2018.8584.
145. Zhao, J.; Fang, Z.; Zha, Z.; Sun, Q.; Wang, H.; Sun, M.; Qiao, B. Quercetin Inhibits Cell Viability, Migration and Invasion by Regulating MiR-16/HOXA10 Axis in Oral Cancer. *Eur. J. Pharmacol.* **2019**, *847*, 11–18, doi:10.1016/j.ejphar.2019.01.006.
146. Kim, S.R.; Lee, E.Y.; Kim, D.J.; Kim, H.J.; Park, H.R. Quercetin Inhibits Cell Survival and Metastatic Ability via the EMT-Mediated Pathway in Oral Squamous Cell Carcinoma. *Molecules* **2020**, *25*, 757, doi:10.3390/molecules25030757.
147. Das, P.; Ghosh, S.; Ashashainy, V.; Nayak, B. Augmentation of Anti-Proliferative Efficacy of Quercetin Encapsulated Chitosan Nanoparticles by Induction of Cell Death via Mitochondrial Membrane Permeabilization in Oral Cancer. *Int. J. Biol. Macromol.* **2023**, *250*, 126151, doi:10.1016/j.ijbiomac.2023.126151.
148. Li, X.; Guo, S.; Xiong, X.-K.; Peng, B.-Y.; Huang, J.-M.; Chen, M.-F.; Wang, F.-Y.; Wang, J.-N. Combination of Quercetin and Cisplatin Enhances Apoptosis in OSCC Cells by Downregulating XIAP through the NF-KB Pathway. *J. Cancer* **2019**, *10*, 4509–4521, doi:10.7150/jca.31045.
149. Yuan, Z.; Wang, H.; Hu, Z.; Huang, Y.; Yao, F.; Sun, S.; Wu, B. Quercetin Inhibits Proliferation and Drug Resistance in KB/VCR Oral Cancer Cells and Enhances Its Sensitivity to Vincristine. *Nutr. Cancer* **2015**, *67*, 126–136, doi:10.1080/01635581.2015.965334.
150. Romanova, D.; Vachálkova, A.; Čipák, L.; Ovesná, Z.; Rauko, P. Study of Antioxidant Effect of Apigenin, Luteolin and Quercetin by DNA Protective Method.

 doi:10.20944/preprints202605.1016.v1

151. Imran, M.; Aslam Gondal, T.; Atif, M.; Shahbaz, M.; Batool Qaisarani, T.; Hanif Mughal, M.; Salehi, B.; Martorell, M.; Sharifi-Rad, J. Apigenin as an Anticancer Agent. *Phytotherapy Research* **2020**, *34*, 1812–1828, doi:10.1002/ptr.6647.
152. Prakash, O.; Kumar, A.; Tiwari, S.; Bajpai, P. The Versatility of Apigenin: Especially as a Chemopreventive Agent for Cancer. *Journal of Holistic Integrative Pharmacy* **2024**, *5*, 249–256, doi:10.1016/j.jhip.2024.10.001.
153. Allemailem, K.S.; Almatroudi, A.; Alharbi, H.O.A.; AlSuhaymi, N.; Alsugoor, M.H.; Aldakheel, F.M.; Khan, A.A.; Rahmani, A.H. Apigenin: A Bioflavonoid with a Promising Role in Disease Prevention and Treatment. *Biomedicines* 2024, *12*.
154. Zhou, Y.; Yu, Y.; Lv, H.; Zhang, H.; Liang, T.; Zhou, G.; Huang, L.; Tian, Y.; Liang, W. Apigenin in Cancer Therapy: From Mechanism of Action to Nano-Therapeutic Agent. *Food and Chemical Toxicology* 2022, *168*.
155. Maggioni, D.; Garavello, W.; Rigolio, R.; Pignataro, L.; Gaini, R.; Nicolini, G. Apigenin Impairs Oral Squamous Cell Carcinoma Growth in Vitro Inducing Cell Cycle Arrest and Apoptosis. *Int. J. Oncol.* **2013**, *43*, 1675–1682, doi:10.3892/ijo.2013.2072.
156. Rath, S.; Jagadeb, M.; Bhuyan, R. Molecular Docking of Bioactive Compounds Derived from Moringa Oleifera with P53 Protein in the Apoptosis Pathway of Oral Squamous Cell Carcinoma. *Genomics Inform.* **2021**, *19*, e46, doi:10.5808/gi.21062.
157. De Marco, F.; Altieri, F.; Giuliani, S.; Falcone, I.; Falcucci, S.; Tedesco, M.; Becelli, R. A Combination of Flavonoids Suppresses Cell Proliferation and the E6 Oncogenic Pathway in Human Papillomavirus-Transformed Cells. *Pathogens* **2025**, *14*, 221, doi:10.3390/pathogens14030221.
158. Obaid A Alharbi, H.; Almatroudi, A.; Alrumaihi, F.; Fahad Alghafis, S.; Alwanian, W.M.; Rahmani, A.H. The Potential Role of Luteolin, a Flavonoid in Cancer Prevention and Treatment. *CyTA - Journal of Food* **2024**, *22*, doi:10.1080/19476337.2024.2381714.
159. Imran, M.; Rauf, A.; Abu-Izneid, T.; Nadeem, M.; Shariati, M.A.; Khan, I.A.; Imran, A.; Orhan, I.E.; Rizwan, M.; Atif, M.; et al. Luteolin, a Flavonoid, as an Anticancer Agent: A Review. *Biomedicine & Pharmacotherapy* **2019**, *112*, 108612, doi:10.1016/j.biopha.2019.108612.
160. Çetinkaya, M.; Baran, Y. Therapeutic Potential of Luteolin on Cancer. *Vaccines (Basel).* 2023, *11*.
161. Amarakoon, D.; Lee, W.-J.; Tamia, G.; Lee, S.-H. Indole-3-Carbinol: Occurrence, Health-Beneficial Properties, and Cellular/Molecular Mechanisms. *Annu. Rev. Food Sci. Technol.* **2023**, *14*, 347–366, doi:10.1146/annurev-food-060721-025531.
162. JR, W.; LY, B.; CF, C.; YC, W.; MH, T. The Dietary Phytochemical 3,3′-Diindolylmethane Induces G2/M Arrest and Apoptosis in Oral Squamous Cell Carcinoma by Modulating Akt-NF-KappaB, MAPK, and P53 Signaling. *Chem. Biol. Interact.* **2012**, *195*.
163. Srikanth, Y.; Reddy, D.H.; Anusha, V.L.; Dumala, N.; Viswanadh, M.K.; Chakravarthi, G.; Nalluri, B.N.; Yadagiri, G.; Ramakrishna, K. Unveiling the Multifaceted Pharmacological Actions of Indole-3-Carbinol and Diindolylmethane: A Comprehensive Review. *Plants* **2025**, *14*, 827, doi:10.3390/plants14050827.
164. Newfield, L.; Goldsmith, A.; Bradlow, H.L.; Auborn, K. Estrogen Metabolism and Human Papillomavirus-Induced Tumors of the Larynx: Chemo-Prophylaxis with Indole-3-Carbinol. *Anticancer Res.* **1993**, *13*.
165. Geevarghese, A. V.; Ranganathan, H. Elucidating the Potential of Phytochemicals in Targeting Various Signalling Pathways of Oral Cancer: Current Update on Their Clinical Translational Potential. *Pharmacological Research - Natural Products* **2025**, *9*, 100388, doi:10.1016/j.prenap.2025.100388.
166. MAO, C.-G.; TAO, Z.-Z.; CHEN, Z.; CHEN, C.; CHEN, S.-M.; WAN, L.-J. Indole-3-Carbinol Inhibits Nasopharyngeal Carcinoma Cell Growth in Vivo and in Vitro through Inhibition of the PI3K/Akt Pathway. *Exp. Ther. Med.* **2014**, *8*, 207–212, doi:10.3892/etm.2014.1696.
167. Baez-Gonzalez, A.S.; Carrazco-Carrillo, J.A.; Figueroa-Gonzalez, G.; Quintas-Granados, L.I.; Padilla-Benavides, T.; Reyes-Hernandez, O.D. Functional Effect of Indole-3 Carbinol in the Viability and Invasive Properties of Cultured Cancer Cells. *Biochem. Biophys. Rep.* **2023**, *35*, 101492, doi:10.1016/j.bbrep.2023.101492.
168. Acharya, A.; Das, I.; Singh, S.; Saha, T. Chemopreventive Properties of Indole-3-Carbinol, Diindolylmethane and Other Constituents of Cardamom Against Carcinogenesis. *Recent Patents on Food, Nutrition & Agriculturee* **2010**, *2*, 166–177, doi:10.2174/2212798411002020166.

 doi:10.20944/preprints202605.1016.v1

169. Katz, E.; Nisani, S.; Chamovitz, D.A. Indole-3-Carbinol: A Plant Hormone Combatting Cancer. *F1000Res.* **2018**, *7*, 689, doi:10.12688/f1000research.14127.1.
170. Williams, D.E. Indoles Derived From Glucobrassicin: Cancer Chemoprevention by Indole-3-Carbinol and 3,3′-Diindolylmethane. *Front. Nutr.* **2021**, *8*, doi:10.3389/fnut.2021.734334.
171. Díaz, L.; Bernadez-Vallejo, S. V.; Vargas-Castro, R.; Avila, E.; Gómez-Ceja, K.A.; García-Becerra, R.; Segovia-Mendoza, M.; Prado-Garcia, H.; Lara-Sotelo, G.; Camacho, J.; et al. The Phytochemical α-Mangostin Inhibits Cervical Cancer Cell Proliferation and Tumor Growth by Downregulating E6/E7-HPV Oncogenes and KCNH1 Gene Expression. *Int. J. Mol. Sci.* **2023**, *24*, doi:10.3390/ijms24033055.
172. Majdalawieh, A.F.; Terro, T.M.; Ahari, S.H.; Abu-Yousef, I.A. α-Mangostin: A Xanthone Derivative in Mangosteen with Potent Anti-Cancer Properties. *Biomolecules* **2024**, *14*, 1382, doi:10.3390/biom14111382.
173. Nittayananta, W.; Srichana, T.; Chuerduangphui, J.; Hitakomate, E.; Netsomboon, K. Formulation of 1% α-Mangostin in Orabase Gel Induces Apoptosis in Oral Squamous Cell Carcinoma. *BMC Complement. Med. Ther.* **2024**, *24*, 276, doi:10.1186/s12906-024-04450-0.
174. Tangsuksan, P.; Chuerduangphui, J.; Takahashi Yupanqui, C.; Srichana, T.; Hitakomate, E.; Pientong, C.; Ekalaksananan, T.; Nittayananta, W. Mucoadhesive Film Containing α-Mangostin Shows Potential Role in Oral Cancer Treatment. *BMC Oral Health* **2021**, *21*, 1–10, doi:10.1186/s12903-021-01845-0.
175. Sharma, U.; Sahni, P.K.; Sharma, B.; Gupta, M.; Kaur, D.; Mathkor, D.M.; Haque, S.; Khatoon, S.; Tuli, H.S.; Mishra, A.; et al. Silymarin: A Promising Modulator of Apoptosis and Survival Signaling in Cancer. *Discover Oncology* **2025**, *16*, 66, doi:10.1007/s12672-025-01800-3.
176. Won, D.-H.; Kim, L.-H.; Jang, B.; Yang, I.-H.; Kwon, H.-J.; Jin, B.; Oh, S.H.; Kang, J.-H.; Hong, S.-D.; Shin, J.-A.; et al. In Vitro and in Vivo Anti-Cancer Activity of Silymarin on Oral Cancer. *Tumor Biology* **2018**, *40*, 101042831877617, doi:10.1177/1010428318776170.
177. Fazeli, M.; Sarvazad, H.; Rahnejat, N.; Rostampour, R.; Rad, M.G.; Eskandari-Roozbahani, N. Investigation of Potential Antiviral Natural Products with an Effect on HPV18 E6 Protein by Molecular Docking Method. *Functional Foods in Health and Disease* **2021**, *11*, 586, doi:10.31989/ffhd.v11i11.840.
178. Xing, Z.; Su, A.; Mi, L.; Zhang, Y.; He, T.; Qiu, Y.; Wei, T.; Li, Z.; Zhu, J.; Wu, W. Withaferin A: A Dietary Supplement with Promising Potential as an Anti-Tumor Therapeutic for Cancer Treatment-Pharmacology and Mechanisms. *Drug Des. Devel. Ther.* 2023, *17*.
179. Panjamurthy, K.; Manoharan, S.; Balakrishnan, S.; Suresh, K.; Nirmal, M.; Senthil, N.; Alias, L. Protective Effect of Withaferin-A on Micronucleus Frequency and Detoxication Agents during Experimental Oral Carcinogenesis. *African Journal of Traditional, Complementary and Alternative Medicines* **2010**, *6*, doi:10.4314/ajtcam.v6i1.57067.
180. Shin, J.-A.; Kim, L.-H.; Ryu, M.H.; Choi, S.-Y.; Jin, B.; Lee, W.; Jung, Y.C.; Ahn, C.-H.; Ahn, M.-H.; Hong, K.-O.; et al. Withaferin A Mitigates Metastatic Traits in Human Oral Squamous Cell Carcinoma Caused by Aberrant Claudin-1 Expression. *Cell Biol. Toxicol.* **2022**, *38*, 147–165, doi:10.1007/s10565-021-09584-2.
181. Gupta, S.K.; Jadhav, S.; Gohil, D.; Panigrahi, G.Ch.; Kaushal, R.K.; Gandhi, K.; Patil, A.; Chavan, P.; Gota, V. Safety, Toxicity and Pharmacokinetic Assessment of Oral Withaferin-A in Mice. *Toxicol. Rep.* **2022**, *9*, 1204–1212, doi:10.1016/j.toxrep.2022.05.012.
182. Jahagirdar, S.; Praveen Kumar, H.; Bhat, S.S.; Poddar, A.; Chattaraj, P.K.; Ahmad, S.F.; Prasad, S.K. In Silico Evaluations of Phytochemicals from *Withania Somnifera* Exhibiting Anticancer Activity against NAD[P]H-Quinone Oxidoreductase. *Hum. Exp. Toxicol.* **2024**, *43*, doi:10.1177/09603271241291399.
183. Elkashty, O.A.; Ashry, R.; Elghanam, G.A.; Pham, H.M.; Su, X.; Stegen, C.; Tran, S.D. Broccoli Extract Improves Chemotherapeutic Drug Efficacy against Head–Neck Squamous Cell Carcinomas. *Medical Oncology* **2018**, *35*, 124, doi:10.1007/s12032-018-1186-4.
184. Iahtisham-Ul-Haq; Khan, S.; Awan, K.A.; Iqbal, M.J. Sulforaphane as a Potential Remedy against Cancer: Comprehensive Mechanistic Review. *J. Food Biochem.* **2022**, *46*, doi:10.1111/jfbc.13886.
185. Bauman, J.E.; Zang, Y.; Sen, M.; Li, C.; Wang, L.; Egner, P.A.; Fahey, J.W.; Normolle, D.P.; Grandis, J.R.; Kensler, T.W.; et al. Prevention of Carcinogen-Induced Oral Cancer by Sulforaphane. *Cancer Prevention Research* **2016**, *9*, doi:10.1158/1940-6207.CAPR-15-0290.

 doi:10.20944/preprints202605.1016.v1

186. Adtani, P.N.; Al-Bayati, S.A.A.F.; Elsayed, W.S. Sulforaphane from Brassica Oleracea Induces Apoptosis in Oral Squamous Carcinoma Cells via P53 Activation and Mitochondrial Membrane Potential Dysfunction. *Pharmaceuticals* **2025**, *18*, doi:10.3390/ph18030393.
187. Wang, X.; He, X.; Zang, X.; Hu, N.; Jin, J.; Yang, S. Lycopene: A Promising Adjuvant to Photodynamic Therapy in Oral Cancer. *Lasers Med. Sci.* **2025**, *40*, 252, doi:10.1007/s10103-025-04504-w.
188. Umapathy, V.R.; MN, P.; S, Bhuminathan.; Jaber, A.A. Therapeutic Application of Lycopene in Preventing Oral Diseases- A Review. *Res. J. Pharm. Technol.* **2024**, *17*, 1393–1397, doi:10.52711/0974-360X.2024.00220.
189. Lu, R.; Dan, H.; Wu, R.; Meng, W.; Liu, N.; Jin, X.; Zhou, M.; Zeng, X.; Zhou, G.; Chen, Q. Lycopene: Features and Potential Significance in the Oral Cancer and Precancerous Lesions. *Journal of Oral Pathology & Medicine* **2011**, *40*, 361–368, doi:10.1111/j.1600-0714.2010.00991.x.
190. Offord, E.A.; Gautier, J.-C.; Avanti, O.; Scaletta, C.; Runge, F.; Krämer, K.; Applegate, L.A. Photoprotective Potential of Lycopene, β-Carotene, Vitamin E, Vitamin C and Carnosic Acid in UVA-Irradiated Human Skin Fibroblasts. *Free Radic. Biol. Med.* **2002**, *32*, 1293–1303, doi:10.1016/S0891-5849(02)00831-6.
191. Livny, O.; Reifen, R.; Madar, Z.; Schwartz, B.; Kaplan, I.; Polak-Charcon, S. Lycopene Inhibits Proliferation and Enhances Gap-Junction Communication of KB-1 Human Oral Tumor Cells. *J. Nutr.* **2002**, *132*, 3754–3759, doi:10.1093/jn/132.12.3754.
192. Rethinam, S. In Vitro Evaluation of Chitosan-Stabilized Lycopene Nanoparticles for Antioxidant and Anticancer Drug Delivery. *J. Maxillofac. Oral Surg.* **2025**, doi:10.1007/s12663-025-02725-8.
193. Beier, V.; Wink, M.; Samstag, Y. Plant-Derived Immunomodulators in Cancer: Balancing Immune Activation and Suppression within the Tumor Microenvironment. *Adv. Biol. Regul.* **2025**, doi:10.1016/j.jbior.2025.101132.
194. Taneja, N.; Alam, A.; Patnaik, R.S.; Taneja, T.; Gupta, S.; K, S.M. Understanding Nanotechnology in the Treatment of Oral Cancer: A Comprehensive Review. *Crit. Rev. Ther. Drug Carrier Syst.* **2021**, *38*, 1–48, doi:10.1615/CritRevTherDrugCarrierSyst.2021036437.
195. Dehghan, M.H.; Siddiqui, A.A.M. Drug Delivery Systems for Oral Cancer Treatment: A Patent Perspective. *Oral Oncology Reports* **2024**, *9*, 100226, doi:10.1016/j.oor.2024.100226.
196. Senevirathna, K.; Jayawickrama, S.M.; Jayasinghe, Y.A.; Prabani, K.I.P.; Akshala, K.; Pradeep, R.G.G.R.; Damayanthi, H.D.W.T.; Hettiarachchi, K.; Dorji, T.; Lucero-Prisno, D.E.; et al. Nanoplatforms: The Future of Oral Cancer Treatment. *Health Sci. Rep.* **2023**, *6*, doi:10.1002/hsr2.1471.
197. Nair, K.L.; Thulasidasan, A.K.T.; Deepa, G.; Anto, R.J.; Kumar, G.S.V. Purely Aqueous PLGA Nanoparticulate Formulations of Curcumin Exhibit Enhanced Anticancer Activity with Dependence on the Combination of the Carrier. *Int. J. Pharm.* **2012**, *425*, 44–52, doi:10.1016/j.ijpharm.2012.01.003.
198. Ashfaq, R.; Rasul, A.; Asghar, S.; Kovács, A.; Berkó, S.; Budai-Szűcs, M. Lipid Nanoparticles: An Effective Tool to Improve the Bioavailability of Nutraceuticals. *Int. J. Mol. Sci.* **2023**, *24*, 15764, doi:10.3390/ijms242115764.
199. Stoeva-Grigorova, S.; Ivanova, N.; Sotirova, Y.; Radeva-Ilieva, M.; Hvarchanova, N.; Georgiev, K. Lipid-Based Nanotechnologies for Delivery of Green Tea Catechins: Advances, Challenges, and Therapeutic Potential. *Pharmaceutics* **2025**, *17*, 985, doi:10.3390/pharmaceutics17080985.
200. Jin, Z.; Al Amili, M.; Guo, S. Tumor Microenvironment-Responsive Drug Delivery Based on Polymeric Micelles for Precision Cancer Therapy: Strategies and Prospects. *Biomedicines* **2024**, *12*, 417, doi:10.3390/biomedicines12020417.
201. Ingrungruengluet, P.; Wang, D.; Li, X.; Yang, C.; Waiprib, Y.; Li, C. Preparation and Primary Bioactivity Evaluation of Novel Water-Soluble Curcumin-Loaded Polymeric Micelles Fabricated with Chitooligosaccharides and Pluronic F-68. *Pharmaceutics* **2023**, *15*, 2497, doi:10.3390/pharmaceutics15102497.
202. Farhoudi, L.; Kesharwani, P.; Majeed, M.; Johnston, T.P.; Sahebkar, A. Polymeric Nanomicelles of Curcumin: Potential Applications in Cancer. *Int. J. Pharm.* **2022**, *617*, 121622, doi:10.1016/j.ijpharm.2022.121622.
203. İspir, E.; İnal, M.; Gün Gök, Z.; Yiğitoğlu, M. Synthesis, Characterization and in Vitro Release Analysis of Pluronic F127 Copolymer Micelles Containing Quercetin as a Hydrophobic Drug. *Polymer Bulletin* **2024**, *81*, doi:10.1007/s00289-023-05040-9.

 doi:10.20944/preprints202605.1016.v1

204. Patra, A.; Satpathy, S.; Shenoy, A.K.; Bush, J.A.; Kazi, M.; Hussain, M.D. Formulation and Evaluation of Mixed Polymeric Micelles of Quercetin for Treatment of Breast, Ovarian, and Multidrug Resistant Cancers. *Int. J. Nanomedicine* **2018**, *13*, doi:10.2147/IJN.S153094.
205. Sunoqrot, S.; Alsadi, A.; Tarawneh, O.; Hamed, R. Polymer Type and Molecular Weight Dictate the Encapsulation Efficiency and Release of Quercetin from Polymeric Micelles. *Colloid Polym. Sci.* **2017**, *295*, doi:10.1007/s00396-017-4183-9.
206. Zhao, L.; Shi, Y.; Zou, S.; Sun, M.; Li, N.; Zhai, G. Formulation and In Vitro Evaluation of Quercetin Loaded Polymeric Micelles Composed of Pluronic P123 and D-a-Tocopheryl Polyethylene Glycol Succinates. *J. Biomed. Nanotechnol.* **2011**, *7*, doi:10.1166/jbn.2011.1298.
207. Soltantabar, P.; Calubaquib, E.L.; Mostafavi, E.; Biewer, M.C.; Stefan, M.C. Enhancement of Loading Efficiency by Coloading of Doxorubicin and Quercetin in Thermoresponsive Polymeric Micelles. *Biomacromolecules* **2020**, *21*, doi:10.1021/acs.biomac.9b01742.
208. Loutfy, S.A.; Abdel-Salam, A.I.; Moatasim, Y.; Gomaa, M.R.; Abdel Fattah, N.F.; Emam, M.H.; Ali, F.; ElShehaby, H.A.; Ragab, E.A.; Alam El-Din, H.M.; et al. Antiviral Activity of Chitosan Nanoparticles Encapsulating Silymarin (Sil–CNPs) against SARS-CoV-2 (in Silico and in Vitro Study). *RSC Adv.* **2022**, *12*, 15775–15786, doi:10.1039/D2RA00905F.
209. Ubaidulla, U.; Sinha, P.; Sangavi, T.; Rathnam, G. Development of Silymarin Entrapped Chitosan Phthalate Nanoparticles for Targeting Colon Cancer. *Journal of Natural Remedies* **2022**, *22*, 659–671, doi:10.18311/jnr/2022/29816.
210. Lawson, M.K. Improvement of Therapeutic Value of Quercetin with Chitosan Nanoparticle Delivery Systems and Potential Applications. *Int. J. Mol. Sci.* 2023, *24*.
211. Liu, H.; Huang, Y.; Huang, M.; Huang, Z.; Wang, Q.; Qing, L.; Li, L.; Xu, S.; Jia, B. Current Status, Opportunities, and Challenges of Exosomes in Oral Cancer Diagnosis and Treatment. *Int. J. Nanomedicine* **2022**, *Volume 17*, 2679–2705, doi:10.2147/IJN.S365594.
212. Wang, J.; Jing, J.; Zhou, C.; Fan, Y. Emerging Roles of Exosomes in Oral Diseases Progression. *Int. J. Oral Sci.* **2024**, *16*, 4, doi:10.1038/s41368-023-00274-9.
213. Mousavi, S.M.; Abbasifard, M.; Abbasi, R.; Tivay, S.; Hosseini, H.; Taghipoor, M.; Kalashgrani, M.Y.; Aljabri, M.D.; Rahman, M.M.; Chiang, W.-H.; et al. Smart Nano Exosomes as Precision Drug Carriers: A New Frontier in Targeted Treatment of Oral Cancer. *Int. J. Pharm.* **2025**, *682*, 125923, doi:10.1016/j.ijpharm.2025.125923.
214. Zhang, Q.; Xiao, Q.; Yin, H.; Xia, C.; Pu, Y.; He, Z.; Hu, Q.; Wang, J.; Wang, Y. Milk-Exosome Based PH/Light Sensitive Drug System to Enhance Anticancer Activity against Oral Squamous Cell Carcinoma. *RSC Adv.* **2020**, *10*, 28314–28323, doi:10.1039/D0RA05630H.
215. Tsao, A.S.; Liu, D.; Martin, J.; Tang, X.; Lee, J.J.; El-Naggar, A.K.; Wistuba, I.; Culotta, K.S.; Mao, L.; Gillenwater, A.; et al. Phase II Randomized, Placebo-Controlled Trial of Green Tea Extract in Patients with High-Risk Oral Premalignant Lesions. *Cancer Prevention Research* **2009**, *2*, 931–941, doi:10.1158/1940-6207.CAPR-09-0121.
216. &NA; Sinecatechins 15% Ointment [Veregen; Bradley Pharmaceuticals] Has Been Launched in the US for the Treatment of External Genital and Perianal Warts. *Inpharma Weekly* **2008**, *NA;*, 19, doi:10.2165/00128413-200816190-00048.
217. Doan, H.Q.; Nguyen, H.P.; Rady, P.; Tyring, S.K. Expression Patterns of Immune-Associated Genes in External Genital and Perianal Warts Treated with Sinecatechins. *Viral Immunol.* **2015**, *28*, 236–240, doi:10.1089/vim.2014.0144.
218. Tatti, S.; Swinehart, J.M.; Thielert, C.; Tawfik, H.; Mescheder, A.; Beutner, K.R. Sinecatechins, a Defined Green Tea Extract, in the Treatment of External Anogenital Warts. *Obstetrics & Gynecology* **2008**, *111*, 1371–1379, doi:10.1097/AOG.0b013e3181719b60.
219. Yap, J.; Slade, D.; Fox, R.; Kaur, B.; Hughes, A.; Ganesan, R.; Velangi, S.; Luesley, D. P194 Epivin: A Phase II Double-Blind Randomised Control Trial Investigating the Use of Epigallocatechin-3-Gallate (Veregen®, Catephen®) vs Placebo in the Treatment of Usual-Typed Vulval Intraepithelial Neoplasia. *International Journal of Gynecological Cancer* **2019**, *29*, A173, doi:10.1136/ijgc-2019-ESGO.251.

 doi:10.20944/preprints202605.1016.v1

220. Elyasi, S.; Hosseini, S.; Razaei, S.; Karimi, G. 939P Evaluation of Oral Nano-Silymarin Formulation Efficacy on Prevention of Radiotherapy Induced Mucositis: A Randomized, Double-Blinded, Placebo-Controlled Clinical Trial. *Annals of Oncology* **2020**, *31*, S672, doi:10.1016/j.annonc.2020.08.1054.
221. Hosseini, S.; Rezaei, S.; Moghaddam, M.R.N.; Elyasi, S.; Karimi, G. Evaluation of Oral Nano-Silymarin Formulation Efficacy on Prevention of Radiotherapy Induced Mucositis: A Randomized, Double-Blinded, Placebo-Controlled Clinical Trial. *PharmaNutrition* **2021**, *15*, 100253, doi:10.1016/j.phanu.2021.100253.
222. Erfanian, S.S.; Ansari, H.; Javanmard, S.H.; Amini, Z.; Hajigholami, A. The Hepatorenal Protective Effects of Silymarin in Cancer Patients Receiving Chemotherapy: A Randomized, Placebo-Controlled Trial. *BMC Complement. Med. Ther.* **2024**, *24*, 329, doi:10.1186/s12906-024-04627-7.
223. Rosen, C.A.; Bryson, P.C. Indole-3-Carbinol for Recurrent Respiratory Papillomatosis: Long-Term Results. *Journal of Voice* **2004**, *18*, 248–253, doi:10.1016/j.jvoice.2003.05.005.
224. Bobrytska, V.V. Therapy Optimization Dysplastic HPV-Associated Processes. *HEALTH OF WOMAN* **2016**, *8*, 29–32, doi:10.15574/HW.2016.114.29.
225. Trusov, N. V; Guseva, G. V; Aksenov, I. V; Avren'eva, L.I.; Kravchenko, L. V; Tutelyan, V.A. Effects of Combined Treatment with Resveratrol and Indole-3-Carbinol. *Eksperimental'noi Biologii i Meditsiny* **2010**, *149*, 174–179.
226. Singh, A.K.; Sharma, N.K.; Mishra, N.; Mahajan, A.; Krishnan, A.; Rajpoot, R.; Kumar, J.A.; Pandey, A. Effects of Curcumin on Oral Cancer at Molecular Level: A Systematic Review. *Natl. J. Maxillofac. Surg.* **2023**, *14*, 9–15, doi:10.4103/njms.njms_29_22.
227. Ferreira, S.B. de S.; Slowik, K.M.; Castro Hoshino, L.V. de; Baesso, M.L.; Murdoch, C.; Colley, H.E.; Bruschi, M.L. Mucoadhesive Emulgel Systems Containing Curcumin for Oral Squamous Cell Carcinoma Treatment: From Pre-Formulation to Cytotoxicity in Tissue-Engineering Oral Mucosa. *European Journal of Pharmaceutical Sciences* **2020**, *151*, doi:10.1016/J.EJPS.2020.105372.
228. de Waure, C.; Bertola, C.; Baccarini, G.; Chiavarini, M.; Mancuso, C. Exploring the Contribution of Curcumin to Cancer Therapy: A Systematic Review of Randomized Controlled Trials. *Pharmaceutics* **2023**, *15*, 1275, doi:10.3390/pharmaceutics15041275.
229. Chen, A.L.; Hsu, C.H.; Lin, J.K.; Hsu, M.M.; Ho, Y.F.; She, T.S.; Ko, J.Y.; Lin, J.T.; Lin, B.R.; Wu, M.S.; et al. Phase I Clinical Trial of Curcumin, a Chemopreventive Agent, in Patients with High-Risk or Pre-Malignant Lesions. *Anticancer Res.* **2001**, *21*.
230. Bhatia, N. Overview of HPV-Related Dermatoses and Applications of Sinecatechins Ointment. *Curr. Dermatol. Rep.* **2012**, *1*, 161–167, doi:10.1007/s13671-012-0027-5.
231. EUCTR2013-003107-19-GB A Trial to Investigate the Use of Veregen Ointment in the Treatment of Vulval Intraepithelial Neoplasia, a Severe Skin Disorder That May Lead to Vulval Cancer. *https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2013-003107-19-GB* **2014**.
232. de Vries, H.J.C.; Soltanipoor, M.; Kezic, S.; Vergunst, C.E. Sinecatechins Ointment 10% (Veregen®) for Genital Warts: Percutaneous Penetration of Epigallocatechin Gallate Concentrations in the Stratum Corneum Collected by Adhesive Tape Stripping Method. *Journal of the European Academy of Dermatology and Venereology* **2018**, *32*, doi:10.1111/jdv.14933.
233. Zhu, J.; Gillissen, B.; Dang Tran, D.L.; May, S.; Ulrich, C.; Stockfleth, E.; Eberle, J. Inhibition of Cell Proliferation and Cell Viability by Sinecatechins in Cutaneous SCC Cells Is Related to an Imbalance of ROS and Loss of Mitochondrial Membrane Potential. *Antioxidants* **2022**, *11*, 1416, doi:10.3390/antiox11071416.
234. Cheng, C.-W.; Shieh, P.-C.; Lin, Y.-C.; Chen, Y.-J.; Lin, Y.-H.; Kuo, D.-H.; Liu, J.-Y.; Kao, J.-Y.; Kao, M.-C.; Way, T.-D. Indoleamine 2,3-Dioxygenase, an Immunomodulatory Protein, Is Suppressed by (−)-Epigallocatechin-3-Gallate via Blocking of γ-Interferon-Induced JAK-PKC-δ-STAT1 Signaling in Human Oral Cancer Cells. *J. Agric. Food Chem.* **2010**, *58*, 887–894, doi:10.1021/jf903377e.
235. Zhu, W.; Mei, H.; Jia, L.; Zhao, H.; Li, X.; Meng, X.; Zhao, X.; Xing, L.; Yu, J. Epigallocatechin-3-Gallate Mouthwash Protects Mucosa from Radiation-Induced Mucositis in Head and Neck Cancer Patients: A Prospective, Non-Randomised, Phase 1 Trial. *Invest. New Drugs* **2020**, *38*, 1129–1136, doi:10.1007/s10637-019-00871-8.
236. Peng, X.; McClements, D.J.; Liu, X.; Liu, F. EGCG-Based Nanoparticles: Synthesis, Properties, and Applications. *Crit. Rev. Food Sci. Nutr.* **2025**, *65*, 2177–2198, doi:10.1080/10408398.2024.2328184.

 doi:10.20944/preprints202605.1016.v1

237. Yoshimura, H.; Yoshida, H.; Matsuda, S.; Ryoke, T.; Ohta, K.; Ohmori, M.; Yamamoto, S.; Kiyoshima, T.; Kobayashi, M.; Sano, K. The Therapeutic Potential of Epigallocatechin-3-gallate against Human Oral Squamous Cell Carcinoma through Inhibition of Cell Proliferation and Induction of Apoptosis: In﷿vitro and In﷿vivo Murine Xenograft Study. *Mol. Med. Rep.* **2019**, *20*, doi:10.3892/mmr.2019.10331.
238. Kato, K.; Long, N.K.; Makita, H.; Toida, M.; Yamashita, T.; Hatakeyama, D.; Hara, A.; Mori, H.; Shibata, T. Effects of Green Tea Polyphenol on Methylation Status of RECK Gene and Cancer Cell Invasion in Oral Squamous Cell Carcinoma Cells. *Br. J. Cancer* **2008**, *99*, 647–654, doi:10.1038/sj.bjc.6604521.
239. Jing, F.; Zhu, L.; Bai, J.; Cai, X.; Zhou, X.; Zhang, J.; Zhang, H.; Li, T. Molecular Mechanisms Underlying the Epigallocatechin-3-Gallate-Mediated Inhibition of Oral Squamous Cell Carcinogenesis. *Arch. Oral Biol.* **2023**, *153*, 105740, doi:10.1016/j.archoralbio.2023.105740.
240. Henning, S.M.; Wang, P.; Carpenter, C.L.; Heber, D. Epigenetic Effects of Green Tea Polyphenols in Cancer. *Epigenomics* **2013**, *5*, 729–741, doi:10.2217/epi.13.57.
241. Sun, Z.; Guo, X.; Li, C.; Ling, J.; Chang, A.; Zhao, H.; Zhuo, X. Exploring the Therapeutic Mechanisms of Resveratrol for Treating Arecoline-induced Malignant Transformation in Oral Epithelial Cells: Insights into Hub Targets. *J. Sci. Food Agric.* **2024**, *104*, 8290–8305, doi:10.1002/jsfa.13664.
242. Pradhan, R.; Paul, S.; Das, B.; Sinha, S.; Dash, S.R.; Mandal, M.; Kundu, C.N. Resveratrol Nanoparticle Attenuates Metastasis and Angiogenesis by Deregulating Inflammatory Cytokines through Inhibition of CAFs in Oral Cancer by CXCL-12/IL-6-Dependent Pathway. *J. Nutr. Biochem.* **2023**, *113*, 109257, doi:10.1016/j.jnutbio.2022.109257.
243. Peñalva, R.; Morales, J.; González-Navarro, C.J.; Larrañeta, E.; Quincoces, G.; Peñuelas, I.; Irache, J.M. Increased Oral Bioavailability of Resveratrol by Its Encapsulation in Casein Nanoparticles. *Int. J. Mol. Sci.* **2018**, *19*, 2816, doi:10.3390/ijms19092816.
244. Sharifi-Rad, J.; Quispe, C.; Mukazhanova, Z.; Knut, E.; Turgumbayeva, A.; Kipchakbayeva, A.; Seitimova, G.; Mahomoodally, M.F.; Lobine, D.; Koay, A.; et al. Resveratrol-Based Nanoformulations as an Emerging Therapeutic Strategy for Cancer. *Front. Mol. Biosci.* **2021**, *8*, doi:10.3389/fmolb.2021.649395.
245. Pradhan, R.; Paul, S.; Acharya, S.S.; Sinha, S.; Dash, S.R.; Kundu, C.N. Nano Formulated Resveratrol Inhibits PD-L1 in Oral Cancer Cells by Deregulating the Association between Tumor Associated Macrophages and Cancer Associated Fibroblasts through IL-6/JAK2/STAT3 Signaling Axis. *J. Nutr. Biochem.* **2024**, *125*, 109568, doi:10.1016/j.jnutbio.2024.109568.
246. Pradhan, R.; Chatterjee, S.; Hembram, K.C.; Sethy, C.; Mandal, M.; Kundu, C.N. Nano Formulated Resveratrol Inhibits Metastasis and Angiogenesis by Reducing Inflammatory Cytokines in Oral Cancer Cells by Targeting Tumor Associated Macrophages. *J. Nutr. Biochem.* **2021**, *92*, 108624, doi:10.1016/j.jnutbio.2021.108624.
247. Kim, S.-H.; Kim, H.-J.; Lee, M.-H.; Yu, S.-K.; Kim, C.S.; Kook, J.-K.; Chun, H.S.; Park, E.; Lee, S.-Y.; Kim, S.G.; et al. Resveratrol Induces Apoptosis of KB Human Oral Cancer Cells. *J. Korean Soc. Appl. Biol. Chem.* **2011**, *54*, 966–971, doi:10.1007/BF03253187.
248. Bundela, S.; Sharma, A.; Bisen, P.S. Potential Compounds for Oral Cancer Treatment: Resveratrol, Nimbolide, Lovastatin, Bortezomib, Vorinostat, Berberine, Pterostilbene, Deguelin, Andrographolide, and Colchicine. *PLoS One* **2015**, *10*, e0141719, doi:10.1371/journal.pone.0141719.
249. Lin, F.; Hsieh, Y.; Yang, S.; Chen, C.; Tang, C.; Chou, M.; Chuang, Y.; Lin, C.; Chen, M. Resveratrol Suppresses <scp>TPA</Scp> -induced Matrix Metalloproteinase-9 Expression through the Inhibition of <scp>MAPK</Scp> Pathways in Oral Cancer Cells. *Journal of Oral Pathology & Medicine* **2015**, *44*, 699–706, doi:10.1111/jop.12288.
250. Chang, W.; Tsai, C.; Yang, J.; Hsu, Y.; Shih, L.; Chiu, H.; Bau, D.; Tsai, F. Resveratrol Inhibited the Metastatic Behaviors of Cisplatin-resistant Human Oral Cancer Cells via Phosphorylation of ERK/P-38 and Suppression of MMP-2/9. *J. Food Biochem.* **2021**, *45*, doi:10.1111/jfbc.13666.
251. Chang, C.-H.; Lee, C.-Y.; Lu, C.-C.; Tsai, F.-J.; Hsu, Y.-M.; Tsao, J.-W.; Juan, Y.-N.; Chiu, H.-Y.; Yang, J.-S.; Wang, C.-C. Resveratrol-Induced Autophagy and Apoptosis in Cisplatin-Resistant Human Oral Cancer CAR Cells: A Key Role of AMPK and Akt/MTOR Signaling. *Int. J. Oncol.* **2017**, *50*, 873–882, doi:10.3892/ijo.2017.3866.

 doi:10.20944/preprints202605.1016.v1

252. Almeida, T.C.; da Silva, G.N.; de Souza, D.V.; de Moraes Malinverni, A.C.; Aguiar, O.; Estadella, D.; Ribeiro, D.A. Resveratrol Effects in Oral Cancer Cells: A Comprehensive Review. *Medical Oncology* **2021**, *38*, 97, doi:10.1007/s12032-021-01548-0.
253. de Jesús Valle, M.J.; Rondon Mujica, A.M.; Zarzuelo Castañeda, A.; Coutinho, P.; de Abreu Duarte, A.C.; Sánchez Navarro, A. Resveratrol Liposomes in Buccal Formulations, an Approach to Overcome Drawbacks Limiting the Application of the Phytoactive Molecule for Chemoprevention and Treatment of Oral Cancer. *J. Drug Deliv. Sci. Technol.* **2024**, *98*, 105910, doi:10.1016/j.jddst.2024.105910.
254. Mukherjee, S.; Baidoo, J.; Sampat, S.; Mancuso, A.; David, L.; Cohen, L.; Zhou, S.; Banerjee, P. Liposomal TriCurin, A Synergistic Combination of Curcumin, Epicatechin Gallate and Resveratrol, Repolarizes Tumor-Associated Microglia/Macrophages, and Eliminates Glioblastoma (GBM) and GBM Stem Cells. *Molecules* **2018**, *23*, 201, doi:10.3390/molecules23010201.
255. Sehercehajic, E.; Hasanefendic, B.; Pasic, A.; Smajic, E. Alchemilla Vulgaris Compounds as Inhibitors of HPV 16 E6 Oncoprotein: Quercetin with Promising in Silico Potential. *Materia Socio Medica* **2025**, *37*, 184, doi:10.5455/msm.2025.37.184-190.
256. Saadh, M.J.; Ahmed, H.H.; Chandra, M.; Al-Hussainy, A.F.; Hamid, J.A.; Mishra, A.; Taher, W.M.; Alwan, M.; Jawad, M.J.; Al-Nuaimi, A.M.A.; et al. Therapeutic Effects of Quercetin in Oral Cancer Therapy: A Systematic Review of Preclinical Evidence Focused on Oxidative Damage, Apoptosis and Anti-Metastasis. *Cancer Cell Int.* **2025**, *25*, 66, doi:10.1186/s12935-025-03694-1.
257. Li, N.; Wang, J. Quercetin Induces Cytotoxicity and Apoptosis, Reduces Metastasis and Drug Resistance in Oral Cancer Cells. *Turkish Journal of Biochemistry* **2024**, *49*, 148–156, doi:10.1515/tjb-2023-0003.
258. Dong, H.; Li, M.; Chen, H.; Tian, L.; Wei, W.; Wang, S.; Cheng, G.; Liu, S. Using Network Pharmacological Analysis and Molecular Docking to Investigate the Mechanism of Action of Quercetin's Suppression of Oral Cancer. *J. Cancer Res. Clin. Oncol.* **2023**, *149*, 15055–15067, doi:10.1007/s00432-023-05290-0.
259. Tubtimsri, S.; Chuenbarn, T.; Manmuan, S. Quercetin Triggers Cell Apoptosis-Associated ROS-Mediated Cell Death and Induces S and G2/M-Phase Cell Cycle Arrest in KON Oral Cancer Cells. *BMC Complement. Med. Ther.* **2025**, *25*, 34, doi:10.1186/s12906-025-04782-5.
260. Huang, C.Y.; Chan, C.Y.; Chou, I.T.; Lien, C.H.; Hung, H.C.; Lee, M.F. Quercetin Induces Growth Arrest through Activation of FOXO1 Transcription Factor in EGFR-Overexpressing Oral Cancer Cells. *Journal of Nutritional Biochemistry* **2013**, *24*, doi:10.1016/j.jnutbio.2013.01.010.
261. Singh, A.A.; Patil, M.P.; Kang, M.J.; Niyonizigiye, I.; Kim, G. Do Biomedical Application of Indole-3-Carbinol: A Mini-Review. *Phytochem. Lett.* 2021, *41*.
262. Weng, J.-R.; Tsai, C.-H.; Kulp, S.K.; Chen, C.-S. Indole-3-Carbinol as a Chemopreventive and Anti-Cancer Agent. *Cancer Lett.* **2008**, *262*, 153–163, doi:10.1016/j.canlet.2008.01.033.
263. Bell, M.C.; Crowley-Nowick, P.; Bradlow, H.L.; Sepkovic, D.W.; Schmidt-Grimminger, D.; Howell, P.; Mayeaux, E.J.; Tucker, A.; Turbat-Herrera, E.A.; Mathis, J.M. Placebo-Controlled Trial of Indole-3-Carbinol in the Treatment of CIN. *Gynecol. Oncol.* **2000**, *78*, 123–129, doi:10.1006/gyno.2000.5847.
264. Gusakov, K.I.; Nazarova, N.M.; Abakarova, P.R.; Tararykova, A.A.; Ivanov, I.A. Antiproliferative Effects of Resveratrol and Indole-3-Carbinol in HPV-Associated Diseases Prevention. *Meditsinskiy sovet = Medical Council* **2022**, *2022*, 151–159, doi:10.21518/2079-701X-2022-16-16-151-159.
265. Enkova, E. V.; Khoperskaya, O. V.; Shamarin, S. V.; Enkova, V. V.; Aseev, A. V. Evidence-Based Medicine: Indole-3-Carbinol and Resveratrol in Human Papillomavirus-Associated Conditions. *Meditsinskiy sovet = Medical Council* **2024**, *18*, 74–81, doi:10.21518/ms2024-398.
266. Majdalawieh, A.F.; Khatib, B.K.; Terro, T.M. α-Mangostin Is a Xanthone Derivative from Mangosteen with Potent Immunomodulatory and Anti-Inflammatory Properties. *Biomolecules* 2025, *15*.
267. Rafi Shaik, M.; Ramasamy, M.; Jain, D.; Muthu, K.; Manivannan, C.; Althaf Hussain, S.; Deepak, P.; Thiyagarajulu, N.; Guru, A.; Perianaika Matharasi Antonyraj, A.; et al. Dual Action of Nanostructured α-Mangostin-Copper Oxide Complexes Against Dental Pathogen Biofilms and Oral Cancer via Apoptosis Gene Modulation. *Chem. Biodivers.* **2025**, *22*, doi:10.1002/cbdv.202401961.
268. Abdullah, M.Z.; Munirah Bakar, L.; Jauhari, S.; Ichwan, A.; Othman, N.; Taher, M. Molecular Docking Study of Naturally Derived β-Mangostin with Antiapoptotic Bcl-2 Proteins Toward Oral Cancer Treatment ARTICLE HISTORY ABSTRACT. *ESTEEM Academic Journal* **2022**, *18*.

 doi:10.20944/preprints202605.1016.v1

269. IRCT2015050622132N1 Evaluation of Silymarin Effects in Prevention and Treatment of Mucositis Induced by Radiotherapy of Head and Neck. *http://www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT2015050622132N1* **2015**.
270. Elyasi, S.; Hosseini, S.; Niazi Moghadam, M.R.; Aledavood, S.A.; Karimi, G. Effect of Oral Silymarin Administration on Prevention of Radiotherapy Induced Mucositis: A Randomized, Double-Blinded, Placebo-Controlled Clinical Trial. *Phytotherapy Research* **2016**, *30*, doi:10.1002/ptr.5704.
271. Hosseini, S.; Elyasi, S.; Niazi Moghadam, M.R.; Aledavood, S.A.; Karimi, G. 371P Effect of Oral Silymarin Administration on Prevention of Radiotherapy Induced Mucositis: A Randomized, Double-Blinded, Placebo-Controlled Clinical Trial. *Annals of Oncology* **2016**, *27*, doi:10.1093/annonc/mdw587.013.
272. ZHANG, Y.; CALLAWAY, E.C. High Cellular Accumulation of Sulphoraphane, a Dietary Anticarcinogen, Is Followed by Rapid Transporter-Mediated Export as a Glutathione Conjugate. *Biochemical Journal* **2002**, *364*, 301–307, doi:10.1042/bj3640301.
273. Shan, Y.; Lin, N.; Yang, X.; Tan, J.; Zhao, R.; Dong, S.; Wang, S. Sulphoraphane Inhibited the Expressions of Intercellular Adhesion Molecule-1 and Vascular Cell Adhesion Molecule-1 through MyD88-Dependent Toll-like Receptor-4 Pathway in Cultured Endothelial Cells. *Nutrition, Metabolism and Cardiovascular Diseases* **2012**, *22*, 215–222, doi:10.1016/j.numecd.2010.06.013.
274. Sarkar, R.; Mukherjee, S.; Biswas, J.; Roy, M. Sulphoraphane, a Naturally Occurring Isothiocyanate Induces Apoptosis in Breast Cancer Cells by Targeting Heat Shock Proteins. *Biochem. Biophys. Res. Commun.* **2012**, *427*, 80–85, doi:10.1016/j.bbrc.2012.09.006.
275. Gunder, L.C.; Blaine-Sauer, S.; Johnson, H.R.; Shin, M.-K.; Auyeung, A.S.; Zhang, W.; Leverson, G.E.; Ward-Shaw, E.T.; King, R.E.; McGregor, S.M.; et al. Efficacy of Topically Administered Dihydroartemisinin in Treating Papillomavirus-Induced Anogenital Dysplasia in Preclinical Mouse Models. *Viruses* **2022**, *14*, 1632, doi:10.3390/v14081632.
276. Goodrich, S.K.; Schlegel, C.R.; Wang, G.; Belinson, J.L. Use of Artemisinin and Its Derivatives to Treat HPV-Infected/Transformed Cells and Cervical Cancer: A Review. *Future Oncology* **2014**, *10*, 647–654, doi:10.2217/fon.13.228.
277. Mondal, A.; Chatterji, U. Artemisinin Represses Telomerase Subunits and Induces Apoptosis in HPV-39 Infected Human Cervical Cancer Cells. *J. Cell. Biochem.* **2015**, *116*, 1968–1981, doi:10.1002/jcb.25152.
278. Tsamesidis, I.; Papadimitriou-Tsantarliotou, A.; Christodoulou, A.; Amanatidou, D.; Avgeros, C.; Stalika, E.; Bousnaki, M.; Michailidou, G.; Beketova, A.; Eleftheriou, P.; et al. Investigating the Cytotoxic Effects of Artemisia Absinthium Extract on Oral Carcinoma Cell Line. *Biomedicines* **2024**, *12*, 2674, doi:10.3390/biomedicines12122674.
279. Tilaoui, M.; Mouse, H.A.; Jaafari, A.; Zyad, A. Differential Effect of Artemisinin Against Cancer Cell Lines. *Nat. Prod. Bioprospect.* **2014**, *4*, 189–196, doi:10.1007/s13659-014-0024-4.
280. Zheng, P.; Shi, S.; Wang, Z.; Ji, Y.; Luo, H.; Ouyang, H.; Shi, Y.; Xing, Y.; Li, D.; Sun, J.; et al. Dihydroartemisinin Inhibits Oral Cancer Cell Migration, Associated with Impairment of Cytoskeleton Organization and Cell Membrane Fluidity. *Food Biosci.* **2025**, *68*, 106648, doi:10.1016/j.fbio.2025.106648.
281. Disbrow, G.L.; Baege, A.C.; Kierpiec, K.A.; Yuan, H.; Centeno, J.A.; Thibodeaux, C.A.; Hartmann, D.; Schlegel, R. Dihydroartemisinin Is Cytotoxic to Papillomavirus-Expressing Epithelial Cells In Vitro and In Vivo. *Cancer Res.* **2005**, *65*, 10854–10861, doi:10.1158/0008-5472.CAN-05-1216.
282. Lança, M.L. de A.; Conceição, N.S.C. da; Malta, I.S.; Meneses, D.O.; Almeida, L.Y.; Kaminagakura, E. Chemopreventive Potential of Artemisinin and Rubus Occidentalis in the Progression of Oral Leukoplakia to Oral Cancer: A Preclinical Murine Study. *Int. J. Mol. Sci.* **2025**, *26*, 8120, doi:10.3390/ijms26178120.
283. Anggradita, L.D.; Kim, J.H.; Kim, M.K.; Son, J.W.; Farhan, M.; Jeberson, J.S.A.; Taghizadeh, A.; Kim, H.W.; Park, J.H.; Yang, J.; et al. Targeting the Integrin Beta 1-Focal Adhesion Kinase Axis with Artemisinin: Biophysical Disruption of Cell Adhesion, Migration, and Invasion in Tongue Cancer. *VIEW* **2025**, *6*, doi:10.1002/VIW.20240089.
284. Mahata, S.; Bharti, A.C.; Shukla, S.; Tyagi, A.; Husain, S.A.; Das, B.C. Berberine Modulates AP-1 Activity to Suppress HPV Transcription and Downstream Signaling to Induce Growth Arrest and Apoptosis in Cervical Cancer Cells. *Mol. Cancer* **2011**, *10*, doi:10.1186/1476-4598-10-39.

 doi:10.20944/preprints202605.1016.v1

285. Komal, K.; Athreyas, V.; Chaudhary, S.; Singh, M. Abstract B36: Berberine Induces Apoptosis in Cervical Carcinoma Cells by Inducing DNA Damage and Inhibition of RAS MAPK Pathway. *Molecular Cancer Research* **2020**, *18*, B36–B36, doi:10.1158/1557-3125.RAS18-B36.
286. Lin, C.C.; Yang, J.S.; Chen, J.T.; Fan, S.; Yu, F.S.; Yang, J.L.; Lu, C.C.; Kao, M.C.; Huang, A.C.; Lu, H.F.; et al. Berberine Induces Apoptosis in Human HSC-3 Oral Cancer Cells via Simultaneous Activation of the Death Receptor-Mediated and Mitochondrial Pathway. *Anticancer Res.* **2007**, *27*.
287. Rauf, A.; Abu-Izneid, T.; Khalil, A.A.; Imran, M.; Shah, Z.A.; Emran, T. Bin; Mitra, S.; Khan, Z.; Alhumaydhi, F.A.; Aljohani, A.S.M.; et al. Berberine as a Potential Anticancer Agent: A Comprehensive Review. *Molecules* **2021**, *26*, 7368, doi:10.3390/molecules26237368.
288. Li, Q.; Zhao, H.; Chen, W.; Huang, P. Berberine Induces Apoptosis and Arrests the Cell Cycle in Multiple Cancer Cell Lines. *Archives of Medical Science* **2023**, *19*, 1530–1537, doi:10.5114/aoms/132969.
289. Samal, S.; Meher, R.K.; Dubey, D.; Mir, S.A.; Nayak, B.; Sahu, M.C.; Naik, P.K.; Rath, G.; Swain, S.K. In-Silico and in-Vitro Evaluation of Docetaxel and Berberine as Potential P53 Modulating Apoptotic Inducers in Oral Squamous Cell Carcinoma. *Asian Pac. J. Trop. Biomed.* **2022**, *12*, 530–540, doi:10.4103/2221-1691.363879.
290. Komal, K.; Sharma, A.; Deshwal, V.K. Abstract A45: Berberine Acts as an Antagonist to Estradiol-Induced Proliferation by Inducing Apoptosis in Cervical Cancer Cells. *Cancer Prevention Research* **2010**, *3*, doi:10.1158/1940-6207.prev-10-a45.
291. Saha, S.K.; Khuda-Bukhsh, A.R. Berberine Alters Epigenetic Modifications, Disrupts Microtubule Network, and Modulates HPV-18 E6-E7 Oncoproteins by Targeting P53 in Cervical Cancer Cell HeLa: A Mechanistic Study Including Molecular Docking. *Eur. J. Pharmacol.* **2015**, *744*, doi:10.1016/j.ejphar.2014.09.048.
292. Mana, T.; Devi, O.B.; Singh, Y.D. Therapeutic Application of Berberine: A Consolidated Review. *Curr. Pharmacol. Rep.* **2023**, *9*, 329–340, doi:10.1007/s40495-023-00330-2.
293. Ashrafizadeh, M.; Fekri, H.S.; Ahmadi, Z.; Farkhondeh, T.; Samarghandian, S. Therapeutic and Biological Activities of Berberine: The Involvement of Nrf2 Signaling Pathway. *J. Cell. Biochem.* **2020**, *121*, 1575–1585, doi:10.1002/jcb.29392.