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Review

Plant Bioactive Constituents and Their Potential Benefits in HPV-Positive Oropharyngeal Squamous Cell Carcinoma—A Narrative Review

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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, particularly 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 represent 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 optimize outcomes. Additionally, the viral oncoproteins E6 and E7, which systematically disrupt host tumor-suppressor networks, provide strong reasons for targeted phytotherapeutic interventions. Therefore, there is increasing 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 with mechanistic evidence in HPV+ OPSCC, highlight their molecular interactions across oncogenic signaling pathways, and discuss evidence-based findings focusing on research published from 2000 to 2025.

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

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1. Introduction

Head and Neck Squamous Cell Carcinoma (HNSCC) is the seventh most common cancer worldwide, with about 890,000 new cases and 450,000 deaths each year, according to GLOBOCAN estimates. It makes up roughly 4.5% of all cancer diagnoses and deaths [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) is involved [2]. HPV-positive tumors account for 5–20% of all HNSCCs and 40–90%

of those arising in the oropharynx, with widely variable rates depending on geographic area, population, and detection assay [3].

In high-income countries, HPV now accounts for 60–80% of oropharyngeal SCC cases [4]. HPV genotype 16 (HPV-16) is the main cause of a growing subset of HPV-HNSCC [5]. It displays a distinct molecular profile and unique epidemiological patterns [6], mainly affecting younger, non-smoking patients, and typically results in a better prognosis than HPV-negative cases [7] (Table 1).

Table 1. The main differences between HPV-positive and HPV-negative HNSCC [8–17].

Feature	HPV-Positive HNSCC	HPV-Negative HNSCC
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 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) [18,19]. This, in turn, activates E2F transcription factors and promotes uncontrolled cell cycle progression [20]. 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 [21].

HPV-positive oropharyngeal SCC remains a significant challenge in diagnosis and treatment, underscoring the urgent need for innovative strategies [22,23]. Despite significant advances in surgical techniques, radiotherapy, and immunotherapy, especially with agents such as pembrolizumab [24] and nivolumab [25] that target PD-1/PD-L1 [26], the outcomes for recurrent or metastatic HPV+ OPSCC remain with 5-year survival rates around 60% across all stages [12,27,28]. Standard treatments can cause considerable side effects, highlighting the need for new solutions [8]. HPV is a firmly established driver in oropharyngeal HNSCC; it is the only site where the virus is transcriptionally active [29]. HPV is IARC-classified as a Group 1 carcinogen and is independently validated by the p16 surrogate [30].

In HNSCCs of the oral cavity (OSCC) [31–33] and larynx (LSCC) [34,35], HPV DNA detection frequently reflects a bystander state rather than active oncogenesis, as E6/E7 mRNA is often absent even in HPV-DNA-positive specimens.

The HPV-HNSCC prognosis depends on the site. HPV positivity confers the most significant survival benefit in OPSCC (>80% disease-free survival rate (DFS) vs. <50% in HPV-negative), is neutral to adverse in OSCC, and is statistically non-significant in LSCC [36]. This gradient directly mirrors the gradient of causal certainty—where HPV is not actively driving carcinogenesis, it logically cannot drive a favorable biology.

Clinical management varies accordingly. Only OPSCC requires mandatory HPV testing, has its own AJCC 8th edition staging, and is the focus of active treatment de-escalation trials [37]. For OSCC and LSCC, HPV status currently does not play a role in guiding staging, treatment intensity, or follow-up protocols—reflecting the scientific consensus that HPV's biological impact on these sites is insufficient to warrant clinical action. All differences between HPV-positive OPSCC, OSCC, and LSCC are thoroughly illustrated in Table S1 in the Supplementary Material.

In this context, plant-derived compounds 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 [38–40]. 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.

2. Methods

The limitations of current therapies for HPV+ OPSCC and the need for agents that target HPV-specific oncogenic pathways have led the authors to review recent scientific literature on plant bioactive compounds. Consequently, a comprehensive search was performed using PubMed, Scopus, Web of Science, and Google Scholar for articles published from 2000 to 2025. The search included keywords related to HPV+ OPSCC, HPV E6/E7 oncoproteins, plant bioactive compounds, specific molecular pathways, in vitro evidence in HPV+ OPSCC cell lines, in vivo evidence in animal models, and clinical trials concerning HPV+ OPSCC prevention and posttreatment outcomes. Only peer-reviewed articles written in English and available as full texts in various journals were included. Conference abstracts, theses, dissertations, non-peer-reviewed papers, and studies in other languages were excluded. The selection of phytochemicals focused on multi-target activity and favorable safety profiles, with an emphasis on preclinical and clinical findings.

3. Molecular Oncogenesis and Conventional Therapeutic Protocol of HPV+ OPSCC

The molecular oncogenesis of HPV-positive oropharyngeal cancer is a multi-step process initiated by persistent HPV-16 infection [41]. The viral E6 and E7 oncoproteins [42] disrupt critical tumor suppressors (p53 and Rb), while simultaneously activating inflammatory pathways, particularly the IL-6/STAT3 axis [43–45]. Additional somatic mutations (NOTCH1, SOX2) and the presence of extrachromosomal DNA further drive malignant transformation [46]. The tumor microenvironment, including immune cell populations and hypoxic conditions, plays a crucial modulatory role in disease progression and treatment response [47,48]. This complex interplay of viral, genetic, and microenvironmental factors distinguishes HPV+ OPSCC from other head and neck cancers. It explains its unique clinical characteristics, including improved initial prognosis but heterogeneous treatment responses (Figure 1).

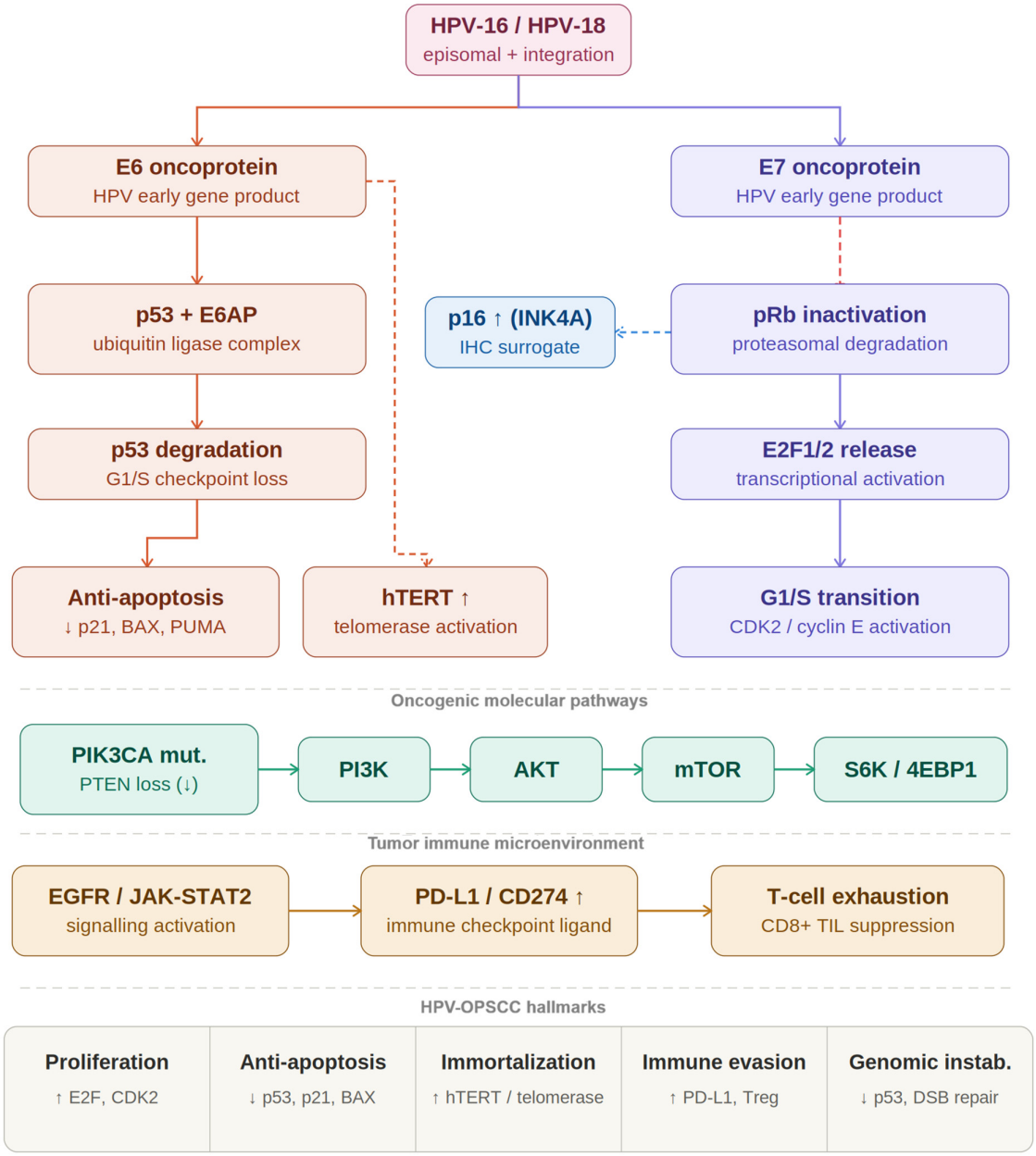

Figure 1. HPV-induced oropharyngeal carcinogenesis. E6 recruits E6AP (a ubiquitin E3 ligase) to form a complex that ubiquitinates p53, targeting it for proteasomal degradation. Loss of p53 abolishes the G1/S DNA-damage checkpoint, suppresses p21/BAX/PUMA-mediated apoptosis, and enables survival under replication stress. E6 also independently activates hTERT, bypassing replicative senescence [49]. E7 binds and degrades pRb (retinoblastoma protein), liberating E2F1/2 transcription factors that drive S-phase gene expression and CDK2/cyclin E activation—forcing cells through the G1→S restriction point. As compensatory feedback, loss of Rb repression leads to accumulation of p16ˆINK4A (INK4A); this is the basis for p16 immunohistochemistry as a clinical HPV surrogate marker. PIK3CA gain-of-function mutations and PTEN loss (the most common co-operating alteration in HPV+ OPSCC) activate the PI3K → AKT → mTOR → S6K/4EBP1 axis, promoting cap-dependent translation, cell survival, and metabolic reprogramming. EGFR and JAK-STAT2 signaling upregulate PD-L1/CD274 on tumor cells. Despite the characteristically high CD8+ TIL infiltration in HPV+ OPSCC (which partly explains the better prognosis), PD-L1 engagement induces T-cell exhaustion—the rationale for anti-PD-1/PD-L1 checkpoint inhibition (pembrolizumab) in recurrent/metastatic disease. All pathways converge on uncontrolled proliferation, resistance to apoptosis, replicative immortality, immune evasion, and genomic instability due to deficient p53-mediated DNA repair.

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 [50]. 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 [51–57]. 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 [58]. From a phytotherapeutic perspective, the E6/p53 pathway is a particularly promising target [59–61]. 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 [62,63].

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 [64]. Consequently, E2F1-3 can activate genes essential for S-phase entry, such as Cyclin E, Cyclin A, and CDK2 [65]. Furthermore, E7 encourages the ubiquitination and proteasomal degradation of pRb [64,66]. A recently discovered additional mechanism involves E7 disrupting the DREAM complex [67], a repressive complex involving E2F4/5, leading to widespread activation of cell-cycle genes independent of E6′s influence on p53. 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 [68].

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:

- The 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) [69–71].
- The 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 [72–75]
- The Wnt/β-catenin pathway supports cancer stem cell maintenance, epithelial–mesenchymal transition (EMT), and resistance to treatment; nuclear β-catenin accumulation has been observed in HPV-positive OPSCC [76].
- In the JAK/STAT pathway, STAT3 is constantly active in OPSCC, aiding immune evasion by upregulating PD-L1 and inhibiting dendritic cell maturation [77–79].
- The MAPK/ERK pathway, downstream of EGFR and RAS, promotes cell proliferation and survival; RAS mutations that activate this pathway are less common in HPV-positive than in HPV-negative OPSCC [80–82].

3.4. Immune Evasion in HPV+ 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) [83–86].

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 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.

CLINICAL PROTOCOL FOR HPV-POSITIVE OROPHARYNGEAL SQUAMOUS CELL CARCINOMA (HPV+ OPSCC)

PHASE 1—Presentation, Workup & Diagnosis

1a. Clinical presentation

- Neck mass (most common presenting feature)
- Odynophagia, dysphagia, otalgia, trismus
- Unilateral tonsillar enlargement
- Typically, younger patients (<60 years), non-smokers or mild smokers (≤10 pack-years)
- Often, no visible primary lesion on external examination

1b. Diagnostic work-up

- Flexible nasopharyngolaryngoscopy
- Panendoscopy ± TORS-assisted base-of-tongue biopsy
- CT neck + chest with contrast
- MRI oropharynx ± neck
- PET-CT for T3–T4, N2–N3 disease, or unknown primary
- EUA ± bilateral tonsillectomy/lingual tonsillectomy if an unknown primary is suspected
- NGS/MGPT genomic profiling for biomarker identification (NCCN v1.2026, footnote g)

1c. Tissue biopsy

- Fine-needle aspiration of neck mass, OR direct biopsy of primary lesion
- MANDATORY: HPV testing on ALL oropharyngeal squamous cell carcinomas

1d. Multidisciplinary team (MDT)—required before treatment decision

Head & neck surgeon · Radiation oncologist · Medical oncologist · Radiologist · Pathologist · Speech & language therapist · Dietitian · Dental oncologist · Clinical nurse specialist · Psycho-oncology

Figure 2. *Cont.*

PHASE 2—HPV Confirmation

p16 Immunohistochemistry (IHC)—first-line surrogate/NCCN Category	Confirmatory HPV Testing
• POSITIVE: ≥70% of tumor cells with nuclear AND cytoplasmic staining at moderate-to-strong intensity • p16+ and HPV+ = improved prognosis compared to p16+ and HPV− (which carries a prognosis similar to HPV− HNSCC) • Distinguishing p16+/HPV+ from p16+/HPV− informs prognosis and is clinically meaningful • Routine p16 testing NOT recommended outside the oropharynx and sinonasal tract (NCCN v1.2026)	• HPV in situ hybridization (ISH): High-risk HPV 16/18 • HPV PCR/genotyping (FFPE): For ambiguous p16 cases • Plasma HPV ctDNA: Emerging surveillance and response biomarker

PHASE 3—Staging: AJCC 8th Edition HPV-Specific System

STAGE I (Favorable)	STAGE II (Favorable)	STAGE III (Standard/Unfavorable)	STAGE IV (Metastatic)
T1–2, N0–1, M0 • Any T1–2 primary + ipsilateral node(s) ≤6 cm • N1 in HPV+ = ≤4 ipsilateral nodes ≤6 cm • HPV+ nodal staging is distinct from HPV− classification	**T1–2 N2 M0 or T3 N0–2 M0** • Ipsilateral nodes 4–5 cm or contralateral/bilateral nodes <6 cm • Or T3 primary with N0–2 • Generally favorable if non-smoker/low pack-years	**T4 or N3, M0** • Large primary (T4) OR nodes >6 cm • Bilateral/contralateral nodes >3 cm • Extranodal extension (ENE): Critical adverse prognostic factor	**Any T, Any N, M1** • Distant metastases (lung most common) • Palliative intent • → See Phase 8: Recurrent/metastatic

PHASE 4—Risk Stratification and Treatment Selection

FAVORABLE RISK—Stage I (T1–2, N0–1)	STANDARD RISK—Stage II–III (T1–3, N0–2)	UNFAVORABLE RISK—Stage III (T4 or N3)
Patient criteria: • ≤10 pack-year tobacco history • No extranodal extension (ENE) • p16+/HPV+ confirmed • Good performance status (ECOG 0–1)	**Patient criteria:** • 11–30 pack-years OR T3 primary OR N2 disease • Resectable or unresectable disease • Standard treatment protocols apply	**Patient criteria:** • >30 pack-years OR T4 OR N3 OR ENE present • Treated as per HPV− HNSCC outside clinical trials • NCCN v1.2026: Consider NGS/MGPT profiling
Treatment options:	**Treatment options:**	**Treatment options:**

Figure 2. *Cont.*

A) Definitive RT alone (NCCN Cat 2A) • IMRT 70 Gy/35# (standard) or 60 Gy (de-escalation) • For T1–2, N0–1 single-modality candidates **B) TORS ± neck dissection (NCCN Cat 2A)** • Transoral robotic surgery for accessible BOT/tonsil/soft palate • Bilateral ND if node-positive • No adjuvant: pT1–2 N0–1, clear margins (>3 mm), no ENE **C) De-escalated chemoRT (clinical trials)** • IMRT 60 Gy + weekly cisplatin 40 mg/m²: 2-yr PFS 90.5% • Full-dose cisplatin preferred outside trials (HNCIG framework)	**A) Definitive concurrent chemoRT (standard of care)** • IMRT 70 Gy/35# + cisplatin 100 mg/m² q3w (D1, 22, 43) • OR weekly cisplatin 40 mg/m² • Cetuximab only if cisplatin ineligible (renal impairment/SNHL) • NOTE: De-ESCALaTE and RTOG 1016 confirmed cisplatin is superior to cetuximab in HPV+ OPSCC **B) TORS + adjuvant RT/CRT (resectable disease)** • Bilateral ND; adjuvant IMRT 56–60 Gy (low–intermediate risk) • 60–66 Gy + cisplatin for high risk: ENE or close margins	**A) Full-dose concurrent chemoRT** • IMRT 70 Gy/35# + cisplatin 100 mg/m² q3w • No de-escalation outside clinical trials • Consider NGS/MGPT profiling for biomarker identification **B) Induction chemotherapy ± CRT (selected cases)** • TPF (docetaxel + cisplatin + 5-FU) for T4b or unresectable N3 • Response-stratified subsequent RT/CRT • Clinical trial enrolment is strongly recommended

***PHASE 5—Active Treatment: Evidence-Based Phytochemical Adjuncts**

Oral Mucositis Prevention & Treatment	Cisplatin Toxicity Protection	Xerostomia, QoL & HPV Prevention Continuum
Curcumin (nanomicelle 80 mg twice daily—SinaCurcumin®) • ↓ OM severity and pain; effective during RT alone or chemoRT (multiple RCTs + 2024 meta-analysis) • 0.1% mouthwash is also effective; earlier onset of effect **Natural bee honey (20 mL swish-and-swallow before/after RT)** • ↓ Grade 3/4 OM incidence and treatment breaks (multiple RCTs) • Ranked top agent in 2024 network meta-analysis for OM and pain	**Silymarin 140 mg twice daily (cisplatin nephroprotection)** • ↓ Cisplatin-induced nephrotoxicity: ↓ Serum creatinine, ↓ BUN (clinical trial) **Silymarin 140 mg twice daily (neuroprotection)** • ↓ Chemotherapy-induced peripheral neuropathy (p38-MAPK inhibition; clinical study) **Green propolis (Taiwanese; topical rinse/swallow during and post-RT)**	**Honey + green propolis rinse/swallow (xerostomia post-RT)** • ↑ QoL (β=10.05, p=0.01) and ↓ xerostomia vs. usual care (3-arm RCT, n=75; 12-week post-RT) **Coconut oil (oil-pulling rinse post-RT)** • ↓ Dry mouth symptoms; safe and low-cost (feasibility study) **Aloe vera gel (xerostomia and mucosal healing post-RT)** • ↑ Mucosal hydration, ↑ EGF, ↑ epithelial healing (active RCT NCT06381635, 2024)

Figure 2. *Cont.*

SAMITAL (bilberry + green tea oral rinse during chemoRT)

- ↓ OM severity and duration—Phase 2 RCT (ROSAM trial)

Silymarin (milk thistle) 420 mg/day or nano-silymarin rinse

- ↓ OM grade and delayed onset vs. placebo (pilot RCTs 2016 and 2021)

Aloe vera gel (topical, 3× daily during and after RT)

- ↓ RT-induced OM grade (systematic review 2024; active RCT NCT06381635)

- ↓ OM symptoms and ↓ xerostomia vs. usual care (3-arm RCT, n=75; 2025)

⚠ **Timing note (all antioxidant agents)**
Administer BEFORE or AFTER radiotherapy fractions—not concurrently. Discuss with the radiation oncologist before starting. Potential herb–drug interactions with cisplatin, 5-FU, and pembrolizumab should be considered.

HPV prevention continuum

- Sinecatechins (Veregen® 15% ointment): FDA-approved for concurrent genital HPV warts (HPV 6/11)
- Indole-3-carbinol (I3C) 200–400 mg/day if recurrent respiratory papillomatosis (RRP) is identified (listed in Iowa RRP protocol 2023)

PHASE 6—Treatment Response Assessment

Imaging and timing	Complete response → proceed to surveillance	Incomplete response/residual disease
• Clinical examination: 4–8 weeks post-RT • CT neck ± chest: 8–12 weeks post-RT • PET-CT: 12 weeks post-definitive CRT (preferred for N+ disease) • MRI: If CT is ambiguous for soft tissue assessment • Plasma HPV ctDNA clearance: Emerging marker of treatment response	• PET-CT: No FDG-avid residual disease • CT: Complete nodal regression or no residual mass >1 cm • Proceed to Phase 7 follow-up protocol	• Residual FDG-avid nodal disease after CRT: Planned neck dissection • Residual primary tumor: Salvage surgery (TORS or open) ± re-irradiation • ± Re-irradiation (SBRT or IMRT re-RT) • MDT re-discussion is mandatory before any salvage intervention • Clinical trial enrolment is strongly recommended

PHASE 7—Follow-Up Surveillance and Survivorship

Years 1–2	Years 3–5	Beyond 5 years	Survivorship & HPV prevention

Figure 2. *Cont.*

• Clinical exam every 1–3 months • CT/MRI at 6 and 12 months • Thyroid function every 6 months (if neck irradiated) • Dental review every 6 months • Audiogram if cisplatin is received	• Clinical exam every 4–6 months • Annual CT or PET-CT if clinically indicated • Annual thyroid function • Ongoing speech/swallowing therapy (SLT) • Dietitian review; PEG weaning if applicable	• Annual clinical examination • Management of late toxicities: ◦ Xerostomia, dysphagia, lymphoedema, fibrosis ◦ Trismus, hearing loss, dental/jaw decay ◦ Hypothyroidism (annual TFT) • Psycho-oncology and survivorship support	• HPV vaccination (Gardasil-9) for unvaccinated close contacts and sexual partners • Smoking cessation (↑ recurrence risk in active smokers) • Alcohol reduction counseling • Screening for second primary tumors (head & neck, lung, esophagus) • Ongoing dental oncology review

PHASE 8—Recurrent and Metastatic Disease

Locoregional recurrence	Recurrent/metastatic—1st line treatment	2nd line and beyond
• Salvage surgery (TORS or open) if resectable and eligible • Consider re-irradiation (SBRT or IMRT re-RT) ± cisplatin • ECOG PS 0–2 required for aggressive salvage strategies • Mandatory MDT re-discussion before any intervention • Clinical trial enrolment is strongly recommended	**Pembrolizumab—Standard of care (KEYNOTE-048)** • PD-L1 CPS ≥20: pembrolizumab monotherapy (superior OS vs. EXTREME regimen) • PD-L1 CPS 1–19: pembrolizumab monotherapy or + chemotherapy • PD-L1 CPS <1 or high disease burden: pembrolizumab + platinum (cisplatin or carboplatin) + 5-FU	**Platinum-refractory disease:** • Nivolumab: Superior OS vs. investigator's choice chemotherapy (CheckMate-141) • Docetaxel, methotrexate, cetuximab (limited efficacy in HPV+) **Investigational—HPV-specific approaches:** • Pembrolizumab + therapeutic HPV-16 vaccine ISA101 (Phase II; NCT03669718) • Pembrolizumab + HPV E7 fusion protein (36% ORR; JNCCN 2024)

Figure 2. Clinical protocol for HPV+ OPSCC. * Phase 5 includes the evidence-based findings of the present study. IHC—INK4a immunohistochemistry; p16 IHC ≥70% strong diffuse staining—this result indicates a strongly positive test, showing the presence of a transcriptionally active High-Risk Human Papillomavirus (HR-HPV) infection, according to Ablaza AC, Gupta R, Fielder T. p16. PathologyOutlines.com website, at https://www.pathologyoutlines.com/topic/stainsp16.html, accessed on 30 May 2026; 8th Edition of AJCC—American Joint Committee on Cancer [87]; TNM system, according to https://www.cancer.gov/about-cancer/diagnosis-staging/staging, accessed on 31 May 2026; T—the main tumor size and extension; N—the number of nearby lymph nodes with cancer; M—metastases; Database for Phases 1, 2, 4, 7, and 8 was National Comprehensive Cancer Network. Head and Neck Cancers, NCCN Guidelines Version 1.2026, available online at https://www.nccn.org/, accessed on 30 May 2026ș 5-year OS—5-year overall survival rate; CRT—chemoradiation; ECE—extracapsular extension;

ECOG PS—Eastern Cooperative Oncology Group performance status; IHC—immunohistochemistry; IMRT—intensity-modulated radiotherapy; Gy—Gray; Fr—Fraction; ISH—in situ hybridization; LVI—lymphovascular invasion; MDT—multidisciplinary team; ND—neck dissection; PNI—perineural invasion; R/M—recurrent/metastatic; RT—radiotherapy; SND—selective neck dissection; TORS—transoral robotic surgery; q3w—every three weeks; TPF—docetaxel + cisplatin + 5-fluorouracil; 5-FU—5-fluorouracil; ORN—osteoradionecrosis.

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 [88–90]. This approach decreases long-term side effects and improves patients' quality of life without compromising high survival rates [91]. When surgical access allows, transoral robotic surgery (TORS) or transoral laser microsurgery (TLM) is preferred [92–94], 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 [95,96]. Several clinical trials (e.g., ECOG-ACRIN 3311, PATHOS) are actively refining these thresholds [93,95–98] (Figure 2).

3.5.2. Locally Advanced (Stage III–IV)

Concurrent chemoradiation remains the standard, typically IMRT to 70 Gy with cisplatin (100 mg/m^2 q3w) [93]. Post-CRT PET-CT at 12 weeks guides the decision for salvage neck dissection [99,100]. Surveillance is intensive during the first two years [101–106], then tapers off, with focus on thyroid function (if the neck was irradiated) [107], swallowing therapy [108–115] and smoking cessation (since smoking worsens prognosis even in HPV+ disease) [116–120]. (Figure 2).

4. Plant Bioactive Constituents: Mechanistic Evidence

Four major categories of plant bioactive compounds were selected: polyphenols, alkaloids, terpenoids, and other classes (Figure 3).

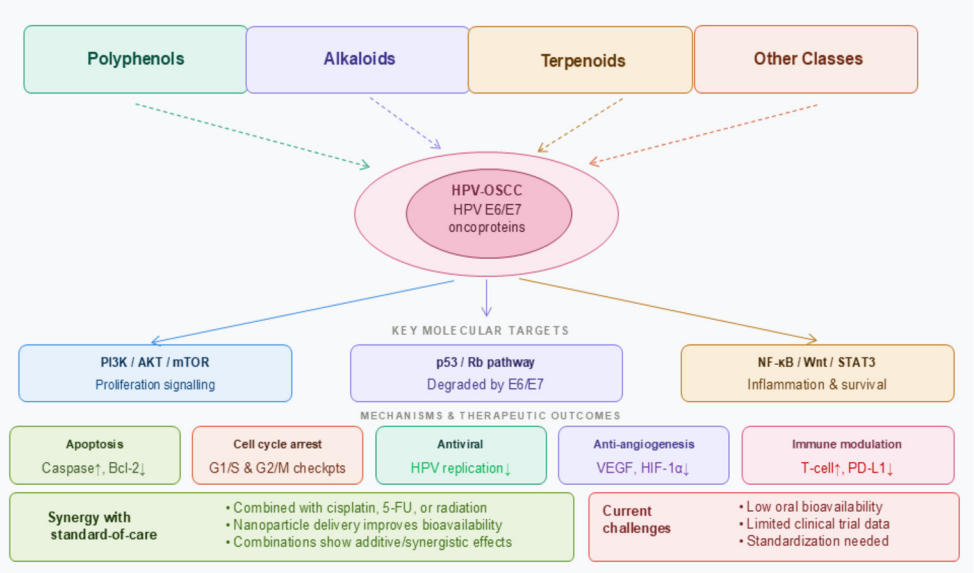

Figure 3. Plant bioactive constituents with potential benefits in HPV-OPSC.

4.1. Curcumin

Curcumin, (1*E*,6*E*)-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. [121] demonstrated 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 [122]. 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 [123].

Other authors offered a thorough review of curcumin's mechanisms of action across multiple pathways in head and neck cancer [124]. 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 [125].
- 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 [126].
- JAK/STAT3: Curcumin reduces STAT3 phosphorylation at Y705, leading to lower transcription of genes like Cyclin D1, c-Myc, and PD-L1 [127].
- Notch signaling: It decreases Notch-1 and its downstream targets HES1/HEY1, thereby reducing invasion and EMT in OSCC cell lines [124].
- miRNA-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 [128].
- Epigenetic reprogramming: It inhibits DNMT1 and HDAC activities, reactivating silenced tumor suppressor genes [129].
- Ferroptosis induction: Recent research has identified this as an additional mechanism, involving GPX4 modulation and lipid peroxide accumulation, that contributes to cancer cell death [130].

It was also reported that copper supplementation enhances curcumin's cytotoxicity in oral cancer cell lines [131].

4.2. (+/−)-Epigallocatechin Gallate

(+/−)-Epigallocatechin Gallate-13C3 (EGCG, [2*R*,3*R*)-5,7-dihydroxy-2-(3,4,5-trihydroxy phenyl)-3,4-dihydro-2*H*-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 [132].

Tsouh et al. 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 [133]. 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 OPSCC cells, displacing EGFR from its signaling hubs and reducing downstream cancer-promoting signals [134].

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 [135,136]. 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 [137,138]. Recent reviews confirm that EGCG has anticancer activity, especially against HPV16-related cancers, and that this promising effect is dose-dependent [139,140].

Recently, a standardized green tea extract called Polyphenon E, marketed as Veregen®, was FDA-approved for treating external genital warts caused by HPV [141].

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 [142]. These findings could be relevant for HPV-positive OPSCC because they involve similar viral cancer mechanisms. The proposed idea was 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 G1/S cell cycle arrest through p21 activation; and (4) reducing phospho-pRb1, counteracting the effects of E7 on cell cycle control [142].

Some studies 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 [143,144]. Researchers also found that combining resveratrol with other polyphenols produces a synergistic effect, leading to the development of TriCurin [145]. 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 [146,147]. It also inhibits STAT3 phosphorylation and lowers MMP-2 and MMP-9 levels, helping to prevent cancer invasion [147]. Its ability to stop metastasis is partly due to its suppression of EMT, as indicated by lower levels of vimentin, E-cadherin, and Snail [148].

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 [149].

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) [145,150]. 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 [151]. 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. At the same time, ECG enhances p300 acetyl transferase activity, shifting the balance toward p53 acetylation and activation [58]. 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 [151].

4.5. Quercetin

Quercetin, 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one, is common in plants and is found in large amounts in onions (*Allium cepa*), elderberries, capers, kale, and tea. It is considered 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 [152–157].

Molecular docking study confirmed quercetin's strong binding affinity for the Bcl-2 protein, outperforming the reference ligand doxorubicin, and provided a structural basis for its pro-apoptotic activity [158]. Other studies reaffirmed its effects on cancer invasion, migration, proliferation, and apoptosis induction across multiple OSCC model systems [158–161].

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-cell-mediated killing compared to untreated HPV+ controls, indicating potential indirect immune-boosting effects in the HPV-positive environment. Moreover, the combination of quercetin and cisplatin increases apoptosis of OSCC cells by downregulating XIAP through the NF-kB pathway [162]. Quercetin also enhances the sensitivity of oral cancer cells to Vincristine [163].

4.6. 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), *Berberis aristata*, *Hydrastis canadensis* (goldenseal), and *Coptis chinensis* (Chinese goldthread). It has a long history of use in traditional Chinese and Ayurvedic medicine [164].

Berberine has dual actions—tumor growth inhibition and immune restoration—especially relevant in OPSCC, where both the virus and the tumor cause immunosuppression. 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 [165,166].

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 [167,168].

These plant metabolites act through various mechanisms in HPV+ OPSCC cell lines (Table 2).

Table 2. Molecular Mechanisms of Plant Constituents in HPV+ OPSCC Cell Lines.

Constituent	Class	Cell Line(s)	Key Findings	Molecular Targets/Mechanisms	References
TriCurin (Curcumin + Resveratrol + Epicatechin gallate)	Polyphenol combination	UMSCC47; UPCI:SCC090 (HPV16+)	↓ Cell viability, clonogenic survival, tumorsphere formation, significant apoptosis, inhibited tumor growth by 85.5% in vivo	↓ HPV16 E6/E7 oncoproteins; ↑ p53; caspase activation	[151]
		HPV+ TC-1; UMSCC47 (HPV16+)	↓ HPV E6; eliminates HPV+ cancer cells; ↑ p53 accumulation; intralesional injection → 80–90% ↓ tumor growth in mice	↓ HPV E6 oncoprotein; ↑ p53 and acetyl-p53; caspase-3 activation	[149]
		HPV+ TC-1 (HPV16+)	Repolarises M2 → M1 tumour-associated macrophages; triggers IL-12 signalling; recruits NK cells and cytotoxic T lymphocytes; immune-mediated tumor suppression	TAM repolarisation; ↑ IL-12; NK/CTL recruitment; PD-L1 pathway modulation	[145]
Curcumin	Polyphenol	CU-OP-2; CU-OP-3; CU-OP-20 (HPV+ OPSCC primary lines)	Dose-dependent ↓ viability and proliferation; synergistic effects with PI3K inhibitor BYL719 and WEE1 inhibitor MK-1775	CDC27 targeting; PI3K/AKT/mTOR inhibition; CDK4/6 pathway; WEE1 G2/M checkpoint	[169]
		93VU147T (HPV16+ oropharyngeal)	Suppresses AP-1 and NF-κB transcription factor activity; selectively reduces HPV16 E6 oncogene transcription	↓ AP-1 and NF-κB activity; ↓ HPV16 E6 mRNA; anti-inflammatory signalling	[170]
Curcumin + Metformin	Polyphenol	UMSCC47; UMSCC1 (HPV+ and HPV−)	Both agents slow proliferation and induce apoptosis; curcumin effects are more pronounced in HPV lines; metformin is more effective in HPV+ lines; no synergy observed	↓ Proliferation; ↑ apoptosis; AMPK pathway (metformin); multiple HNSCC biomarkers affected	[170–172]
Lycium barbarum phenolic extract (flavonols, flavan-3-ols, hydroxycinnamic acid amides)	Phenolic plant extract	UPCI:SCC090 (HPV16+); CAL27	G_0/G_1 arrest and S-phase accumulation in SCC090; ↓ E6/E7 mRNA ($p < 0.05$); ↑ p53 protein; ↓ Ki-67 and Bcl-2 expression	Cell cycle arrest; ↓ HPV E6/E7 oncogene expression; p53 stabilisation; anti-proliferative and immunomodulatory	[173]
Berberine	Alkaloid	HSC-3 (oral/oropharyngeal SCC)	Dose- and time-dependent irreversible growth inhibition; G_0/G_1 cell cycle arrest; apoptosis via caspase-3 activation and ↓ mitochondrial membrane potential	Caspase-3 activation; G_0/G_1 arrest; mitochondrial pathway apoptosis; ↓ MMP	[174]
Quercetin	Polyphenol/Flavonol	UMSCC-47 (HPV+, tongue)	↓ Cell viability in vitro; Ca^{2+} response via T2R14 bitter taste receptor; mitochondrial depolarisation; cytotoxicity in ex vivo tumor slices	T2R14 agonism; intracellular Ca^{2+} signalling; mitochondrial membrane depolarisation; apoptosis induction	[157]

Table 2. *Cont.*

Constituent	Class	Cell Line(s)	Key Findings	Molecular Targets/Mechanisms	References
Fisetin (flavonoid)	Polyphenol/Flavonol	HPV-18 E6/E7 models (in silico + OSCC lines)	Lead photosensitizer targeting HPV-18 E6 and E7 oncoproteins via molecular docking; established anti-proliferative activity in OSCC cell lines.	HPV-18 E6/E7 oncoprotein binding; photodynamic inhibition; anti-proliferative, antiviral, antioxidant	[175]
EGCG (epigallocatechin-3-gallate; green tea)	Polyphenol/Catechin	SCC-9 (OSCC); FaDu (head & neck SCC)	Near-complete inhibition of invasion; ↓ MMP-2 and uPA; anti-EMT (↓ Snail-1, vimentin); ↓ FAK/Src phosphorylation; inhibited DNMT activity up to 80%	MMP-2/9 inhibition; anti-EMT; DNMT inhibition (epigenetic); FAK/Src pathway; reactivates silenced tumour suppressors	[176]
Proanthocyanidins (PAC)	Polyphenol/Tannin	HPV-transfected OSCC; SiHa (HPV+)	PAC inhibits the proliferation of HPV-transfected OSCC cells dose-dependently; tested in cervical carcinoma and non-cancerous lines	↓ Cell proliferation; anti-HPV; modulates p53 and Rb pathway activity	[177]

↓—inhibition; ↑—activation.

4.7. 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 [134]. 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 [134]. 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 [134,178].

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 [179–181].

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 [182].

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) [178]. In the acidic environment of the stomach, I3C further condenses to form diindolylmethane (DIM), which contributes to many of I3C's bioactivities [183,184].

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 [185].

Indole-3-carbinol inhibits nasopharyngeal carcinoma cell growth in vivo and in vitro through apoptosis based on the PI3K/Akt pathway [186].

4.10. α-Mangostin

α-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. [187] provided direct molecular evidence that α-Mangostin inhibits cervical cancer cell proliferation and tumor growth by downregulating the E6/E7 HPV oncogenes and the KCNH1 potassium channel gene, 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 [187].

The anti-OSCC evidence for α-MG, highlights 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 [188,189].

Critically, a recent clinical-stage development study tested a 1% α-mangostin orabase gel formulation directly against OSCC cells [190]. Additionally, mucoadhesive films loaded with α-MG demonstrated anti-HPV16 activity at both attachment and post-attachment stages, establishing dual antiviral and anticancer activities within a single mucosal delivery format [191].

4.11. Silymarin

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, (2*R*,3*R*)-3,5,7-trihydroxy-2-[(2*R*,3*R*)-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxy methyl)-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 [192]. 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 [193,194].

Silymarin was also shown to have anti-HPV activity, as confirmed by molecular docking [195].

Numerous in vitro studies have been conducted on HPV-positive cervical cancer cell lines. HPV-related cervical cancer and HPV+ OPSCC share identical viral drivers and core molecular mechanisms and show excellent treatment responses. Both are caused by high-risk HPV strains (mainly HPV-16) and differ from virus-negative cancers in their unique cellular and prognostic profiles. The mechanistic pathways involved in their cytotoxic activity against HPV-induced cervical cancer are shown in Table 3.

Table 3. Molecular Mechanisms of Plant Constituents in HPV-Cervical Cancer Cell Lines.

Constituent	Class	Cell Line(s) [HPV Status]	Key Findings	Molecular Targets	Reference
Tanshinone IIA + Curcumin	Combination (diterpenoid + polyphenol)	W12 episomal HPV16; W12 integrated HPV16; CaSki; SiHa	Both agents inhibit W12 and cervical cancer cell growth; TanIIA represses HPV16 E1, E2, E4, E6, E7 transcripts; ↑ p53; curcumin + TanIIA synergistic; molecular docking indicates Na+/K+-ATPase binding	↓ HPV16 E1/E2/E4/E6/E7; ↑ p53; Na+/K+-ATPase bioelectric signalling	[196]
Curcumin	Polyphenol	HeLa (HPV18+); CaSki (HPV16+)	Dose- and time-dependent ↓ cell viability; ↑ apoptosis (flow cytometry); ↓ mitochondrial membrane potential (JC-1); ↓ invasion and migration (transwell + wound-healing); selectively ↓ E6 > E7; ↓ Bcl-2/N-cadherin/vimentin; ↑ Bax/cleaved caspase-3/E-cadherin	↓ HPV E6 (primarily) and E7; ↑ p53; mitochondrial apoptosis; anti-EMT	[197]
α-Mangostin (*Garcinia mangostana*)	Xanthonoid	SiHa (HPV16+); CaSki (HPV16+); HeLa (HPV18+); C33a (HPV−)	Concentration-dependent ↓ cell proliferation in all HPV+ lines; G1/S arrest; ↓ E6 and E7 oncogene expression; ↓ KCNH1 potassium channel gene; significant tumor growth inhibition in the mouse xenograft model	↓ HPV E6/E7 oncoproteins; ↓ KCNH1; G1/S arrest; antiviral + antineoplastic	[187]
Luteolin + Asiatic acid (flavonoid + triterpenoid)	Combination	CaSki (HPV16+); HeLa (HPV18+)	Combination is more effective than either agent alone; sub-G1 phase arrest; caspase-mediated intrinsic apoptosis; ↑ mitoROS; ↓ invasion and migration (wound-healing assay); inhibited xenograft tumor growth in vivo with minimal toxicity to normal cells	↓PI3K/AKT/p70S6K; ↓ JNK/p38 MAPK; ↓ FAK/integrin β1/paxillin; ↑ ERK; caspase cascade activation	[198]
EGCG (green tea; *Camellia sinensis*)	Polyphenol/ Catechin	SiHa (HPV16+); CaSki (HPV16+); HeLa (HPV16/18+)	EGCG nanoformulations ↓ cell viability dose- and time-dependently; G2/M arrest in SiHa and HeLa; modulates oncomiRs (miR-210↑, miR-29a, miR-203, miR-125b); inhibits TGF-β-induced EMT; regulates DNA methylation via DNMT inhibition	↓ DNMTs (epigenetic); G2/M checkpoint arrest; anti-EMT; miRNA modulation; TGF-β pathway	[199]
		HFK-HPV18 (keratinocytes); VIN (HPV18+)	↓ Proliferation in monolayer and organotypic raft culture stimulates proteasomal degradation of E6 and E7 oncoproteins; ↑ p53 and Rb; suppresses E4 late viral protein; blocks productive HPV replication in differentiating keratinocytes	Proteasomal E6/E7 degradation; ↑ p53/Rb; ↓ HPV late protein E4; blocks productive viral replication	[200]

Table 3. *Cont.*

Constituent	Class	Cell Line(s) [HPV Status]	Key Findings	Molecular Targets	Reference
Quercetin (flavonol; onions, capers)	Polyphenol/ Flavonol	SiHa (HPV16+); HeLa (HPV18+)	Selective toxicity toward HPV+ lines vs. normal fibroblasts (7–8× higher IC50 in normal cells); G2 phase arrest; ↑ Bax/Bcl-2 ratio; caspase 3/7 activation; ↑ p53 in an E6 expression-independent manner; apoptotic morphological changes	G2 arrest; ↑ p53 (E6-independent); ↑ Bax/↓ Bcl-2; caspase 3/7 activation; selective HPV+ cytotoxicity	[201]
EGCG (green tea; *Camellia sinensis*)	Polyphenol/ Catechin	SiHa (HPV16+); CaSki (HPV16+); HeLa (HPV16/18+); C33A (HPV−)	Dose- and time-dependent ↓ proliferation; IC50 90.74 µg/mL (24h) in HeLa; modulates tumour-suppressive miRNAs: ↑ miR-210 and miR-29a in CaSki/SiHa; ↑ miR-125b and miR-203 in SiHa; distinct miRNA profiles by HPV subtype	miRNA modulation (miR-210, miR-29a, miR-203, miR-125b); ↓ proliferation; HPV subtype-specific epigenetic effects	[136]
Berberine (*Berberis* spp.)	Alkaloid	SiHa (HPV16+); HeLa (HPV18+)	Selectively inhibits constitutively active AP-1; dose- and time-dependent ↓ E6 and E7 oncogene expression; ↓ oncogenic c-Fos; ↑ p53 and Rb; ↓ hTERT (telomerase); growth arrest and apoptosis; no toxicity to normal cells	AP-1 inhibition; ↓ HPV E6/E7; ↑ p53/Rb; ↓ hTERT; c-Fos downregulation	[202]
Tanshinone IIA (*Salvia miltiorrhiza*; Danshen)	Terpenoid/ Diterpenoid	CaSki (HPV16+); SiHa (HPV16+); HeLa (HPV18+); C33a (HPV−)	↓ Proliferation in all HPV+ lines; S-phase arrest; ↓ HPV E6 and E7 (mechanistic study in CaSki); modulates E6AP and E2F1; ↑ p53 accumulation and p53-dependent targets; ↓ Bcl-2/↑ Bax; caspase-3 activation; PARP cleavage; p53-mediated apoptosis	↓ HPV E6/E7; ↑ p53; S-phase arrest; E6AP/E2F1 modulation; Bcl-2/Bax; caspase-3; PARP cleavage	[203]
α-Mangostin (*Garcinia mangostana*)	Xanthonoid	SiHa (HPV16+); HeLa (HPV18+)	↓ Cell viability dose-dependently; loss of mitochondrial membrane potential; ↑ cytochrome C release; ↑ Bax/↓ Bcl-2; caspase-9/caspase-3 cascade; ↑ ROS → activates p38 MAPK via ASK1; tumour growth inhibition in xenograft model	ROS generation; ASK1/p38 MAPK activation; mitochondrial apoptosis; Bax/Bcl-2; caspase-9/3	[204]
Apigenin (parsley, chamomile)	Polyphenol/ Flavone	SiHa (HPV16+); CaSki (HPV16+); HeLa (HPV18+); HaCaT (normal, control)	Selective cytotoxicity in all HPV+ lines vs. non-tumorigenic HaCaT; Annexin V+ apoptosis; ↑ ROS and H_2O_2; ↓ mitochondrial membrane potential; ↑ lipid peroxidation; ↓ migration and invasion	Oxidative stress (↑ ROS/H_2O_2); mitochondrial redox impairment; apoptosis; anti-migratory	[178]

↓—inhibition; ↑—activation.

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

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 reduces cap-dependent translation of oncoproteins, including Cyclin D1 and c-Myc, thereby increasing G1 arrest.

5.4. Tumor Microenvironment and Immune Remodeling

HPV+ 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 (Table 4).

Table 4. Molecular Mechanisms of Plant Constituents in HPV+ Cancer Animal Models.

Constituent	Class	Animal Model	Key In Vivo Findings	Mechanisms Confirmed In Vivo	Reference
TriCurin *(Curcumin + Resveratrol + Epicatechin gallate)*	Polyphenol combination	Model type: Immunocompetent mouse (TC-1) Detail: C57BL/6 mice implanted with TC-1 cells (HPV16 E6/E7/c-Ha-Ras+); intratumoral TriCurin injection	Intratumoral TriCurin repolarised M2 → M1 tumor-associated macrophages; ↑ IL-12 in tumor; recruited NK cells and CD8+ CTLs; immune-mediated tumor suppression confirmed in immunocompetent host only (not in nude mice), proving the immune mechanism is essential.	TAM repolarisation (ARG1 ↓, IL-10 ↓, iNOS ↑, IL-12 ↑); NK cell + CTL intratumoral recruitment; adaptive immune activation	[149]

Table 4. *Cont.*

Constituent	Class	Animal Model	Key In Vivo Findings	Mechanisms Confirmed In Vivo	Reference
TriCurin *(Curcumin + Resveratrol + Epicatechin gallate)*	Polyphenol combination	Model type: TC-1 syngeneic + HPV+ HNSCC xenograft Detail: (i) TC-1 HPV16+ tumors in C57BL/6 mice; (ii) UMSCC47 and UPCI: SCC090 xenograft in nude mice. Intratumoral/intralesional injection.	TC-1 tumors: 80–90% growth reduction vs. vehicle; UMSCC47/SCC090 xenografts: 85.5% tumour growth inhibition ($p < 0.05$, $n = 7$); ↓ E6/E7 in tumour tissue; ↑ p53, ↑ acetyl-p53 (activated), ↑ caspase-3; 4.7-fold greater E6 inhibition vs. curcumin alone; no adverse effects in tumour-naïve mice.	↓ HPV16 E6/E7 in vivo; ↑ p53 + acetyl-p53; caspase-3 activation; antitumour effect stronger than single agents	[151]
Resveratrol *(stilbene; grapes, berries)*	Polyphenol/ Stilbene	Model type: TC-1 syngeneic Detail: C57BL/6 mice s.c. implanted with TC-1 cells (HPV16 E6/E7/c-Ha-Ras+); i.p. resveratrol treatment	Significantly inhibited TC-1 tumor development; ↓ E6 protein in tumor tissue; ↓ VEGF levels; tumor size reduction associated with cell cycle arrest mechanism (↓ PCNA); distinct mechanism from pterostilbene (growth arrest rather than apoptosis).	↓ HPV E6 oncoprotein in vivo; ↓ VEGF (anti-angiogenic); ↓ PCNA (cell cycle arrest); tumour growth suppression	[146]
Pterostilbene *(stilbene; blueberries; resveratrol analogue)*	Polyphenol/ Stilbene	Model type: TC-1 syngeneic Detail: C57BL/6 mice s.c. implanted with TC-1 cells (HPV16 E6/E7/c-Ha-Ras+); i.p. pterostilbene; head-to-head with resveratrol in same study	Significantly inhibited TC-1 tumor development; ↓ E6 protein in tumor tissue; ↓ VEGF levels; tumor size reduction via apoptosis (↑ cleaved caspase-3); more potent than resveratrol in the same model; distinct mechanism (apoptotic rather than cell cycle arrest).	↓ HPV E6 oncoprotein in vivo; ↑ activated caspase-3 (apoptosis); ↓ VEGF; superior efficacy vs. resveratrol in same model	[205]
Curcumin-loaded liposomes *(PDT photosensitizer; liposomal nanoformulation)*	Polyphenol/ Nanoformulation	Model type: VX2 rabbit (CRPV+ HNSCC model) Detail: CRPV-positive VX2 cells from New Zealand White rabbit (established animal model for papillomavirus-associated HNSCC); tested alongside UD-SCC-2 (HPV16+ HNSCC) and HeLa (HPV18+)	Curcumin liposomes + PDT: dose-dependent ↓ cell viability in VX2 (CRPV+), UD-SCC-2 (HPV16+), and HeLa; ↑ apoptosis; ↓ proliferation, migration, and colony formation in HPV-associated lines; liposomal formulation more effective than free curcumin; VX2 rabbit confirmed PDT sensitivity of papillomavirus-associated HNSCC.	PDT-mediated ROS generation and apoptosis; ↓ cell migration and colony formation; papillomavirus-specific sensitivity demonstrated; nanoformulation enhances delivery	[206]
Curcumin CUR-LCNPs *(lipid-coated polymeric nanoparticles; PDT)*	Polyphenol/ Nanoformulation	Model type: HPV+ HNSCC panel (in vitro/translational) Details: 3 HPV+ HNSCC lines (incl. UD-SCC-2, HPV16+) and 3 HPV− lines; no pure in vivo xenograft endpoint but included for translational relevance	CUR-LCNPs (153 nm, 92.7% encapsulation) + PDT: significant tumor cell killing across all 6 HNSCC lines; no significant difference between HPV+ and HPV− groups (IC50 9.34 vs. 6.88 μM); superior to free curcumin; confirms suitability of curcumin PDT for HPV+ HNSCC regardless of HPV status.	ROS-mediated PDT cytotoxicity; mitochondrial depolarisation; nanoparticle uptake independent of HPV status; photosensitizer efficacy confirmed	[207]

Table 4. *Cont.*

Constituent	Class	Animal Model	Key In Vivo Findings	Mechanisms Confirmed In Vivo	Reference
α-Mangostin *(Garcinia mangostana)*	Xanthonoid	Model type: HPV16+ xenograft Detail: Athymic nude mice s.c. implanted with SiHa (HPV16+) or CaSki (HPV16+) cervical cancer cells	Significant inhibition of SiHa and CaSki xenograft tumor growth; ↓ E6 and E7 oncogene expression in tumor tissue; ↓ KCNH1 potassium channel gene; ↓ PCNA (proliferation marker); ↑ apoptosis in tumor sections; good tolerability in mice.	↓ HPV E6/E7 oncoproteins in vivo; ↓ KCNH1; ↓ PCNA; ↑ apoptosis; antineoplastic and antiviral activity confirmed in vivo	[204]
Luteolin + Asiatic acid *(flavonoid + triterpenoid combination)*	Combination (flavonoid + terpenoid)	Model type: HPV16+ xenograft Detail: Nude mice s.c. implanted with CaSki cells (HPV16+); oral/i.p combination treatment	Combination markedly inhibited CaSki xenograft tumor growth vs. single agents or control; minimal cytotoxicity to normal tissues; ↓ tumor weight and volume; PI3K/AKT and JNK/p38 pathway suppression confirmed in excised tumor tissue; superior to either agent alone.	↓PI3K/AKT/p70 S6K; ↓ JNK/p38 MAPK; ↓ FAK signalling; ↑ ERK; caspase cascade confirmed in vivo; low host toxicity	[198]
EGCG + E7-LAMP DNA vaccine *(EGCG as immunoadjuvant; green tea)*	Polyphenol/ immunoadjuvant	Model type: TC-1 syngeneic (immunocompetent) Detail: C57BL/6 mice with established TC-1 tumours (HPV16 E7+); oral EGCG + Sig/E7/LAMP-1 DNA vaccination	Oral EGCG alone: modest antitumor effect. Combined with E7/LAMP DNA vaccine: complete tumor regression; ↑ E7-specific CD8+ cytotoxic T cells vs. vaccine alone; enhanced primary and memory T cell responses; no severe systemic toxicity (no hair loss, weight loss, or lymphopenia).	↑ CD8+ T cell-mediated antitumor immunity; immunoadjuvant synergy with therapeutic HPV vaccine; ↑ tumor-specific cytotoxicity in vivo	[208]
Apigenin + E7-HSP70 DNA vaccine *(flavone; parsley; chemosensitiser + immunoadjuvant)*	Polyphenol/Flavone	Model type: TC-1 syngeneic (immunocompetent) Detail: C57BL/6 mice with TC-1 tumours (HPV16 E7+); apigenin + E7-HSP70 DNA vaccine combination	Apigenin rendered TC-1 tumor cells more susceptible to E7-specific CTL lysis; combined with the E7-HSP70 DNA vaccine → the highest frequency of primary and memory E7-specific CD8+ T cells among all groups; potent therapeutic antitumor effects; apigenin enhanced apoptotic tumor cell death in a dose-dependent manner.	↑ MHC-I antigen presentation; ↑ E7-specific CD8+ T cell frequency; apoptosis induction; ↑ memory T cell response; potentiates therapeutic HPV immunization	[209]

↓—inhibition; ↑—activation.

6. Bioavailability Challenges and Nanoscale Delivery Systems

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.

Therefore, nanoscale delivery systems present a valuable approach to overcoming the challenges faced by traditional plant-derived medicines, such as poor water solubility, chemical instability, and low bioavailability. By encapsulating bioactive phytochemicals within microscopic carriers, these advanced systems enhance systemic circulation, improve cellular absorption, and facilitate targeted or controlled release at the site of disease.

Thus, nanoparticle-based delivery systems have been shown to significantly improve the therapeutic potential of phytochemicals, making them promising candidates for safer, more effective cancer treatments. The convergence of nanotechnology with phytochemical therapy represents a paradigm shift for HPV+ OPSCC treatment [210].

6.1. Liposomal Nanovesicles

Liposomes are phospholipid bilayer vesicles capable of encapsulating both hydrophilic and lipophilic phytochemicals, making them highly versatile for polyphenolic compounds that are relevant to HPV-driven oncogenesis. Liposomal nanovesicles exhibit enhanced transport across cell membranes and mucosal barriers, cancer-specific targeting, improved stability of encapsulated phytochemicals against degradation, and controlled, sustained release at tumor sites.

Given that HPV+ OPSCC tumors are in the oropharynx, liposomal systems can be engineered to exhibit mucoadhesive properties, thereby prolonging contact time with the tumor microenvironment. Polymer-coated mucoadhesive liposomes can remain attached to intestinal/mucosal surfaces for sufficient periods to enable prolonged drug absorption. Furthermore, topical liposomal antiviral delivery has been specifically explored for HPV infections, demonstrating improved drug penetration and localized action. Liposomal nanovesicles offer a compelling and effective strategy for delivering plant bioactive compounds in the fight against HPV+ OPSCC. One of their notable advantages is the ability to enhance the bioavailability of curcumin, resveratrol, and epicatechin gallate [211]. This ensures sustained and concentrated exposure to critical targets, including the HPV16 E6/E7 oncoproteins, the p53/pRB tumor suppressor pathways, and the EGFR/PI3K signaling networks—key components in HPV-driven oropharyngeal carcinogenesis. Importantly, TriCurin, formulated as a liposomal nanoformulation, has emerged as a leading HPV-specific phytochemical, demonstrating substantial preclinical efficacy in relevant cell lines and xenograft models. This advancement underscores the potential of combining nanoparticle technology with phytochemicals to improve treatment outcomes for patients with HPV+ OPSCC.

6.2. Polymeric Nanoparticles (PLGA and Chitosan-Based)

Encapsulation of phytochemicals in poly(lactic-co-glycolic acid) (PLGA) nanoparticles addresses significant challenges, including poor water solubility, limited bioavailability, and rapid metabolic degradation. This biocompatible and FDA-approved delivery system enables sustained release, protects plant-derived compounds from enzymatic degradation, and enhances targeted therapeutic delivery.

Chitosan-based nanoparticles (CSNPs) are an innovative solution for delivering phytochemicals in HPV-positive cancers [212] Their biocompatibility and biodegradability make them highly effective nanocarriers, safeguarding therapeutic plant compounds from degradation. Furthermore, CSNPs enhance cellular uptake and help to overcome drug resistance. These attributes make them a promising targeted treatment option for cervical, oral, and head-and-neck cancers, potentially improving therapeutic outcomes. The quercetin–chitosan system is particularly noteworthy because this combination increases quercetin bioavailability in HPV+ OPSCC. Quercetin has demonstrated anti-HPV oncogenic activity by targeting E6/E7 viral proteins, and its delivery via chitosan nanoparticles directly addresses the bioavailability limitation in HPV-driven cancers. Chitosan/sulfonyl-ether-β-cyclodextrin (SBE-β-CD)-conjugated delivery systems for quercetin demonstrated a remarkable improvement in bioavailability in HPV-related cancer cells (HeLa cells), with IC50 values indicating increased cytotoxicity (43.55 μM).

6.3. Nanoemulsions and Microemulsions

Nanoemulsions and microemulsions are oil-in-water or water-in-oil colloidal dispersions with droplet sizes typically ranging from 20–200 nm and, respectively, 10–100 nm, designed to solubilize hydrophobic phytochemicals. They enhance mucosal absorption in the oropharyngeal region, improve chemical stability during processing and digestion, and can be produced in liquid, gel, paste, or solid forms for flexible administration routes.

Curcumin nanoemulsion (Cur-NE) has demonstrated significant efficacy in reducing the mRNA expression levels of HPV E6 and E7 oncogenes, while simultaneously increasing the levels of p53 and Rb proteins in TC-1 (HPV positive) cells at concentrations lower than those required for free curcumin ($p < 0.05$). Additionally, Cur-NE exhibited markedly greater tumor suppression and growth inhibition in subcutaneous TC-1 tumors than free curcumin ($p < 0.01$) [213]. These results provide compelling evidence of a nanoemulsion's potential to effectively target HPV oncoproteins, demonstrating verified efficacy in vivo.

6.4. Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) are colloidal carriers composed of a solid lipid matrix, including glycerides, fatty acids, and waxes. These particles are typically 10 to 1000 nm in size and are stabilized by surfactants. In the context of oropharyngeal squamous cell carcinoma (OPSCC), SLNs offer a significant advantage over nanoemulsions and polymeric nanoparticles due to their combination of solid-state chemical protection and mucoadhesive compatibility. They protect labile phytochemicals (EGCG, curcumin, resveratrol) from enzymatic/oxidative degradation, prolong mucosal drug levels without repeated dosing, and are safe for long-term locoregional treatment. Incorporated in gels, sponges, or films, they can be delivered directly to the oropharynx and tonsils.

Research has demonstrated that curcumin-encapsulated lipidic nanoconstructs (CLEN-SLN) [214] achieve an impressive 69.78-fold increase in oral bioavailability relative to free curcumin, and a ninefold increase compared to a commercially available formulation (CurcuWIN®). Furthermore, this formulation enhances the solubility of curcumin by a factor of 1.4 million, compared to its intrinsic solubility of 11 ng/mL, exhibiting zero-order release kinetics and a 104-fold increase in stability at a pH of 6.8.

Curcumin-loaded SLNs reduced tumor growth more effectively than free curcumin, suppressed key pro-survival proteins (XIAP and Mcl-1) and inflammatory cytokines (IL-6 and TNF-α), and showed additive effects with chemotherapy.

The local application of curcumin to the oral mucosa using a mucoadhesive sponge containing curcumin solid lipid nanoparticles has been identified as an effective strategy for treating precancerous oral lesions [215]. This treatment regimen involves a low dose of 6 mg per day for 6 weeks, resulting in decreased pain and accelerated healing of these lesions. These findings represent a noteworthy advancement in the clinical translation of phytochemical SLNs for oropharyngeal mucosal applications [216].

6.5. Cyclodextrin Inclusion Complexes

Cyclodextrins (CDs) form host–guest inclusion complexes with phytochemicals, encapsulating them within their hydrophobic cavity to improve aqueous solubility [217]. CD complexes enhance the loading capacity and carriage of plant bioactive constituents, protect against chemical degradation, and increase bioavailability for targeted delivery.

The strongest evidence related to HPV (human papillomavirus) comes from two specific formulations. The RES/HP-β-CD complex (RHSD) has been shown to significantly downregulate the HPV oncogenes E6 and E7 in vivo while upregulating the levels of P53 and Rb1. This approach demonstrated greater efficacy on these proteins compared to free resveratrol, achieving a 438.6-fold increase in solubility and transforming the crystalline

structure of resveratrol into an amorphous form. Notably, this is the only cyclodextrin-phytochemical formulation with direct evidence of in vivo HPV oncoprotein suppression to date.

For curcumin-cyclodextrin complexes, the established in vivo model is the TC-1 system. When administered orally, these complexes reduced the size of implanted lung tumors in orthotopic settings. In vitro experiments showed impaired tumor cell proliferation and increased apoptosis, while the combination of curcumin-CD and gemcitabine enhanced therapeutic effects in C57Bl/6 mice. TC-1 cells express HPV16 E6/E7, making this study directly relevant to HPV+ OPSCC.

The SBE-β-CD/quercetin inclusion complex system demonstrated the best results in HMW chitosan formulations for HPV-related cervical cancer cells, showing a remarkable improvement in quercetin bioavailability. This approach is directly translatable to HPV-OPSCC, given the shared viral oncogenic mechanisms.

6.6. AI-Assisted Nanoparticle Design

Artificial Intelligence and Machine Learning are now being integrated into phytochemical profiling and nanoparticle design, offering predictive algorithms to improve green synthesis methods and optimization of loading efficiency.

Rapid assessment of plant extracts using high-throughput omics could accelerate the identification of optimal nanocarrier formulations for HPV+ OPSCC-specific phytochemical delivery. Artificial intelligence is reshaping the discovery of natural product-derived antitumor agents by enabling faster compound screening, more reliable pharmacological predictions, and more efficient optimization throughout the drug discovery process. By combining machine learning and deep learning approaches with multi-omics data and advanced bioinformatics tools, AI has greatly expanded our ability to explore the chemical diversity of phytochemicals and to identify candidates with genuine anticancer potential [218].

When integrated with metabolomic, proteomic, and cheminformatic analyses, AI-driven strategies provide a more systematic and informed approach to prioritizing bioactive compounds and understanding their possible mechanisms of action. This represents a meaningful shift away from traditional trial-and-error screening toward more targeted and data-driven phytochemical discovery.

Addressing these challenges will require improved data curation practices, the development of transparent and explainable AI models, and closer collaboration between computational scientists, experimental researchers, and clinicians.

Overall, AI-driven phytochemical screening stands out as both a necessary and promising strategy for developing new chemotherapeutic agents. As AI technologies mature and become more accessible, their thoughtful integration, supported by experimental validation and clinical insight, is likely to play an increasingly important role in advancing precision oncology and natural product–based cancer therapies. Challenges related to regulatory guidelines, scalability, and long-term safety must still be addressed to fully realize their clinical potential.

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 and HPV+ OPSCC

There are 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 (Safety and Efficacy of APG-157 in Head and Neck Cancer, NCT05312710, available online at https://clinicaltrials.gov/study/NCT05312710, accessed on 10 May 2026).

7.2. Polyphenon E (EGCG) for Oral Leukoplakia

A Phase I/II trial at MD Anderson shows acceptable safety and signs of efficacy in reducing premalignant lesions [219].

7.3. Veregen (Sinecatechins/EGCG)

Sinecatechins are FDA-approved for HPV-related external genital warts [220–222]. 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. 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 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 [223].

7.4. Silymarin for Radiotherapy-Induced Mucositis

Clinical observations (420 mg/day or 70 mg/5 mL oral nano-Silymarin solution) showed a significant reduction in the onset and severity of grade 3–4 mucositis [224–226].

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—a highly relevant aspect, as mucositis is the most debilitating acute toxicity associated with radiotherapy for OPSCC [194,224–228].

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 [193,229,230].

7.5. I3C for Recurrent Respiratory Papillomatosis

I3C 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 [183].

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 [231].

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 [185]. However, further research is needed to determine the most effective application methods.

Plant constituents for managing outcomes after surgery, chemotherapy, and radiotherapy are shown in Table 5.

Table 5. Plant constituents and their various mechanistic pathways in HPV+ OPSCC outcomes and therapy.

Constituent	Outcome Addressed	Evidence Level	Key Findings	Mechanistic Pathway
Curcumin *Nanomicelle capsules—SinaCurcumin® 80 mg twice daily × 7 weeks* [232]	Oral mucositis	RCT	OM severity was significantly lower in the curcumin group vs. the placebo at weeks 1, 4, and 7 ($p < 0.001$); ↓ pain scores; effective for chemoradiotherapy-induced OM in HNC patients (n = 50 RCT)	↓ NF-κB and pro-inflammatory cytokines (TNF-α, IL-6); antioxidant mucosal protection; ↓ ROS-mediated tissue damage
Curcumin *Mouthwash 0.1% w/v and nanomicelle soft gel SinaCurcumin® 40 mg—3× daily during RT* [233]	Oral mucositis	RCT	Both formulations ↓ radiation-induced OM severity and pain vs. placebo (n = 37 RCT, HNC); mouthwash showed earlier onset of effect; nanomicelle better at week 3; well tolerated during RT alone or chemoRT	↓ Oxidative stress at mucosal level; anti-inflammatory (NF-κB); wound-healing promotion; ↓ ulceration depth
Curcumin *Systematic review and meta-analysis of 8 RCTs + network pharmacology* [234]	Oral mucositis	SR/meta-analysis	Meta-analysis confirmed curcumin ↓ OM severity and pain in HNC patients receiving RT and/or CT; network pharmacology + molecular docking identified NF-κB, TP53, and AKT1 as key targets; evidence supports curcumin as an adjunct to standard OM care	NF-κB, TP53, AKT1, VEGF pathway modulation; anti-inflammatory + antioxidant dual mechanism confirmed computationally and clinically
Natural bee honey *Topical application during RT—20 mL swish and swallow before and after RT.* [235]	Oral mucositis	RCT	Multiple RCTs: ↓ Radiation-induced OM severity and incidence of intolerable grade 3/4 mucositis; ↓ treatment breaks and loss of treatment days ($p < 0.0001$); does not interfere with tumor RT response; 2024 network meta-analysis ranked honey among top agents for OM incidence and pain reduction	Antimicrobial (↓ secondary Candida/bacterial infection); antioxidant (flavonoids, phenolic acids); wound healing (↑ epithelial regeneration); anti-inflammatory (↓ prostaglandins)
Taiwanese green propolis *Flavonoid-rich bee product—oral rinse/swallow during and post-RT* [236]	Oral mucositis	RCT	3-arm RCT (n = 75 HNC patients; Jen et al. 2025): Propolis group ↓ patient-reported OM symptoms and ↓ xerostomia vs. usual care; honey group ↑ QoL ($\beta = 10.05$, $p = 0.01$) and ↓ OM severity; both superior to standard care across 12-week post-RT follow-up	Chrysin and caffeic acid phenethyl ester (CAPE): Anti-inflammatory (↓ IL-1β, TNF-α), antioxidant, antimicrobial; mucosal barrier protection and epithelial regeneration
Silymarin (milk thistle) *Silybum marianum—oral 420 mg/day (three divided doses); nano-silymarin 70 mg/5 mL* [224,228]	Oral mucositis	RCT	Oral silymarin 420 mg/day: Significantly ↓ reduced mucositis grade and delayed onset vs. placebo ($p < 0.01$); also ↓ oral pain and xerostomia scores; nano-silymarin RCT (2021) confirmed findings with improved bioavailability; safe, well-tolerated.	Anti-inflammatory (↓ NF-κB, TNF-α); antioxidant (↑ GSH, SOD); mucosal cytoprotection; ↓ radiation-induced ROS damage to epithelium
SAMITAL *Standardized bilberry (Vaccinium myrtillus) + green tea phytocomplex—oral rinse during chemoRT* [237,238]	Oral mucositis	RCT	Phase 2 double-blind RCT—ROSAM trial (n = 120 HNC patients): SAMITAL oral rinse ↓ OM severity and duration vs. placebo; ↓ pain; ↓ treatment interruptions; trend toward ↑ QoL; well tolerated across the full course of concurrent chemoradiotherapy	Anthocyanins (bilberry): mucosal integrity, anti-inflammatory; EGCG (green tea): antioxidant, antimicrobial; combined cytoprotective effect on oral epithelium

Table 5. *Cont.*

Constituent	Outcome Addressed	Evidence Level	Key Findings	Mechanistic Pathway
Aloe vera *Aloe barbadensis—gel; topical application 3× daily during and after RT* [239]	Oral mucositis	Clinical trial	Multiple clinical trials and a 2024 systematic review confirm aloe vera gel ↓ grade and progression of RT-induced OM in HNC; it has also been studied for xerostomia and burning mouth. Active RCT (NCT06381635, 2024) comparing aloe vera + Manuka honey vs. saline; salivary TGF-β1 and EGF assessed	Acemannan polysaccharides: ↑ Fibroblast growth + epithelial repair; ↑ salivary EGF; ↓ IL-1β; antimicrobial; ↓ mucosal oxidative stress
Silymarin/silybin B *Milk thistle—oral 140 mg twice daily; prophylactic use during cisplatin-based CT* [240]	Cisplatin toxicity	Clinical trial	Clinical trial: Silymarin prophylaxis ↓ of cisplatin-induced nephrotoxicity (↓ serum creatinine, ↓ BUN); safe and well-tolerated adjunct. Silybin B (active isoform) confirmed to ↓ apoptosis, DNA damage, and cell cycle arrest in cisplatin-treated neuronal cells (mouse model, 2022). Hepatoprotective effects have also been documented.	↑ GSH and SOD (renal antioxidant defence); ↓ cisplatin accumulation in renal tubular cells; ↓ oxidative DNA damage; hepatoprotective (↓ AST/ALT); neuroprotective (↓ p38-MAPK apoptosis)
Silymarin *Milk thistle—oral 140 mg twice daily; adjunct during/post chemotherapy* [193]	Peripheral neuropathy	Clinical trial	Clinical study: Silymarin 140 mg twice daily significantly improved chemo-induced peripheral neuropathy; ↓ pain scores; minimal side effects (mild GI symptoms only); protective against oxaliplatin- and cisplatin-induced neurotoxicity; p38-MAPK inhibition confirmed as protective mechanism	↓ p38-MAPK-mediated neuronal apoptosis; ↑ BDNF (brain-derived neurotrophic factor); ↓ oxidative stress in neural tissue; anti-neuroinflammatory (↓ microglial activation)
Resveratrol *Stilbene (grapes, berries)—preclinical and* in vitro *studies; HNSCC models* [241]	Radiosensitisation	Preclinical/in vitro	Resveratrol ↑ sensitivity of HNSCC cells to RT; ↓ NF-κB and JAK/STAT survival signaling post-irradiation; ↓ DNA repair capacity in tumor cells; pre/post-RT administration ↓ hematopoietic ROS, ↓ NOX4/COX-2; also protects normal tissue (antioxidant dual role); 2026 systematic review confirms radiosensitizing potential in HNSCC	↓ NF-κB, ↓ JAK/STAT; ↓ DNA repair (Ku70/Ku80) in tumour cells; AMPK activation; ↓ NOX4/COX-2; pro-apoptotic in irradiated cancer cells; antioxidant protection of normal tissues
EGCG + HPV E7 DNA vaccine *Green tea catechin—oral administration; immunoadjuvant in TC-1 syngeneic HPV+ model* [208]	Radiosensitisation	Preclinical/in vitro	Oral EGCG + E7/LAMP DNA vaccine → complete tumor regression in TC-1 HPV+ mouse model; ↑ E7-specific CD8+ T cells vs. vaccine alone; enhanced primary and memory T cell responses; no systemic toxicity, no hair loss, no lymphopenia—favorable safety profile for combination with RT/CT	↑ CD8+ cytotoxic T cell-mediated immunity; immunoadjuvant synergy with therapeutic HPV vaccine; no myelosuppression; NK cell and CTL potentiation
Resveratrol + cisplatin *Combination treatment—HNSCC cell line PE/CA-PJ49;* in vitro [242]	Chemosensitisation	Preclinical/in vitro	RSV + cisplatin: ↑ Tumor cell viability loss vs. cisplatin alone; ↑ p21 expression; ↑ apoptosis; ↓ cell cycle progression; selectivity for tumor cells over normal HUVEC endothelial cells; resveratrol amplifies cisplatin-induced DNA damage response via G1 arrest	↑ p21 (CDKN1A); G1 cell cycle arrest; ↑ apoptosis; amplifies cisplatin DNA double-strand break response; selectivity for tumour vs. normal cells

Table 5. *Cont.*

Constituent	Outcome Addressed	Evidence Level	Key Findings	Mechanistic Pathway
Curcumin + cisplatin *Combination treatment—HNSCC and HPV+ OPSCC cell lines; in vitro* [243]	Chemosensitisation	Preclinical/in vitro	Curcumin + cisplatin: ↑ Apoptosis and ↓ proliferation vs. monotherapy; ↓ IC50 of cisplatin when combined; ↑ p21; greater effect on tumor than normal cells. Curcumin targets CDC27 in HPV+ OPSCC cell lines (CU-OP-2/3/20); synergistic with PI3K inhibitor BYL719 and WEE1 inhibitor MK-1775	Synergistic apoptosis induction; ↓ cisplatin dose required for equivalent effect; p21↑; NF-κB inhibition; CDC27 targeting (HPV+ specific); PI3K/AKT/mTOR pathway
Honey + green propolis *Bee honey/Taiwanese green propolis—topical rinse and swallow; post-RT* [236]	Xerostomia/QoL	RCT	3-arm RCT (n = 75): Honey ↑ QoL scores (β = 10.05, p = 0.01) and ↓ OM severity; propolis ↓ patient-reported xerostomia vs. usual care; both superior to standard care across 12-week post-RT follow-up; well tolerated; GEE method analysis	↑ Salivary flow stimulation; antimicrobial (↓ Candida); mucosal hydration; anti-inflammatory (↓ salivary cytokines); flavonoid-mediated salivary gland protection
Coconut oil *Cocos nucifera—oil pulling/topical rinse; post-RT xerostomia management* [244]	Xerostomia/QoL	Clinical trial	Feasibility study (Ottawa HNC patients ≥18 months post-RT, ≥50 Gy): Coconut oil safe, inexpensive, well tolerated; patient-reported ↓ dry mouth symptoms; no adverse events; identified as promising low-cost intervention; larger RCT required for efficacy confirmation	Mucosal lubrication (lauric acid and medium-chain fatty acids); antimicrobial (lauric acid); anti-inflammatory; ↓ friction and mucosal dryness symptoms
Aloe vera *Aloe barbadensis—gel 3× daily; post-RT xerostomia and mucosal healing* [239]	Xerostomia/QoL	Clinical trial	Active RCT NCT06381635 (Ain Shams University, 2024): Testing aloe vera gel + Manuka honey for RT-induced mucositis and xerostomia in HNC patients; salivary TGF-β1 and EGF as biomarkers; prior studies confirm aloe vera ↓ burning sensation, improves mucosal hydration and epithelial healing post-RT	Acemannan polysaccharides: ↑ Fibroblast proliferation + epithelial repair; ↑ EGF; ↓ IL-1β; humectant (↓ water loss from mucosa); antimicrobial

↓—inhibition; ↑—activation.

Plant-based constituents can play a preventive role in HPV-ONSCC by directly inhibiting HPV-induced papillomatosis (Table 6).

Table 6. Phytochemicals and their antiviral potential on HPV-induced papillomatosis.

Constituent/ Formulation	Anatomical Site	HPV Types Targeted	Evidence Level	Year	Key Findings	OPSCC Preventive Link	Mechanism of Action
Sinecatechins (Veregen®) *Polyphenon E—EGCG-rich green tea extract; 15% topical ointment 3× daily for up to 16 weeks* [245]	Genital/ perianal warts	HPV 6, HPV 11 (low-risk); active against HPV 16 in vitro	FDA-approved/ RCT/Phase II–III	2006/ 2009	FDA-approved botanical drug (2006, first ever) for condylomata acuminata. Phase III RCTs (n = 1005): 15% ointment → 52–57% wart clearance vs. 33–37% placebo; lower recurrence rate vs. imiquimod; active on oral and anal warts. Full wart clearance is maintained with fewer relapses than podophyllotoxin.	Direct antiviral/prevention	↓ AP-1 transcription → ↓ HPV gene expression; EGCG ↓ HPV E6/E7; pro-apoptotic; anti-inflammatory; immunostimulatory (↑ CD8+ T cell response); antiproliferative

Table 6. *Cont.*

Constituent/ Formulation	Anatomical Site	HPV Types Targeted	Evidence Level	Year	Key Findings	OPSCC Preventive Link	Mechanism of Action
Sinecatechins—post-ablation sequential therapy *10% ointment after CO2 laser or cryotherapy; PACT-II trial* [223]	Genital/ perianal warts	HPV 6, HPV 11	RCT/Phase II–III	2022	PACT-II prospective assessor-blinded pilot RCT: Sinecatechins 10% applied after cryotherapy ablation of external genital warts → significantly ↓ reduced condyloma recurrence rate vs. no further treatment; well tolerated; supports sequential strategy combining rapid ablative clearance with botanical immunostimulation to prevent viral re-establishment.	Indirect/ mechanistic	↓ Viral reservoir post-ablation; EGCG immunostimulation ↑ local HPV-specific immunity; ↓ risk of viral spread to oropharynx via reduced genital load
Polyphenon E/EGCG (oral) *Green tea catechin extract—200 mg oral capsule daily; 8–12 weeks* [219]	Cervico-vaginal	HPV 16, HPV 18 (high-risk); persistent infection	RCT/Phase II–III	2003/ 2014	Ahn et al.: 69% clinical response in HPV-infected cervical lesions vs. 10% untreated controls (n = 51). Garcia et al. Phase 2 RCT: 17.1% complete response (HPV DNA negative + normal histology) with Polyphenon E in persistent high-risk HPV + CIN1. Oral + topical combined approach: 74–75% response rate; EGCG capsule alone: 60% response.	Direct antiviral/prevention	↓ AP-1 → ↓ HPV transcription; EGCG ↓ E6/E7 oncoprotein levels; ↑ p53; immunostimulatory; ↓ viral persistence; epigenetic (DNMT inhibition); ↓ cell proliferation
EGCG + Folic acid + Vitamin B12 + Hyaluronic acid (Pervistop®) *Oral supplement: 200 mg EGCG + 400 mcg folic acid + 1 mg B12 + 50 mg HA; 1–2 caps/day for 3–6 months* [246]	Cervico-vaginal + Anal	Multiple high-risk HPV types (cervical + anal)	Clinical trial/study	2023/ 2024	Calcagno et al. 2024 [246]: 5 clinical cases with persistent cervical or anal HPV infection—all 5 patients had HPV DNA negative and cytological lesions improved after 3–6 months of Pervistop®. Prior clinical study (2023) confirmed HPV clearance and CIN regression with this combination. In vitro: EGCG + FA + B12 + HA combination synergistically ↑ induces apoptosis, ↑ p53, ↓ E6/E7 (stronger than any single molecule).	Direct antiviral/prevention	EGCG: ↓ E6/E7, ↑ p53; Folic acid: ↑ DNA integrity, ↓ viral integration risk; B12: ↑ immune surveillance; HA: mucosal integrity; synergistic antiviral + immunosupportive
Myrtle (*Myrtus communis*) *Vaginal suppository: 10% aqueous extract + 0.5% essential oil; 20 suppositories per menstrual cycle × 3 months* [247]	Cervicovaginal	HPV 16, HPV 18, and other high-risk cervicovaginal types	RCT/Phase II–III	2018	Nikakhtar et al. RCT (n = 60 women with cervicovaginal HPV): HPV DNA negative at end of study 92.6% vs. 62.6% placebo ($p = 0.036$); cervical lesion size reduction 71.4% vs. 30.4% ($p = 0.015$). Separate clinical study: topical myrtle leaf poultice superior to salicylic acid for hand/foot warts. 2025 in silico study (virtual screening): Active phytochemicals dock to HPV L1 capsid protein, E6, and E7 targets.	Direct antiviral/prevention	Tannins and flavonoids (myricetin, quercetin, ellagic acid): antiviral (↓ HPV replication), antimutagenic, pro-apoptotic; ↓ viral persistence; L1 capsid binding confirmed in silico
Curcumin + polyherbal vaginal cream (Basant) *Curcumin + reetha + amla (Phyllanthus emblica) + aloe vera—vaginal cream 1 application/day × 30 days* [248]	Cervicovaginal	Multiple high-risk HPV types	RCT/Phase II–III	2013	Basu et al. Phase II RCT (n = 287 HPV+ women): Curcumin vaginal capsules and Basant polyherbal cream → HPV clearance significantly greater than placebo arms; amla + reetha + curcumin combination showed non-significant trend toward greater HPV 16/18 clearance; well tolerated (mild vaginal irritation in Basant arm only); supports curcumin as anti-HPV topical agent.	Indirect/ mechanistic	Curcumin: ↓ HPV E6/E7, ↑ p53, ↓ NF-κB; Amla (ellagic acid, vitamin C): antiviral, ↑ immunity; Aloe vera: ↑ mucosal immunity (acemannan); Reetha: antimicrobial + antiviral saponins
Curcumin (oral/intravaginal—ongoing RCTs) *Oral 500 mg twice daily for CIN3 (Baylor RCT) OR intravaginal 2000 mg weekly × 20 weeks (Emory RCT)* [249]	Cervicovaginal + Oral/OPSCC prevention	HPV 16, HPV 18 (CIN 2/3, high-risk)	RCT/Phase II–III	2020/ ongoing	Baylor RCT (NCT02554344): Oral curcumin 500 mg twice daily × 12 weeks for CIN3—colposcopy and NF-κB assessed at 6 and 12 weeks. Emory study: Intravaginal curcumin for LSIL/HSIL in women with and without HIV. Curcumin nanoemulsion (2025): ↓ HPV E6/E7 oncogenes in TC-1 HPV+ model in vitro and in vivo. Systematic review (2024): A meta-analysis of curcumin supports CIN regression and HPV clearance.	Direct antiviral/prevention	↓ HPV E6/E7 → ↑ p53/Rb restoration; ↓ NF-κB; ↓ AP-1; ↓ CIN progression; curcumin nanoemulsion ↑ bioavailability and intratumoural delivery

Table 6. *Cont.*

Constituent/ Formulation	Anatomical Site	HPV Types Targeted	Evidence Level	Year	Key Findings	OPSCC Preventive Link	Mechanism of Action
Herbal treatments—systematic review *Polyphenon E (oral), curcumin vaginal, myrtle vaginal, EGCG oral, olive oil vaginal spray* [250]	Cervicovaginal	Multiple HPV types (high-risk and low-risk)	Systematic review	2024	Demir & Cetinkaya systematic review (RCTs up to December 2023): Herbal treatments show a significant reduction in ASCUS/LSIL cytological abnormalities; moderate evidence for HPV DNA clearance; most robust evidence for Polyphenon E (oral), myrtle suppository, and curcumin vaginal capsules; all well tolerated; authors conclude herbal interventions represent a promising and safe strategy for HPV clearance.	Indirect/ mechanistic	Class-level antiviral + immunostimulatory effect across polyphenols, terpenes, and essential oils; systematic clearance of high-risk HPV from cervicovaginal epithelium = primary prevention for HPV-driven cancers, including OPSCC
Indole-3-carbinol (I3C) *Cruciferous vegetables (broccoli, cabbage, cauliflower)—oral 200–400 mg adults twice daily; weight-based in children* [251,252]	Respiratory (RRP)	HPV 6, HPV 11 (RRP); HPV 16/18 (CIN)	Clinical trial/study	1998/ 2004	Derkay et al. Phase I (1998): Established the safety and tolerability of I3C for RRP in adult and pediatric patients. Rosen & Bryson long-term clinical study (2004, n = 45 RRP patients, 5-year follow-up): 11/33 (33%) experienced remission and required no further surgery while on I3C; no immediate or long-term side effects; pediatric response confirmed. Separate preliminary trial: I3C 200–400 mg/day resulted in a statistically significant regression of CIN 2/3. Listed in the University of Iowa RRP treatment protocol (updated January 2023).	Direct antiviral/prevention	↑ 2-OHE1:16α-OHE1 ratio (anti-oestrogenic); ↓ NF-κB; ↓ PI3K/AKT; ↓ cyclin D1; ↓ Wnt/β-catenin; ↓ HPV-driven epithelial proliferation; ↓ malignant transformation risk of RRP
Diindolylmethane (DIM) *Acid-catalyzed dimeric metabolite of I3C—oral supplement 108–300 mg/day* [183]	Respiratory (RRP)	HPV 6, HPV 11	Preclinical + clinical	Ongoing	DIM is the stable bioactive metabolite of I3C formed during digestion; it shares I3C's anti-HPV properties but with superior bioavailability and chemical stability. Used clinically as an adjunct to surgery in RRP management. DIM 108 mg/day (30-day clinical trial): ↑ Urinary 2-OHE1 in post-menopausal women. DIM 300 mg/day (thyroid cancer trial): Modified estrogen metabolism confirming systemic bioactivity. Preclinical: ↑ Immune surveillance in HPV+ cells; ↓ papilloma recurrence in model systems.	Indirect/ mechanistic	↑ 2-OHE1:16α-OHE1 ratio; ↓ NF-κB; ↓ Wnt/β-catenin; ↑ p27/p21; immunomodulatory; ↓ HPV-driven respiratory epithelium proliferation; ↓ malignant transformation risk in RRP
Nigella sativa + *Moringa oleifera* + *Musa acuminata* peel *Herbal mixture; polymer film-forming topical system for plantar/cutaneous HPV warts* [253]	Multi-site/plantar	HPV 1, 2, 4 (cutaneous); network pharmacology targets HPV 6/11/16/18	RCT/Phase II–III	2024	Polymer film herbal mixture significantly ↓ reduced wart size and quantity vs. placebo in outpatient clinic patients. LC-HRMS identified 49 bioactive metabolites. Network pharmacology: Thymoquinone (N. sativa), isothiocyanates (Moringa), and lectins (Musa) target HPV-relevant genes, including EGFR, TP53, and AKT1. Thymoquinone is antiviral in separate studies, including ↓ a reduction in HPV E6 expression.	Preclinical pathway	Thymoquinone (N. sativa): ↓ NF-κB, ↓ PI3K/AKT, antiviral; Isothiocyanates (Moringa): pro-apoptotic, ↑ p53; Lectins (Musa): immune stimulation; ↓ HPV viral load in infected epithelium

↓—inhibition; ↑—activation.

8. Current Key Findings

Most plant bioactive compounds analyzed in the present review have demonstrated significant anti-HPV effects and anticancer activity against HPV-induced oropharyngeal and cervical cancers in preclinical studies.

8.1. Mechanistically Coherent Antiviral Targeting

Multiple compounds (curcumin, EGCG, berberine, tanshinone IIA, resveratrol) converge on the same HPV oncogenic axis—E6/E7 oncoprotein degradation and p53/Rb restoration—providing a biologically plausible and consistent mechanistic rationale.

8.2. Regulatory Proof of Concept

Sinecatechins (Veregen®) represents the first FDA-approved botanical drug for HPV-driven disease, demonstrating that plant-derived anti-HPV therapeutics can reach the highest regulatory standard.

8.3. Clinical RCT Evidence Supports Treatment Outcomes

Specifically for oral mucositis, multiple independent RCTs (curcumin, honey, silymarin, SAMITAL) and a 2024 systematic review/meta-analysis provide strong clinical evidence that several plant agents can reduce a key severe complication of HPV+ OPSCC treatment.

8.4. Immune Modulation in Immunocompetent Models

TriCurin studies using the TC-1 syngeneic model demonstrated that the anti-tumor effect depends on TAM repolarisation and CD8+ T cell recruitment—an immune mechanism absent in xenograft models, providing additional translational weight.

8.5. Favorable Safety Profiles

The overwhelming majority of plant compounds reviewed show no significant toxicity to normal cells at therapeutic doses, with several (silymarin, honey, aloe vera) demonstrating better tolerability than standard pharmacological agents in direct comparisons.

8.6. Synergistic Combination Evidence

Combinations (TriCurin, luteolin + asiatic acid, resveratrol + cisplatin) consistently outperform single agents in vitro and in vivo, suggesting combination phytotherapy or phyto-chemotherapy synergy may be more clinically relevant than monotherapy.

8.7. Coherent OPSCC Prevention Pathway

The mechanistic link between treating HPV papillomatosis at any site (genital, cervical, respiratory) and reducing oropharyngeal cancer risk is well-supported: shared HPV 16/18 strains, E6/E7-mediated carcinogenesis, and systemic viral load reduction all point toward a prevention cascade.

8.8. Nanoformulation Progress

Nanoparticle delivery systems (CUR-LCNPs, nano-silymarin, liposomal curcumin) are actively addressing the bioavailability limitations of polyphenols, with several showing superior efficacy to free compounds in head-to-head comparisons.

8.9. Growing Recency of Evidence

Several key studies were published in 2023–2025—including the only study using primary HPV+ OPSCC patient-derived cell lines [254], the most comprehensive tanshinone + curcumin W12 model study [196], and the most recent sinecatechins RCT [246], demonstrating an active and expanding research field.

In summary, these phytochemicals may provide a scientifically supported, mechanistically consistent, and toxicologically safe adjuvant approach for HPV-positive oral cancer (Figure 4).

Evidence Levels Key

FDA-approved	RCT / Systematic review	Phase 2 RCT / Clinical trial	Animal model (in vivo)	In vitro only
Highest regulatory standard—botanical drug approved by the FDA for HPV-driven disease	Randomized controlled trial evidence is the strongest clinical evidence	Early-phase clinical trial or feasibility study evidence	In vivo animal data; preclinical, but includes immune and pharmacokinetic context	Cell line and mechanistic data only; no in vivo or clinical validation

Key Compounds and Highest Evidence Level Achieved

Color coding in the Class and Evidence level columns follows the key above.

Compound	Class	Highest evidence level	Key evidence and notes
Curcumin *Polyphenol (turmeric)*	Polyphenol	**RCT + Systematic review/meta-analysis (2024)**	• Multiple RCTs: Oral mucositis (nanomicelle 80 mg twice daily; 0.1% mouthwash) • 2024 systematic review and meta-analysis (8 RCTs) confirmed benefit for OM • In vitro: HPV+ OPSCC cell lines (CU-OP series) -- down E6/E7, NF-kB (Kostopoulou 2024) • Synergy with cisplatin and PI3K/WEE1 inhibitors in vitro • RCTs ongoing for CIN3 (NCT02554344, Baylor)
EGCG / Sinecatechins (Veregen) *Green tea; Camellia sinensis*	Polyphenol / Catechin	**FDA-approved + Phase II-III RCTs**	• FDA-approved botanical drug (Veregen 15%) for genital warts—first-ever (2006) • Phase III RCTs: 52–57% wart clearance vs. 33–37% placebo • Phase 2 RCT (Garcia et al. 2014): 17.1% complete HPV clearance in CIN1 • TC-1 animal model: EGCG + E7 DNA vaccine—complete tumour regression • In vitro: Proteasomal E6/E7 degradation; anti-DNMT; anti-EMT

Figure 4. *Cont.*

TriCurin *Curcumin + Resveratrol + Epicatechin gallate*	Polyphenol combination	**HPV+ HNSCC xenograft + TC-1 syngeneic animal model**	• UMSCC47/SCC090 xenograft: 85.5% tumour growth inhibition (Piao et al. 2017) • TC-1 syngeneic: 80–90% tumour growth reduction; down HPV E6/E7; up p53 • Immunocompetent TC-1: TAM repolarisation M2-to-M1; up IL-12; NK + CTL recruitment (Mukherjee et al. 2018) • Most complete preclinical evidence package of any compound combination reviewed • No clinical trials yet in HPV+ OPSCC patients
Silymarin *Milk thistle; Silybum marianum*	Polyphenol / Flavonolignan	**Multiple RCTs + Clinical trials**	• RCTs: Down oral mucositis severity and delayed onset (420 mg/day; nano-silymarin 2016, 2021) • Clinical trial: Down cisplatin-induced nephrotoxicity (down creatinine, down BUN) • Clinical study: Downregulation of chemo-induced peripheral neuropathy (p38-MAPK inhibition) • Most versatile compound reviewed—active across 3 clinical outcome domains. • Well tolerated; mild GI side effects only
Indole-3-carbinol (I3C) *Cruciferous vegetables (broccoli, cabbage)*	Glucosinolate metabolite	**Phase I + Long-term clinical study**	• Phase I (Derkay et al. 1998): Established safety and tolerability in RRP • Long-term clinical study (Rosen & Bryson 2004; n = 45; 5-yr follow-up): 33% surgical remission • Listed in the University of Iowa RRP treatment protocol (updated January 2023) • Preliminary trial: Significant regression of CIN 2/3 at 200–400 mg/day • Strongest plant evidence for RRP—directly relevant to OPSCC prevention pathway
Honey + Green propolis	Complex phenolic mixtures	**Multiple RCTs + Network meta-analysis (2024)**	• Multiple RCTs: Down radiation-induced OM grade and incidence of grade 3/4 OM • Down treatment breaks and loss of treatment days (p<0.0001)

Figure 4. *Cont.*

Natural bee honey; Taiwanese green propolis			• Network meta-analysis (Coppini et al. Oral Dis 2024): Top agent for OM incidence and pain • 3-arm RCT (Jen et al. 2025; $n = 75$): Honey up QoL (b = 10.05, $p = 0.01$); propolis down xerostomia • Antimicrobial, antioxidant, wound-healing, safe, and inexpensive
Resveratrol/Pterostilbene *Grapes/berries; blueberries*	Polyphenol/Stilbene	**TC-1 syngeneic animal model + In vitro**	• TC-1 mouse model: Both agents significantly inhibited HPV+ tumor development • Down HPV E6 protein in tumour tissue; down VEGF (anti-angiogenic) • Resveratrol: Down PCNA (cell cycle arrest); pterostilbene: up caspase-3 (apoptosis) • Chemosensitization: Resveratrol + cisplatin upregulates apoptosis in HNSCC (in vitro; Bostan et al. 2020) • Radiosensitizer potential in HNSCC models (Fallah et al. 2026 review)
Myrtle (*Myrtus communis*) *Vaginal suppository; Mediterranean plant*	Tannin/phenolic plant extract	**Double-blind RCT**	• Nikakhtar et al. 2018 RCT (n = 60): 92.6% HPV DNA clearance vs. 62.6% placebo ($p = 0.036$) • Cervical lesion size reduction: 71.4% vs. 30.4% ($p = 0.015$) • 2025 in silico: Myrtle phytochemicals dock to HPV L1, E6, and E7 targets • Active constituents: Myricetin, quercetin, ellagic acid, tannins • Clinically actionable now for cervicovaginal HPV clearance
Berberine *Berberis spp.; Coptis chinensis*	Alkaloid	**In vitro (HPV+ cell lines)**	• SiHa (HPV16+) and HeLa (HPV18+): Selectively inhibits constitutively active AP-1 • Down HPV E6 and E7; up p53 and Rb; down hTERT (telomerase); down oncogenic c-Fos • Growth arrest and apoptosis; non-toxic to normal cells in the same assay

Figure 4. *Cont.*

			• HSC-3 (oral SCC): G0/G1 arrest + caspase-3 activation (Chiu et al. 2007) • No in vivo or clinical data in OPSCC
alpha-Mangostin *Garcinia mangostana pericarp*	Xanthonoid	**HPV16+ xenograft + In vitro (2023)**	• SiHa + CaSki xenograft (Diaz et al. 2023): significant tumor growth inhibition in vivo • Downregulation of the E6 and E7 oncogene expression in tumor tissue; downregulation of the KCNH1 potassium channel • Down PCNA; up apoptosis in tumor sections; good tolerability in mice • Novel mechanism: KCNH1 downregulation (additional to E6/E7 suppression) • No clinical trials; no OPSCC-specific clinical data
SAMITAL *Bilberry + green tea standardized phytocomplex*	Standardized phytocomplex	**Phase 2 double-blind RCT (ROSAM trial)**	• ROSAM Phase 2 double-blind RCT (Fasanaro et al. 2022; *n* = 120 HNC patients) • Down oral mucositis severity and duration vs. placebo during chemoradiotherapy • Down pain; down treatment interruptions; trend toward up QoL • Combines anthocyanins (bilberry) + EGCG (green tea) for mucosal cytoprotection • Well tolerated across the full course of concurrent chemoradiotherapy
Tanshinone IIA + Curcumin *Salvia miltiorrhiza (Danshen) + Curcuma longa*	Diterpenoid + Polyphenol combination	**HPV16+ cell lines (W12, CaSki); In vitro (2025)**	• Einbond et al. 2025: Tested on W12 episomal HPV16, W12 integrated HPV16, CaSki, SiHa • Tanshinone IIA repressed complete HPV16 transcriptome: E1, E2, E4, E6 and E7 • Synergistic with curcumin; upregulates p53 • Molecular docking: Na+/K+-ATPase as putative binding target (bioelectric signaling) • Most recent mechanistic study (2025); no in vivo or clinical data yet

Figure 4. *Cont.*

Evidence by Domain

Domain	Best evidence level	Top compound(s)	Key gap
HPV+ OPSCC cell lines (in vitro)	**In vitro**	TriCurin, curcumin (CU-OP series), berberine, quercetin, EGCG, alpha-mangostin	Very few true HPV+ OPSCC-specific cell lines exist (UMSCC47, SCC090, CU-OP series only). Most data were extrapolated from cervical HPV16+ lines (SiHa, CaSki, HeLa) as surrogates, which may not fully reflect oropharyngeal biology.
HPV+ animal models (in vivo)	**TC-1 syngeneic + HPV+ HNSCC xenograft**	TriCurin, resveratrol, pterostilbene, alpha-mangostin, EGCG + therapeutic vaccine	No orthotopic HPV+ oropharyngeal model exists. TC-1 is lung epithelial-derived. No phytochemical study in HPV+ OPSCC patient-derived xenografts (PDX). Results may not reflect oropharyngeal carcinogenesis.
Post-treatment: oral mucositis	**Systematic review/meta-analysis of RCTs**	Curcumin, honey, silymarin, SAMITAL (bilberry + green tea), aloe vera	All RCTs in general HNC populations; HPV+ OPSCC patients were not separately stratified. Optimal timing relative to RT fractions unresolved. Antioxidant paradox risk with concurrent RT.
Post-treatment: cisplatin toxicity & neuropathy	**Clinical trial**	Silymarin (140 mg twice daily)	Small sample sizes. No HPV-specific patient stratification. Limited long-term follow-up data. No head-to-head comparison with standard supportive care agents.
Chemosensitization (cisplatin synergy)	**In vitro only**	Resveratrol + cisplatin, curcumin + cisplatin	No clinical trial data in HPV+ OPSCC. Antioxidant paradox: Same ROS-scavenging properties that sensitize tumor cells may protect them if administered concurrently. Timing and sequencing are completely unresolved.

Figure 4. *Cont.*

Radiosensitisation	**Preclinical/in vitro + review**	Resveratrol, EGCG + therapeutic HPV vaccine (TC-1 model)	No clinical trial in HPV+ OPSCC. Antioxidant paradox applies. EGCG/vaccine immune data from the 2011 TC-1 study; no updated clinical translation.
HPV papillomatosis treatment	**FDA-approved + Phase II-III RCTs**	Sinecatechins/Polyphenon E (genital), I3C (RRP), myrtle vaginal suppository (cervicovaginal), curcumin vaginal (CIN)	No RCT in oral papillomatosis specifically. RRP evidence from small long-term studies. HPV clearance and OPSCC risk reduction are not directly measured.
OPSCC prevention via HPV clearance	**Phase 2 RCT (indirect prevention)**	Polyphenon E/EGCG (oral), myrtle (cervicovaginal), curcumin (vaginal/oral), EGCG + FA + B12 + HA (Pervistop)	All evidence is indirect: HPV clearance from cervical/genital sites, not oropharyngeal. No study has used oropharyngeal HPV clearance or OPSCC incidence as a primary endpoint.

Figure 4. Evidence-based plant products with potential benefits in HPV+ OPSCC.

9. Limitations and Critical Gaps

9.1. No Dedicated HPV+ OPSCC Clinical Trial for Any Compound as an Anti-Cancer Therapy

Despite abundant in vitro and animal model data, no compound has completed a Phase II or III randomized controlled trial in HPV+ OPSCC patients as the target population, with tumor response as the primary endpoint. The entire anti-cancer evidence base remains preclinical.

9.2. Cell Line Model Gap

The majority of in vitro data has been generated using HPV16+ cervical cancer lines (SiHa, CaSki, HeLa) as surrogates for HPV+ OPSCC biology. Only a small number of true HPV+ OPSCC cell lines exist (UMSCC47, UPCI: SCC090, CU-OP series), and most have been used in only one or two published studies. Results from cervical lines may not fully translate to oropharyngeal biology.

9.3. Bioavailability Challenge

Polyphenols such as curcumin, quercetin, and resveratrol have notoriously low oral bioavailability (curcumin <1% in some estimates), rapid first-pass metabolism, and poor solubility. The in vitro concentrations required for HPV E6/E7 suppression are often far higher than physiologically achievable plasma levels. Nanoformulations are promising but remain largely in early-phase development.

9.4. Antioxidant Paradox During Treatment

The same ROS-scavenging properties that protect normal tissues from radiotherapy and cisplatin toxicity may, in theory, protect tumor cells from treatment-induced killing. The optimal timing of phytochemical administration relative to RT/CT remains unresolved, and concurrent use of antioxidant-rich supplements during active treatment carries theoretical risks, with limited supporting clinical safety data.

9.5. Animal Model Limitations

The TC-1 syngeneic model (the most widely used HPV+ preclinical model) was derived from mouse lung epithelial cells, not oropharyngeal tissue. No orthotopic HPV+ oropharyngeal model exists. No phytochemical study has been published using patient-derived xenografts (PDX) from HPV+ OPSCC. Results from TC-1 or SiHa/CaSki xenograft models may not reflect the biology of oropharyngeal carcinogenesis.

9.6. Post-Treatment Clinical Data Are Not HPV-Specific

All RCTs for mucositis (curcumin, honey, silymarin, SAMITAL, aloe vera) were conducted in general head and neck cancer populations. HPV+ OPSCC patients have a distinct biology, better prognosis, and different treatment responses from HPV-negative HNSCC. Subgroup analyses by HPV status are rarely reported.

9.7. Standardization and Reproducibility Remain Difficult

The phytochemical content of plant extracts can vary greatly depending on species, growing conditions, and preparation methods. Additionally, most studies lack detailed phytochemical profiling of the extracts used. As a result, comparing studies that use the same nominal compound, such as curcumin, is challenging.

9.8. Small Sample Sizes and Publication Bias

Many clinical trials in this space have low enrolment (n = 30–75), are conducted at single centers, and are predominantly from specific geographic regions. Positive results are more likely to be published, inflating apparent efficacy. Most combination studies remain in vitro with no in vivo validation.

9.9. Moderate Herb–Drug Interaction Risk

Compounds such as curcumin, resveratrol, EGCG, and berberine are known modulators of CYP450 and P-gp. In patients receiving cisplatin, 5-FU, or immunotherapy (pembrolizumab—standard of care in recurrent/metastatic HPV+OPSCC), pharmacokinetic herb–drug interactions could alter efficacy and toxicity in unpredictable ways. This risk is largely unstudied in the OPSCC context.

10. Essential Considerations and Future Directions

Plant bioactive constituents represent a biologically well-founded, mechanistically coherent, and pharmacologically active field in HPV+ OPSCC research. The evidence base spans a broad spectrum—from in vitro antiviral activity to clinical trials for treatment toxicity management to an FDA-approved compound for HPV-driven lesions. However, the translation gap between preclinical promise and clinical proof remains substantial, and no plant-derived agent can yet be recommended as an anti-cancer therapy specifically for HPV+ OPSCC based on current evidence.

The highest-quality, most clinically relevant evidence supports the use of plant agents to improve outcomes in severe conditions. Curcumin (multiple RCTs + meta-analysis), honey and propolis (RCTs + network meta-analysis 2024), silymarin (RCTs for mucositis, a clinical trial for nephrotoxicity and neuropathy), and SAMITAL (Phase 2 RCT) are a group of agents with enough clinical evidence to justify their inclusion in supportive care protocols—not as cancer treatments, but as adjuncts that lower treatment-related morbidity.

TriCurin (curcumin + resveratrol + epicatechin gallate) has the most comprehensive preclinical evidence package: HPV+ HNSCC cell line data, TC-1 syngeneic model, HPV+ HNSCC xenograft (85.5% inhibition), and a mechanistic immunological study demonstrating TAM reprogramming. EGCG and its combinations (Polyphenon E, Pervistop®) possess

both mechanistic depth and clinical trial support across multiple sites and HPV disease states. Both are strong candidates for early-phase clinical trials in HPV+ OPSCC.

The prevention pathway—which involves clearing HPV 16/18 from genital, cervical, and respiratory sites to decrease oropharyngeal exposure and viral load—is the most immediately applicable clinical strategy. Sinecatechins (FDA-approved), indole-3-carbinol (with clinical evidence in RRP and included in the Iowa protocol), and myrtle/Polyphenon E (used in cervicovaginal RCTs) are compounds where clinical use can currently be justified, and where the mechanistic connection to lower OPSCC risk is most clear.

The following research gaps should be urgently addressed:

- Dedicated HPV+ OPSCC clinical trials: Phase I/II trials of curcumin (alone or as TriCurin), EGCG, and berberine in HPV+ OPSCC patients are urgently needed. Trial design should stratify by HPV status and incorporate HPV E6/E7 suppression as a pharmacodynamic biomarker.
- Orthotopic animal model development: A syngeneic, orthotopic HPV+ oropharyngeal tumor model in immunocompetent mice would transform the translational value of preclinical phytochemical studies. The current TC-1 model is an insufficient surrogate.
- HPV-stratified subgroup analysis in treatment RCTs: Future clinical trials testing plant agents for mucositis or other treatment outcomes should report HPV status and conduct pre-planned subgroup analyses to determine whether effects differ by HPV positivity.
- Bioavailability solutions at scale: Nano-formulation strategies (liposomal, polymeric NP, nano-micelles) for curcumin, EGCG, and resveratrol require Phase I pharmacokinetic trials in OPSCC patients to confirm that oropharyngeal tissue levels are therapeutically relevant.
- Herb–drug interaction profiling: Systematic assessment of CYP450 and P-glycoprotein interactions for the leading compounds combined with pembrolizumab (now standard of care in recurrent HPV+ HNSCC) is an unmet safety research need.

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 OPSCCs—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), which may derepress integration-silenced viral genomes.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/cimb48060626/s1. Table S1: Comparative Evidence of HPV-HNSCCs: OPSCC vs. OSCC vs. LSCC.

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Abbreviations

The following abbreviations were used in the manuscript:

^{13}C3	carbon-13 labeled compound with 3 atoms of ^{13}C
2D	two-dimensional
2R,3R	the spatial orientation of two chiral centers in a molecule
93VU147T	research compound identifier
AJCC	American Joint Committee on Cancer
AKT	protein kinase B
AP-1	activator protein 1
ARE	antioxidant response element
B1	regulatory protein
Bax	B-cell lymphoma 2-associated X protein
Bcl-2	B-cell lymphoma 2
Bcl-xL	B-cell lymphoma-extra large
BIM	Bcl-2 Interacting Mediator of Cell Death
C/EBPβ	CCAAT/Enhancer-Binding Protein beta
CCAAT	short DNA sequence
C57BL/6	cell line, a productive inbred strain of lab mouse
Ca9-22	cell-line human gingival squamous carcinoma-derived cells
CaSki	human cervical cancer cell line
CBP	CREB-binding protein
CD8+	cluster of differentiation 8–positive
CDK	cyclin-dependent kinase
CDK1-6	cyclin-dependent kinases 1- 6
CDKN1A	cyclin-dependent kinase inhibitor 1
c-Ha-ras	cellular Harvey rat sarcoma viral oncogene homolog
CI	confidence interval
cIAP-2	cellular inhibitor of apoptosis protein 2
c-Myc	cellular myelocytomatosis oncogene
COX-2	cyclooxygenase-2
CR	clinical response
CREB	cAMP response element-binding protein
CRT	chemoradiotherapy
Cyclin D1	cyclin family protein
DIM	diindolylmethane
DNA	Deoxyribonucleic Acid
DNMT	DNA methyltransferase
DNMT1	DNA (cytosine-5)-methyltransferase 1
DR5	death receptor 5
DREAM	DP, RB-like, E2F, and MuvB complex—protein complex
DP	dimerization partner protein
RB-like	retinoblastoma-like
E2F	E2 promoter-binding factors
MuvB	multi-vulval class B
E1A	early region 1A (adenoviral protein)
E2F1-5	E2 promoter-binding factors 1–5
E6/E7	HPV early proteins 6 and 7
E6-AP	E6-associated protein

E6–E6AP	viral protein E6 and cellular protein E6AP
ECE	extranodal extension/extracapsular
ECG	epicatechin gallate
ECOG-ACRIN 3311	clinical study
ECOG	Eastern Cooperative Oncology Group
ACRIN	American College of Radiology Imaging Network
3311	the study number in the internal registry
EGCG	epigallocatechin -3-gallate
EGFR	epidermal growth factor receptor
EMT	epithelial–mesenchymal transition
ENE	extranodal extension
ERK	extracellular signal-regulated kinase
ERK1/2	extracellular signal-regulated kinases 1 and 2
FADD	fas-associated protein with death domain
FAS	fas cell surface death receptor
Fas/FasL	receptor–ligand system involved in apoptosis induction
FDA	Food and Drug Administration
Fe^{2+}	the divalent iron ion
G1/S	gap 1 synthesis
G2/M	"gap2" face to the mitosis phase
GJIC	gap junctional intercellular communication
GPX4	glutathione peroxidase 4
GSK3β	glycogen synthase kinase 3 beta
Gy	gray
H&N EXAM	head and neck examination
HaCaT	human keratinocyte cell line
HDAC	histone deacetylase
HeLa	human cervical cancer cell line
HES1	hairy and enhancer of split 1
HEY1	hairy/enhancer-of-split related with YRPW motif 1
HIF-1α	hypoxia-inducible factor 1 alpha
HNSCC	head and neck squamous cell carcinoma
HO-1	heme oxygenase 1
HPV	human Papillomavirus
HPV 16	human Papillomavirus 16
HPV 18	human Papillomavirus 18
HPV E6	human Papillomavirus early protein 6
HPV L1	human Papillomavirus L1 protein
HPV OPC	human Papillomavirus–positive oropharyngeal cancer
HPV PCR	human Papillomavirus polymerase chain reaction
HPV URR	human Papillomavirus upstream regulatory region
HPV+	human Papillomavirus positive
HPV16-E6	human Papillomavirus 16 Early protein 6
HPV16+ TC-1	HPV16 positive TC-1 cell line
HPV68	human Papillomavirus type 68
HSC-3	cell-line, cells derived from human oral squamous carcinoma
HSC-4	cell-line, cells derived from human oral cavity squamous cell carcinoma
hTERT	human TERT
TERT	telomerase reverse transcriptase
I3C	indole-3-carbinol
IHC	immunohistochemistry
IL-1β	interleukin-1 beta
IL-6	interleukin 6
IL-8	interleukin 8

IMRT	intensity-modulated radiation therapy
ITCs	isothiocyanates
JAK	janus kinase
KCNH1	a voltage-gated potassium channel
KEAP1	kelch-like ECH-associated protein 1
ECH	Echinoderm microtubule-associated protein
LNPs	lipid nanoparticles
LXCXE	leucine–any amino acid–cysteine–any amino acid–glutamic acid
MAPK	mitogen-activated protein kinase
CH	cysteine/histidine
MARCHF8	membrane-associated RING-CH-type finger 8
RING	really interesting new gene
MDM2	mouse double minute 2
MDSCs	myeloid-derived suppressor cells
MHC-1	major histocompatibility complex class I
miR-31	microRNA-31
miRNA	microRNA
MMP-2	matrix metalloproteinase-2
MMP-9	matrix metalloproteinase-9
MRI	magnetic resonance imaging
mRNA	messenger RNA
mTOR	mechanistic target of rapamycin
MTT	methyl/thiazolyl/tetrazolium
MYC	myelocytomatosis oncogene
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
nHOK	normal human oral keratinocytes
NK	natural killer
NOTCH1	neurogenic locus notch homolog protein 1
NQO1	quinone/oxidoreductase/the first identified member of the family
Nrf2	nuclear factor erythroid 2-related factor 2
HNSCC	head & neck squamous cell carcinoma
OPCs	oligodendrocyte progenitor cells
OPSCC	oropharyngeal squamous cell carcinoma
OSCC	oral squamous cell carcinoma
p16	protein 16
p16ˆINK4a	inhibitor of cyclin-dependent kinase 4a
p21	tumor suppressor protein
p27	protein 27
p300	E1A-binding protein p300
p53	tumor protein p53
PARP	Poly (ADP-ribose) polymerase
ADP	adenosine diphosphate
PATHOS	post-operative adjuvant treatment for HPV-positive tumors
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
pEGFR	phosphorylated epidermal growth factor receptor
PET-CT	positron emission tomography–computed tomography
pH	potentia hydrogenii
PI3K	phosphoinositide 3-kinase
PLGA	poly-lactic-co-glycolic acid
PORT	post-operative radiotherapy
pRb	retinoblastoma protein
pSTAT3	phosphorylated STAT3
pT	pathological tumor stage

PTEN	phosphatase and TENsin homolog
PUMA	p53 upregulated modulator of apoptosis
RAS	rat sarcoma
Rb	retinoblastoma protein
RCT	randomized controlled trial
ROS	reactive oxygen species
RT	radiotherapy
SCC	squamous cell carcinoma
SCC25	cell line—human oral squamous carcinoma-derived cells
SOX2	SRY-Box Transcription Factor 2
SRY	sex-determining region Y
S-phase	synthesis phase
STAT	signal transducer and activator of transcription
STAT3	signal transducer and activator of transcription 3
STUB1	STIP1 homology and U-box containing protein 1
STIP	stress-induced phosphoprotein 1
T cells (Tregs)	regulatory T lymphocytes
T3	primary tumor
T4	locally advanced tumor
TC-1	murine (mouse) tumor cell line
TGF-β1	transforming growth factor beta 1
TLM	transoral laser microsurgery
TME	tumor microenvironment
TNF-α	tumor necrosis factor alpha
TNM	tumor/nodes/metastasis
TORS	transoral robotic surgery
TP53	tumor protein 53
TNF	tumor necrosis factor
TRAIL	TNF-related apoptosis-inducing ligand
TriCurin	curcumin/epicatechin gallate/resveratrol
TSH	thyroid-stimulating hormone
URR	upstream regulatory region
uVIN	usual vulvar intraepithelial neoplasia
VEGF	vascular endothelial growth factor
WFA	wisteria floribunda agglutinin
Wnt/β-catenin	wingless/integrated β-catenin = beta-catenin
XIAP	X-linked inhibitor of apoptosis protein
Y705	tyrosine (Y) at position 705
YRPW	tyrosine/arginine/proline/tryptophan—short amino acid motif
α-MG	α-methylglucoside
β-catenin	beta-catenin
μM	micromolar

References

1. Barsouk, A.; Aluru, J.S.; Rawla, P.; Saginala, K.; Barsouk, A. Epidemiology, Risk Factors, and Prevention of Head and Neck Squamous Cell Carcinoma. *Med. Sci.* **2023**, *11*, 42. [CrossRef]
2. Chung, C.H.; Gillison, M.L. Human Papillomavirus in Head and Neck Cancer: Its Role in Pathogenesis and Clinical Implications. *Clin. Cancer Res.* **2009**, *15*, 6758–6762. [CrossRef] [PubMed]
3. Zaravinos, A. An Updated Overview of HPV-Associated Head and Neck Carcinomas. *Oncotarget* **2014**, *5*, 3956–3969. [CrossRef]
4. 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 J. Natl. Cancer Inst.* **2023**, *115*, 1544–1554. [CrossRef] [PubMed]
5. Kokkinis, E.; Bastas, N.S.; Mega, I.; Tsironis, C.; Lianou, A.D. Association of HPV with Oral and Oropharyngeal Cancer: Current Evidence. *Maedica—A J. Clin. Med.* **2024**, *19*, 804–806. [CrossRef] [PubMed]

6. 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. [CrossRef]
7. 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. *Rev. Argent. Cir.* **2025**, *117*, e-1827.
8. 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* **2021**, *13*, 5206. [CrossRef] [PubMed]
9. Shankar, K.; Walker, S.E. Analysis of Divergent Gene Expression between HPV + and HPV- Head and Neck Squamous Cell Carcinoma Patients. *Infect. Agent. Cancer* **2025**, *20*, 31. [CrossRef] [PubMed]
10. Tabatabaeian, H.; Bai, Y.; Huang, R.; Chaurasia, A.; Darido, C. Navigating Therapeutic Strategies: HPV Classification in Head and Neck Cancer. *Br. J. Cancer* **2024**, *131*, 220–230. [CrossRef] [PubMed]
11. Tosi, A.; Parisatto, B.; Menegaldo, A.; Spinato, G.; Guido, M.; Del Mistro, A.; Bussani, R.; Zanconati, F.; Tofanelli, M.; Tirelli, G.; et al. The Immune Microenvironment of HPV-Positive and HPV-Negative Oropharyngeal Squamous Cell Carcinoma: A Multiparametric Quantitative and Spatial Analysis Unveils a Rationale to Target Treatment-Naïve Tumors with Immune Checkpoint Inhibitors. *J. Exp. Clin. Cancer Res.* **2022**, *41*, 279. [CrossRef] [PubMed]
12. 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. [CrossRef] [PubMed]
13. Pollaers, K.; Hinton-Bayre, A.; Friedland, P.L.; Farah, C.S. AJCC 8th Edition Oral Cavity Squamous Cell Carcinoma Staging—Is It an Improvement on the AJCC 7th Edition? *Oral Oncol.* **2018**, *82*, 23–28. [CrossRef]
14. Zeeshan, M.; Malik, P.A.; Mateen, L.; Aziz, S.; Uppal, A.A.; Aslam, H.; Aimen Ikram, M. Impact of HPV Subtypes on Prognosis and Treatment in Oropharyngeal Cancers. *J. Neonatal Surg.* **2025**, *13*, 457–462. [CrossRef]
15. 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. [CrossRef] [PubMed]
16. Salomon, N.; Selmi, A.; Grunwitz, C.; Kong, A.; Stanganello, E.; Neumaier, J.; Petschenka, J.; Diken, M.; Kreiter, S.; Türeci, Ö.; et al. Local Radiotherapy and E7 RNA-LPX Vaccination Show Enhanced Therapeutic Efficacy in Preclinical Models of HPV16+ Cancer. *Cancer Immunol. Immunother.* **2022**, *71*, 1975–1988. [PubMed]
17. Stukan, A.I.; Porhanov, V.A.; Bodnya, V.N.; Chuhraj, O.Y.; Makarova, Y.M.; Elizbaryan, I.S. Molecular and Genetic Profile of Head and Neck Squamous Cell Carcinoma. *Med. Her. South Russ.* **2018**, *9*, 50–57. [CrossRef]
18. 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. [CrossRef] [PubMed]
19. Oh, J.-E.; Kim, J.-O.; Shin, J.-Y.; Zhang, X.-H.; Won, H.-S.; Chun, S.-H.; Jung, C.-K.; Park, W.-S.; Nam, S.-W.; Eun, J.-W.; et al. Molecular Genetic Characterization of P53 Mutated Oropharyngeal Squamous Cell Carcinoma Cells Transformed with Human Papillomavirus E6 and E7 Oncogenes. *Int. J. Oncol.* **2013**, *43*, 383–393. [CrossRef]
20. 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. *J. Biol. Chem.* **2002**, *277*, 2923–2930. [CrossRef] [PubMed]
21. Ye, J.; Zheng, L.; He, Y.; Qi, X. Human Papillomavirus Associated Cervical Lesion: Pathogenesis and Therapeutic Interventions. *MedComm* **2023**, *4*, e368. [CrossRef] [PubMed]
22. Cortiana, V.; Nadar, S.; Gambill, J.; Mahendru, D.; Theyver, A.; Coloma, H.S.; Park, C.H.; Leyfman, Y. Understanding and Treating HPV-Associated Oropharyngeal Carcinoma: Insights from a MedNewsWeek Keynote Lecture by Dr Theodoros N. Teknos and Literature Review. *Ther. Adv. Med. Oncol.* **2025**, *17*, 17588359251322290. [CrossRef] [PubMed]
23. Li, X.; Qiu, H.; Wu, Q. Lymphatic Dissemination of HPV-Positive Oropharyngeal Squamous Cell Carcinoma: Underlying Mechanisms and Treatment Innovations. *Front. Immunol.* **2025**, *16*, 1601572. [CrossRef] [PubMed]
24. Harrington, K.J.; Burtness, B.; Greil, R.; Soulières, D.; Tahara, M.; de Castro, G.; Psyrri, A.; Brana, I.; Basté, N.; Neupane, P.; et al. Pembrolizumab With or Without Chemotherapy in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: Updated Results of the Phase III KEYNOTE-048 Study. *J. Clin. Oncol.* **2023**, *41*, 790–802. [CrossRef] [PubMed]
25. Haddad, R.; Concha-Benavente, F.; Blumenschein, G.; Fayette, J.; Guigay, J.; Colevas, A.D.; Licitra, L.; Kasper, S.; Vokes, E.E.; Worden, F.; et al. Nivolumab Treatment beyond RECIST-defined Progression in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck in CheckMate 141: A Subgroup Analysis of a Randomized Phase 3 Clinical Trial. *Cancer* **2019**, *125*, 3208–3218. [CrossRef]
26. Al-Azzawi, H.M.A.; Hamza, S.A.; Paolini, R.; Lim, M.; Patini, R.; Celentano, A. PD-L1/PD-1 Expression in the Treatment of Oral Squamous Cell Carcinoma and Oral Potentially Malignant Disorders: An Overview of Reviews. *J. Pers. Med.* **2025**, *15*, 126. [CrossRef] [PubMed]

27. 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* **2022**, *14*, 4321. [CrossRef] [PubMed]
28. 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. *J. Clin. Oncol.* **2019**, *37*, e17544. [CrossRef]
29. Lim, Y.X.; D'Silva, N.J. HPV-Associated Oropharyngeal Cancer: In Search of Surrogate Biomarkers for Early Lesions. *Oncogene* **2024**, *43*, 543–554. [CrossRef] [PubMed]
30. Cabibi, D.; Napolitano, C.; Giannone, A.G.; Micciulla, M.C.; Porcasi, R.; Lo Coco, R.; Bosco, L.; Vinciguerra, M.; Capra, G. Predictive Role of the P16 Immunostaining Pattern in Atypical Cervical Biopsies with Less Common High Risk HPV Genotypes. *Diagnostics* **2021**, *11*, 1947. [CrossRef] [PubMed]
31. de Carvalho Melo, B.A.; Vilar, L.G.; de Oliveira, N.R.; de Lima, P.O.; de Barros Pinheiro, M.; Domingueti, C.P.; Pereira, M.C. Human Papillomavirus Infection and Oral Squamous Cell Carcinoma - a Systematic Review. *Braz. J. Otorhinolaryngol.* **2021**, *87*, 346–352. [CrossRef] [PubMed]
32. Benson, E.; Li, R.; Eisele, D.; Fakhry, C. The Clinical Impact of HPV Tumor Status upon Head and Neck Squamous Cell Carcinomas. *Oral Oncol.* **2014**, *50*, 565–574. [CrossRef] [PubMed]
33. Tokuzen, N.; Nakashiro, K.-I.; Tojo, S.; Goda, H.; Kuribayashi, N.; Uchida, D. Human Papillomavirus-16 Infection and P16 Expression in Oral Squamous Cell Carcinoma. *Oncol. Lett.* **2021**, *22*, 528. [CrossRef] [PubMed]
34. Centa, A. Relationship of HPV with Laryngeal Cancer: A Systematic Review. *J. Tumor Med. Prev.* **2024**, *4*, 555640. [CrossRef]
35. Gallus, R.; Gheit, T.; Holzinger, D.; Petrillo, M.; Rizzo, D.; Petrone, G.; Miccichè, F.; Mattiucci, G.C.; Arciuolo, D.; Capobianco, G.; et al. Prevalence of HPV Infection and P16INK4a Overexpression in Surgically Treated Laryngeal Squamous Cell Carcinoma. *Vaccines* **2022**, *10*, 204. [CrossRef] [PubMed]
36. Fonsêca, T.C.; Jural, L.A.; Marañón-Vásquez, G.A.; Magno, M.B.; Roza, A.L.O.C.; Ferreira, D.M.T.P.; Maia, L.C.; Romañach, M.J.; Agostini, M.; Abrahão, A.C. Global Prevalence of Human Papillomavirus-Related Oral and Oropharyngeal Squamous Cell Carcinomas: A Systematic Review and Meta-Analysis. *Clin. Oral Investig.* **2023**, *28*, 62. [CrossRef] [PubMed]
37. Van Gysen, K.; Stevens, M.; Guo, L.; Jayamanne, D.; Veivers, D.; Wignall, A.; Pang, L.; Guminski, A.; Lee, A.; Hruby, G.; et al. Validation of the 8th Edition UICC/AJCC TNM Staging System for HPV Associated Oropharyngeal Cancer Patients Managed with Contemporary Chemo-Radiotherapy. *BMC Cancer* **2019**, *19*, 674. [CrossRef] [PubMed]
38. Grigore, R.; Bejenaru, P.L.; Bertești eanu, G.S.; Nedelcu-Stancalie, R.I.; Schipor-Diaconu, T.E.; Rujan, S.A.; Taher, B.P.; Bertești eanu, Ș.V.G.; Popescu, B.; Popescu, I.D.; et al. Impact of Oncological Treatment on Quality of Life in Patients with Head and Neck Malignancies: A Systematic Literature Review (2020–2025). *Curr. Oncol.* **2025**, *32*, 379. [CrossRef] [PubMed]
39. Shaari, D.S.; Kapustin, D.A.; Yoon, M.; Rubin, S.J.; Khorsandi, A.; Ramirez, R.J.; Schiff, M.; Urken, M.L. Radiation-Induced Pharyngeal Necrosis and Cervical Spine Osteoradionecrosis in Patients With Oropharyngeal Squamous Cell Carcinoma. *Head Neck* **2025**, *47*, E11–E22. [PubMed]
40. Moslemi, D.; Nokhandani, A.M.; Otaghsaraei, M.T.; Moghadamnia, Y.; Kazemi, S.; Moghadamnia, A.A. Management of Chemo/Radiation-Induced Oral Mucositis in Patients with Head and Neck Cancer: A Review of the Current Literature. *Radiother. Oncol.* **2016**, *120*, 13–20. [CrossRef] [PubMed]
41. Feller, L.; Wood, N.H.; Khammissa, R.A.; Lemmer, J. Human Papillomavirus-Mediated Carcinogenesis and HPV-Associated Oral and Oropharyngeal Squamous Cell Carcinoma. Part 1: Human Papillomavirus-Mediated Carcinogenesis. *Head Face Med.* **2010**, *6*, 14. [CrossRef] [PubMed]
42. Scarth, J.A.; Patterson, M.R.; Morgan, E.L.; Macdonald, A. The Human Papillomavirus Oncoproteins: A Review of the Host Pathways Targeted on the Road to Transformation. *J. Gen. Virol.* **2021**, *102*, 001540. [CrossRef] [PubMed]
43. Wang, Z.; Fan, F.; Li, Z.; Ye, F.; Wang, Q.; Gao, R.; Qiu, J.; Lv, Y.; Lin, M.; Xu, W.; et al. Structural Insights into the Functional Mechanism of the Ubiquitin Ligase E6AP. *Nat. Commun.* **2024**, *15*, 3531. [CrossRef] [PubMed]
44. Sailer, C.; Offensperger, F.; Julier, A.; Kammer, K.-M.; Walker-Gray, R.; Gold, M.G.; Scheffner, M.; Stengel, F. Structural Dynamics of the E6AP/UBE3A-E6-P53 Enzyme-Substrate Complex. *Nat. Commun.* **2018**, *9*, 4441. [CrossRef] [PubMed]
45. Jansma, A.L.; Martinez-Yamout, M.A.; Liao, R.; Sun, P.; Dyson, H.J.; Wright, P.E. The High-Risk HPV16 E7 Oncoprotein Mediates Interaction between the Transcriptional Coactivator CBP and the Retinoblastoma Protein PRb. *J. Mol. Biol.* **2014**, *426*, 4030–4048. [CrossRef] [PubMed]
46. Shah, P.A.; Huang, C.; Li, Q.; Kazi, S.A.; Byers, L.A.; Wang, J.; Johnson, F.M.; Frederick, M.J. NOTCH1 Signaling in Head and Neck Squamous Cell Carcinoma. *Cells* **2020**, *9*, 2677. [CrossRef] [PubMed]
47. Liu, X.; Liu, P.; Chernock, R.D.; Lang Kuhs, K.A.; Lewis, J.S.; Li, H.; Gay, H.A.; Thorstad, W.L.; Wang, X. Impact of Human Papillomavirus on the Tumor Microenvironment in Oropharyngeal Squamous Cell Carcinoma. *Int. J. Cancer* **2022**, *150*, 521–531. [PubMed]

48. Zhao, Y.; Yu, J.; Zheng, C.; Zhou, B. Establishment of a Prognostic Model for Hypoxia-Associated Genes in OPSCC and Revelation of Intercellular Crosstalk. *Front. Immunol.* **2024**, *15*, 1371365. [CrossRef] [PubMed]
49. Oh, S.T.; Kyo, S.; Laimins, L.A. Telomerase Activation by Human Papillomavirus Type 16 E6 Protein: Induction of Human Telomerase Reverse Transcriptase Expression through Myc and GC-Rich Sp1 Binding Sites. *J. Virol.* **2001**, *75*, 5559–5566. [CrossRef] [PubMed]
50. Martinez-Zapien, D.; Ruiz, F.X.; Poirson, J.; Mitschler, A.; Ramirez, J.; Forster, A.; Cousido-Siah, A.; Masson, M.; Pol, S.; Vande; et al. Structure of the E6/E6AP/P53 Complex Required for HPV-Mediated Degradation of P53. *Nature* **2016**, *529*, 541–545. [CrossRef]
51. Benedict, B.; van Harn, T.; Dekker, M.; Hermsen, S.; Kucukosmanoglu, A.; Pieters, W.; Delzenne-Goette, E.; Dorsman, J.C.; Petermann, E.; Foijer, F.; et al. Loss of P53 Suppresses Replication-Stress-Induced DNA Breakage in G1/S Checkpoint Deficient Cells. *Elife* **2018**, *7*, e37868. [CrossRef] [PubMed]
52. Huang, G.; Meng, L.; Tsai, R. P53 Configures the G2/M Arrest Response of Nucleostemin-Deficient Cells. *Cell Death Discov.* **2015**, *1*, 15060. [CrossRef]
53. Rodriguez-Pastrana, I.; Birli, E.; Coutts, A.S. P53-Dependent DNA Repair during the DNA Damage Response Requires Actin Nucleation by JMY. *Cell Death Differ.* **2023**, *30*, 1636–1647. [CrossRef] [PubMed]
54. Toufektchan, E.; Toledo, F. The Guardian of the Genome Revisited: P53 Downregulates Genes Required for Telomere Maintenance, DNA Repair, and Centromere Structure. *Cancers* **2018**, *10*, 135. [CrossRef] [PubMed]
55. Murphy, M.; Mabruk, M.J.E.M.F.; Lenane, P.; Liew, A.; Mccann, P.; Buckley, A.; Billet, P.; Leader, M.; Kay, E.; Murphy, G.M. The Expression of P53, P21, Bax and Induction of Apoptosis in Normal Volunteers in Response to Different Doses of Ultraviolet Radiation. *Br. J. Dermatol.* **2002**, *147*, 110–117. [CrossRef] [PubMed]
56. Löhr, K.; Möritz, C.; Contente, A.; Dobbelstein, M. P21/CDKN1A Mediates Negative Regulation of Transcription by P53. *J. Biol. Chem.* **2003**, *278*, 32507–32516. [CrossRef] [PubMed]
57. Lu, X.; Yang, C.; Yin, C.; Van Dyke, T.; Simin, K. Apoptosis Is the Essential Target of Selective Pressure against P53, Whereas Loss of Additional P53 Functions Facilitates Carcinoma Progression. *Mol. Cancer Res.* **2011**, *9*, 430–439. [CrossRef] [PubMed]
58. Xie, X.; Piao, L.; Bullock, B.N.; Smith, A.; Su, T.; Zhang, M.; Teknos, T.N.; Arora, P.S.; Pan, Q. Targeting HPV16 E6-P300 Interaction Reactivates P53 and Inhibits the Tumorigenicity of HPV-Positive Head and Neck Squamous Cell Carcinoma. *Oncogene* **2014**, *33*, 1037–1046. [PubMed]
59. Ranasinghe, V.; McMillan, N. Novel Therapeutic Strategies for Targeting E6 and E7 Oncoproteins in Cervical Cancer. *Crit. Rev. Oncol. Hematol.* **2025**, *211*, 104721. [CrossRef] [PubMed]
60. Wani, A.K.; Akhtar, N.; Mir, T.U.G.; Singh, R.; Jha, P.K.; Mallik, S.K.; Sinha, S.; Tripathi, S.K.; Jain, A.; Jha, A.; et al. Targeting Apoptotic Pathway of Cancer Cells with Phytochemicals and Plant-Based Nanomaterials. *Biomolecules* **2023**, *13*, 194. [CrossRef] [PubMed]
61. Jamal, A. Identification of Phytochemicals as Potential Inhibitors against E6 Protein of High-Risk Human Papillomavirus 16(HPV 16) via In-Silico Structure-Based Virtual Screening Approach. *Adv. Life Sci.* **2023**, *10*, 498. [CrossRef]
62. Fang, Y.; Liao, G.; Yu, B. Small-Molecule MDM2/X Inhibitors and PROTAC Degraders for Cancer Therapy: Advances and Perspectives. *Acta Pharm. Sin. B* **2020**, *10*, 1253–1278. [CrossRef] [PubMed]
63. Zhu, I.Y.; Lloyd, A.; Critchley, W.R.; Saikia, Q.; Jade, D.; Divan, A.; Zeqiraj, E.; Harrison, M.A.; Brown, C.J.; Ponnambalam, S. Structure and Function of MDM2 and MDM4 in Health and Disease. *Biochem. J.* **2025**, *482*, 241–262. [CrossRef] [PubMed]
64. Mir, B.A.; Ahmad, A.; Farooq, N.; Priya, M.V.; Siddiqui, A.H.; Asif, M.; Manzoor, R.; Ishqi, H.M.; Alomar, S.Y.; Rahaman, P.F. Increased Expression of HPV-E7 Oncoprotein Correlates with a Reduced Level of PRb Proteins via High Viral Load in Cervical Cancer. *Sci. Rep.* **2023**, *13*, 15075. [CrossRef] [PubMed]
65. He, W.; Staples, D.; Smith, C.; Fisher, C. Direct Activation of Cyclin-Dependent Kinase 2 by Human Papillomavirus E7. *J. Virol.* **2003**, *77*, 10566–10574. [CrossRef] [PubMed]
66. Gbala, I.; Kavcic, N.; Banks, L. The Retinoblastoma Protein Contributes to Maintaining the Stability of HPV E7 in Cervical Cancer Cells. *J. Virol.* **2025**, *99*, e0220324. [CrossRef] [PubMed]
67. Nor Rashid, N.; Yusof, R.; Watson, R.J. A B-Myb - DREAM Complex Is Not Critical to Regulate the G2/M Genes in HPV-Transformed Cell Lines. *Anticancer Res.* **2014**, *34*, 6557–6563.
68. Skof, A.S.; Rotenberg, L.; Hannemann, P.V.F.; Thies, S.; Boschetti-Grützmacher, E.; Kaufmann, A.M. Human Papillomavirus E7 and P16INK4a MRNA Multiplexed Quantification by a QuantiGeneTM Proof-of-Concept Assay Sensitively Detects Infection and Cervical Dysplasia Severity. *Diagnostics* **2023**, *13*, 1135. [CrossRef] [PubMed]
69. Markopoulos, G.; Roupakia, E.; Tokamani, M.; Alabasi, G.; Sandaltzopoulos, R.; Marcu, K.; Kolettas, E. Roles of NF-KB Signaling in the Regulation of MiRNAs Impacting on Inflammation in Cancer. *Biomedicines* **2018**, *6*, 40. [CrossRef] [PubMed]
70. Karin, M.; Greten, F.R. NF-KB: Linking Inflammation and Immunity to Cancer Development and Progression. *Nat. Rev. Immunol.* **2005**, *5*, 749–759. [CrossRef] [PubMed]

71. Hoesel, B.; Schmid, J.A. The Complexity of NF-KB Signaling in Inflammation and Cancer. *Mol. Cancer* **2013**, *12*, 86. [CrossRef] [PubMed]
72. Barroso, L.; Veiga, P.; Melo, J.B.; Carreira, I.M.; Ribeiro, I.P. Molecular and Genetic Pathogenesis of Oral Cancer: A Basis for Customized Diagnosis and Treatment. *Biology* **2025**, *14*, 842. [CrossRef] [PubMed]
73. Horn, D.; Hess, J.; Freier, K.; Hoffmann, J.; Freudlsperger, C. Targeting EGFR-PI3K-AKT-MTOR Signaling Enhances Radiosensitivity in Head and Neck Squamous Cell Carcinoma. *Expert Opin. Ther. Targets* **2015**, *19*, 795–805. [CrossRef] [PubMed]
74. Janecka-Widła, A.; Majchrzyk, K.; Mucha-Małecka, A.; Biesaga, B. EGFR/PI3K/Akt/MTOR Pathway in Head and Neck Squamous Cell Carcinoma Patients with Different HPV Status. *Pol. J. Pathol.* **2021**, *72*, 296–314. [CrossRef] [PubMed]
75. Freudlsperger, C.; Burnett, J.R.; Friedman, J.A.; Kannabiran, V.R.; Chen, Z.; Van Waes, C. EGFR–PI3K–AKT–MTOR Signaling in Head and Neck Squamous Cell Carcinomas: Attractive Targets for Molecular-Oriented Therapy. *Expert Opin. Ther. Targets* **2011**, *15*, 63–74. [PubMed]
76. Xie, J.; Huang, L.; Lu, Y.-G.; Zheng, D.-L. Roles of the Wnt Signaling Pathway in Head and Neck Squamous Cell Carcinoma. *Front. Mol. Biosci.* **2021**, *7*, 590912. [CrossRef] [PubMed]
77. Song, Y.; Gui, C.; Xian, Q.; Lv, N.; Ji, M.; Zhou, Y. Previously Undescribed Effects and Mechanisms of STAT-3 in HPV -induced DNA Re-replication in Response to DNA Damage. *FEBS J.* **2025**, *292*, 6592–6607. [CrossRef] [PubMed]
78. Morgan, E.L.; Wasson, C.W.; Hanson, L.; Kealy, D.; Pentland, I.; McGuire, V.; Scarpini, C.; Coleman, N.; Arthur, J.S.C.; Parish, J.L.; et al. STAT3 Activation by E6 Is Essential for the Differentiation-Dependent HPV18 Life Cycle. *PLoS Pathog.* **2018**, *14*, e1006975. [CrossRef] [PubMed]
79. Gaykalova, D.A.; Manola, J.B.; Ozawa, H.; Zizkova, V.; Morton, K.; Bishop, J.A.; Sharma, R.; Zhang, C.; Michailidi, C.; Considine, M.; et al. NF-κB and Stat3 Transcription Factor Signatures Differentiate HPV-positive and HPV-negative Head and Neck Squamous Cell Carcinoma. *Int. J. Cancer* **2015**, *137*, 1879–1889. [CrossRef] [PubMed]
80. 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* **2019**, *11*, 584. [CrossRef] [PubMed]
81. Xu, K.; Yang, Q.; Chen, W.; Li, Z.; Wu, Y.; Ren, F.; Li, X. Research Progress on Carcinogenic Factors and Personalized Treatment of Oral Cancer. *Discov. Oncol.* **2025**, *17*, 59. [CrossRef] [PubMed]
82. Medda, A.; Duca, D.; Chiocca, S. Human Papillomavirus and Cellular Pathways: Hits and Targets. *Pathogens* **2021**, *10*, 262. [CrossRef] [PubMed]
83. 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*, e01726. [CrossRef] [PubMed]
84. Kannan, N.; Ramalingam, K.; Ramani, P.; Marrapodi, M.M.; Franco, R.; Russo, D.; Cicciù, M.; Minervini, G. Immune Evasion Mechanisms and Cutting-Edge Therapeutic Strategies of PD-L1 Pathway in Oral Squamous Cell Carcinoma: An Umbrella Review. *Explor. Immunol.* **2025**, *5*, 1003228. [CrossRef]
85. D'Costa, Z.J.; Jolly, C.; Androphy, E.J.; Mercer, A.; Matthews, C.M.; Hibma, M.H. Transcriptional Repression of E-Cadherin by Human Papillomavirus Type 16 E6. *PLoS ONE* **2012**, *7*, e48954. [CrossRef] [PubMed]
86. Noman, M.Z.; Desantis, G.; Janji, B.; Hasmim, M.; Karray, S.; Dessen, P.; Bronte, V.; Chouaib, S. PD-L1 Is a Novel Direct Target of HIF-1α, and Its Blockade under Hypoxia Enhanced MDSC-Mediated T Cell Activation. *J. Exp. Med.* **2014**, *211*, 781–790. [CrossRef] [PubMed]
87. Machczyński, P.; Majchrzak, E.; Niewinski, P.; Marchlewska, J.; Golusiński, W. A Review of the 8th Edition of the AJCC Staging System for Oropharyngeal Cancer According to HPV Status. *Eur. Arch. Oto-Rhino-Laryngol.* **2020**, *277*, 2407–2412. [CrossRef] [PubMed]
88. Mulcahy, C.F.; Gross, N.D. Advances in Surgical Therapy for HPV-Associated Squamous Cell Carcinoma. *Curr. Otorhinolaryngol. Rep.* **2022**, *10*, 475–482. [CrossRef]
89. 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. [CrossRef] [PubMed]
90. 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. [CrossRef] [PubMed]
91. 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. *Radiother. Oncol.* **2024**, *192*, S17–S20. [CrossRef]
92. 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 Otolaryngol.–Head Neck Surg.* **2024**, *150*, 1002. [CrossRef] [PubMed]

93. 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). *J. Clin. Oncol.* **2020**, *38*, 6500. [CrossRef]
94. 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*, 164–197. [PubMed]
95. Hargreaves, S.; Beasley, M.; Hurt, C.; Jones, T.M.; Evans, M. Deintensification of Adjuvant Treatment After Transoral Surgery in Patients With Human Papillomavirus-Positive Oropharyngeal Cancer: The Conception of the PATHOS Study and Its Development. *Front. Oncol.* **2019**, *9*, 936. [CrossRef] [PubMed]
96. Owadally, W.; Hurt, C.; Timmins, H.; Parsons, E.; Townsend, S.; Patterson, J.; Hutcheson, K.; Powell, N.; Beasley, M.; Palaniappan, N.; et al. PATHOS: A Phase II/III Trial of Risk-Stratified, Reduced Intensity Adjuvant Treatment in Patients Undergoing Transoral Surgery for Human Papillomavirus (HPV) Positive Oropharyngeal Cancer. *BMC Cancer* **2015**, *15*, 602. [CrossRef] [PubMed]
97. Ferris, R.L.; Flamand, Y.; Holsinger, F.C.; Weinstein, G.S.; Quon, H.; Mehra, R.; Garcia, J.J.; Hinni, M.L.; Gross, N.D.; Sturgis, E.M.; et al. A Novel Surgeon Credentialing and Quality Assurance Process Using Transoral Surgery for Oropharyngeal Cancer in ECOG-ACRIN Cancer Research Group Trial E3311. *Oral Oncol.* **2020**, *110*, 104797. [CrossRef] [PubMed]
98. Marur, S.; Li, S.; Cmelak, A.J.; Gillison, M.L.; Zhao, W.J.; Ferris, R.L.; Westra, W.H.; Gilbert, J.; Bauman, J.E.; Wagner, L.I.; et al. E1308: Phase II Trial of Induction Chemotherapy Followed by Reduced-Dose Radiation and Weekly Cetuximab in Patients With HPV-Associated Resectable Squamous Cell Carcinoma of the Oropharynx—ECOG-ACRIN Cancer Research Group. *J. Clin. Oncol.* **2017**, *35*, 490–497. [CrossRef] [PubMed]
99. 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. *Am. J. Neuroradiol.* **2020**, *41*, 859–865. [CrossRef] [PubMed]
100. 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. *Am. J. Roentgenol.* **2023**, *220*, 160–172. [CrossRef] [PubMed]
101. Koivunen, P. Surveillance after Treatment for Head and Neck Cancer. *Curr. Opin. Otolaryngol. Head Neck Surg.* **2026**, *34*, 83–87. [CrossRef] [PubMed]
102. Kang, H.; Kennedy, T.A.; Yu, E. *Head and Neck Squamous Cell Cancer: Approach to Staging and Surveillance*; Springer: Berlin/Heidelberg, Germany, 2024; pp. 251–264.
103. Nocon, C.C.; Kennedy, A.; Jaffe, J.; Pruitt, J.; Kuchta, K.; Bhayani, M.K. Costs Associated With Imaging Surveillance After Treatment for Head and Neck Cancer. *JAMA Otolaryngol.—Head Neck Surg.* **2021**, *147*, 632. [CrossRef] [PubMed]
104. Hayashi, Y.; Suzuki, K.; Kono, Y.; Sakagami, T.; Fujisawa, T.; Yagi, M.; Iwai, H. The Utility of Dwibs in Surveillance after Treatment of Head and Neck Cancer. *Toukeibu Gan* **2025**, *51*, 276–280. [CrossRef]
105. Heineman, T.E.; Kuan, E.C.; St. John, M.A. When Should Surveillance Imaging Be Performed after Treatment for Head and Neck Cancer? *Laryngoscope* **2017**, *127*, 533–534. [CrossRef] [PubMed]
106. McLaren, O.; Perkins, C.; Zhu, Y.; Smith, M.; Williams, R. Patient Perspectives on Surveillance after Head and Neck Cancer Treatment: A Systematic Review. *Clin. Otolaryngol.* **2021**, *46*, 1345–1353. [CrossRef] [PubMed]
107. Kalfert, D.; Ludvikova, M.; Pesta, M.; Ludvik, J.; Dostalova, L.; Kholová, I. Multifunctional Roles of MiR-34a in Cancer: A Review with the Emphasis on Head and Neck Squamous Cell Carcinoma and Thyroid Cancer with Clinical Implications. *Diagnostics* **2020**, *10*, 563. [CrossRef] [PubMed]
108. Malik, A.; Sharin, F.; Balaji, A.; Mathur, Y.; Nair, S.; Chaturvedi, P.; Nair, D. Swallowing in Advanced Oral Cancers: A Prospective Observational Study. *J. Cancer Res. Ther.* **2024**, *20*, 340–348. [CrossRef] [PubMed]
109. 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 Res.* **2019**, *7*, 1–10. [CrossRef] [PubMed]
110. 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. *Int. J. Radiat. Oncol. Biol. Phys.* **2024**, *118*, e47–e48. [CrossRef]
111. Costa, D.R.; Santos, P.S.d.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*, 2050312120974152. [CrossRef] [PubMed]
112. 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. *Radiother. Oncol.* **2023**, *182*, S581–S582. [CrossRef]

113. 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 Syst. Rev.* **2016**, *2016*, CD011112. [CrossRef] [PubMed]
114. 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*, 284–293. [CrossRef] [PubMed]
115. 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*, 102713. [CrossRef] [PubMed]
116. 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. *Eur. Arch. Oto-Rhino-Laryngol.* **2022**, *279*, 3645–3655.
117. McBride, S.M.; Ali, N.N.; Margalit, D.N.; Chan, A.W. Active Tobacco Smoking and Distant Metastasis in Patients with Oropharyngeal Cancer. *Int. J. Radiat. Oncol. *Biol. *Phys.* **2012**, *84*, 183–188. [CrossRef] [PubMed]
118. 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*, 2725–2734. [CrossRef] [PubMed]
119. Cantrell, S.C.; Reid, H.H.; Li, G.; Wei, Q.; Sturgis, E.M.; Ginsberg, L.E. Influence of Smoking History on Imaging Characteristics Among Patients With Human Papillomavirus-Positive Oropharyngeal Cancer. *J. Comput. Assist. Tomogr.* **2014**, *38*, 667–673. [CrossRef] [PubMed]
120. 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. [CrossRef]
121. Mishra, A. Curcumin Modulates Cellular AP-1, NF-KB, and HPV16 E6 Proteins in Oral Cancer. *Ecancermedicalscience* **2015**, *9*, 525. [CrossRef] [PubMed]
122. Vahedian Sadeghi, R.; Parsania, M.; Sadeghizadeh, M.; Haghighat, S. Investigation of Curcumin-Loaded OA400 Nanoparticle's Effect on the Expression of E6 and E7 Human Papilloma-Virus Oncogenes and P53 and Rb Factors in HeLa Cell Line. *Iran. J. Pharm. Res.* **2022**, *21*, e130762. [CrossRef] [PubMed]
123. Ma, C.; Zhuang, Z.; Su, Q.; He, J.; Li, H. Curcumin Has Anti-Proliferative and Pro-Apoptotic Effects on Tongue Cancer in Vitro: A Study with Bioinformatics Analysis and in Vitro Experiments. *Drug Des. Devel. Ther.* **2020**, *14*, 509–518. [CrossRef] [PubMed]
124. 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. [CrossRef] [PubMed]
125. 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. [CrossRef] [PubMed]
126. Banik, U.; Parasuraman, S.; Adhikary, A.K.; Othman, N.H. Curcumin: The Spicy Modulator of Breast Carcinogenesis. *J. Exp. Clin. Cancer Res.* **2017**, *36*, 98. [CrossRef] [PubMed]
127. Ashrafizadeh, M.; Rafiei, H.; Mohammadinejad, R.; Afshar, E.G.; Farkhondeh, T.; Samarghandian, S. Potential Therapeutic Effects of Curcumin Mediated by JAK/STAT Signaling Pathway: A Review. *Phytother. Res.* **2020**, *34*, 1745–1760. [CrossRef] [PubMed]
128. Zhao, R.; Du, S.; Liu, Y.; Lv, C.; Song, Y.; Chen, X.; Zhang, B.; Li, D.; Gao, S.; Cui, W.; et al. Mucoadhesive-to-Penetrating Controllable Peptosomes-in-Microspheres Co-Loaded with Anti-MiR-31 Oligonucleotide and Curcumin for Targeted Colorectal Cancer Therapy. *Theranostics* **2020**, *10*, 3594–3611. [CrossRef] [PubMed]
129. Teiten, M.; Dicato, M.; Diederich, M. Curcumin as a Regulator of Epigenetic Events. *Mol. Nutr. Food Res.* **2013**, *57*, 1619–1629. [CrossRef] [PubMed]
130. Liu, N.; Cui, Y.-T.; Zheng, Y.; Fang, S.-M.; Liao, L.-X.; Luo, T.-T.; Zhong, Z.-H.; Hu, X.-Y.; Zhou, M.-H.; Tu, Y.-Y. Curcumin Induces Ferroptosis in Ovarian Cancer Cells through the Nrf2/GPX4 Regulation Axis. *Am. J. Cancer Res.* **2026**, *16*, 1729–1744. [CrossRef] [PubMed]
131. 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. [CrossRef] [PubMed]
132. Farhan, M. Green Tea Catechins: Nature's Way of Preventing and Treating Cancer. *Int. J. Mol. Sci.* **2022**, *23*, 10713. [CrossRef] [PubMed]
133. 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*. [CrossRef] [PubMed]
134. 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*, 1592395. [CrossRef] [PubMed]
135. Date, A.A.; Destache, C.J. Natural Polyphenols: Potential in the Prevention of Sexually Transmitted Viral Infections. *Drug Discov. Today* **2016**, *21*, 333–341. [CrossRef] [PubMed]

136. Zhu, Y.; Huang, Y.; Liu, M.; Yan, Q.; Zhao, W.; Yang, P.; Gao, Q.; Wei, J.; Zhao, W.; Ma, L. Epigallocatechin Gallate Inhibits Cell Growth and Regulates MiRNA Expression in Cervical Carcinoma Cell Lines Infected with Different High-risk Human Papillomavirus Subtypes. *Exp. Ther. Med.* **2018**, 1742–1748. [CrossRef] [PubMed]
137. 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. [CrossRef]
138. Xu, J.; Xu, Z.; Zheng, W. A Review of the Antiviral Role of Green Tea Catechins. *Molecules* **2017**, *22*, 1337. [CrossRef] [PubMed]
139. Tang, Y.; Chen, Q.; Chen, J.; Mo, Z.; Li, H.; Peng, L.; Ke, Y.; Liang, B.; Li, R.; Zhu, H. Green Tea Polyphenols Cause Apoptosis and Autophagy in HPV-16 Subgene-Immortalized Human Cervical Epithelial Cells via the Activation of the Nrf2 Pathway. *Nutr. Cancer* **2022**, *74*, 3769–3778. [CrossRef] [PubMed]
140. 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. [CrossRef] [PubMed]
141. Stockfleth, E.; Meyer, T. Sinecatechins (Polyphenon E) Ointment for Treatment of External Genital Warts and Possible Future Indications. *Expert Opin. Biol. Ther.* **2014**, *14*, 1033–1043. [CrossRef] [PubMed]
142. 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. [CrossRef] [PubMed]
143. Shafabakhsh, R.; Reiter, R.J.; Aschner, M.; Mirzaei, H.; Asemi, Z. Resveratrol and Cervical Cancer: A New Therapeutic Option. *Mini-Rev. Med. Chem.* **2023**, *23*, 159–169. [CrossRef] [PubMed]
144. Obrador, E.; Salvador-Palmer, R.; Jihad-Jebbar, A.; López-Blanch, R.; Dellinger, T.H.; Dellinger, R.W.; Estrela, J.M. Pterostilbene in Cancer Therapy. *Antioxidants* **2021**, *10*, 492. [CrossRef] [PubMed]
145. 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 Immunol. Immunother.* **2018**, *67*, 761–774. [CrossRef] [PubMed]
146. Nadile, M.; Retsidou, M.I.; Gioti, K.; Beloukas, A.; Tsiani, E. Resveratrol against Cervical Cancer: Evidence from In Vitro and In Vivo Studies. *Nutrients* **2022**, *14*, 5273. [CrossRef] [PubMed]
147. Yu, H.; Pan, C.; Zhao, S.; Wang, Z.; Zhang, H.; Wu, W. Resveratrol Inhibits Tumor Necrosis Factor-α-Mediated Matrix Metalloproteinase-9 Expression and Invasion of Human Hepatocellular Carcinoma Cells. *Biomed. Pharmacother.* **2008**, *62*, 366–372. [CrossRef] [PubMed]
148. Guo, K.; Feng, Y.; Zheng, X.; Sun, L.; Wasan, H.S.; Ruan, S.; Shen, M. Resveratrol and Its Analogs: Potent Agents to Reverse Epithelial-to-Mesenchymal Transition in Tumors. *Front. Oncol.* **2021**, *11*, 644134. [CrossRef] [PubMed]
149. 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*, 60904–60916. [CrossRef] [PubMed]
150. 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 W12 Cervical Cells Harbouring Extrachromosomal or Integrated HPV16 DNA. *Br. J. Cancer* **2021**, *124*, 901–913. [PubMed]
151. 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 Papillomavirus-Positive Head and Neck Squamous Cell Carcinoma. *Oncotarget* **2017**, *8*, 60025–60035. [PubMed]
152. Li, N.; Wang, J. Quercetin Induces Cytotoxicity and Apoptosis, Reduces Metastasis and Drug Resistance in Oral Cancer Cells. *Turk. J. Biochem.* **2024**, *49*, 148–156.
153. 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.
154. 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. [CrossRef] [PubMed]
155. Thakore, V.P.; Uppalapati, S.S.; Kumar, S.P.; Mandoli, A.; Patel, P.S.; Jain, N.K. Computational and Experimental Investigation of Kaempferol and Quercetin as Potential Inhibitors of MMP1 in Oral Cancer. *Comput. Biol. Chem.* **2026**, *120*, 108716. [CrossRef] [PubMed]
156. Son, H.-K.; Kim, D. Quercetin Induces Cell Cycle Arrest and Apoptosis in YD10B and YD38 Oral Squamous Cell Carcinoma Cells. *Asian Pac. J. Cancer Prev.* **2023**, *24*, 283–289. [CrossRef] [PubMed]
157. Turner, G.; Sywanycz, S.M.; Buchler, B.L.; Wardlow, R.D.; Lee, R.J.; Carey, R.M. Quercetin as a Bitter Taste Receptor Agonist with Anticancer Effects in Head and Neck Cancer Cells. *Nutrients* **2025**, *17*, 3224. [CrossRef] [PubMed]

158. 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. [CrossRef] [PubMed]
159. Selvaraj, S.; Venkidasamy, B. Quercetin, a Natural Antioxidant Compound for the Treatment of Oral Cancer Therapy. *Oral Oncol. Rep.* **2024**, *10*, 100247. [CrossRef]
160. 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. *J. Chin. Med. Assoc.* **2013**, *76*, 146–152. [CrossRef] [PubMed]
161. Haghiac, M.; Walle, T. Quercetin Induces Necrosis and Apoptosis in SCC-9 Oral Cancer Cells. *Nutr. Cancer* **2005**, *53*, 220–231. [CrossRef] [PubMed]
162. 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. [CrossRef] [PubMed]
163. 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. [PubMed]
164. Ivan, I.M.; Olaru, O.T.; Popovici, V.; Chițescu, C.L.; Popescu, L.; Luță, E.A.; Ilie, E.I.; Brașoveanu, L.I.; Hotnog, C.M.; Nițulescu, G.M.; et al. Antioxidant and Cytotoxic Properties of *Berberis vulgaris* (L.) Stem Bark Dry Extract. *Molecules* **2024**, *29*, 2053. [CrossRef] [PubMed]
165. Ho, Y.-T.; Yang, J.-S.; Li, T.-C.; Lin, J.-J.; Lin, J.-G.; Lai, K.-C.; Ma, C.-Y.; Wood, W.G.; Chung, J.-G. Berberine Suppresses in Vitro Migration and Invasion of Human SCC-4 Tongue Squamous Cancer Cells through the Inhibitions of FAK, IKK, NF-KB, u-PA and MMP-2 and -9. *Cancer Lett.* **2009**, *279*, 155–162. [CrossRef] [PubMed]
166. Liu, D.; Li, L.; Zhang, J.; Qin, H.; Zhang, M.; Sun, X.; Han, Y.; Wang, F.; Wang, Z.; Cai, Z. Berberine Promotes Apoptosis and Inhibits the Migration of Oral Squamous Carcinoma Cells through Inhibition of the RAGE/PI3K/AKT/MTOR Pathway. *Biomed. Pharmacother.* **2025**, *187*, 118147. [CrossRef] [PubMed]
167. Tan, Y.; Luo, W.; Li, Y. Multitarget Mechanism of Berberine against Cervical Cancer: An Integrated Study of Network Pharmacology and Molecular Docking. *Lett. Drug Des. Discov.* **2026**, *23*, 100332. [CrossRef]
168. Singh, T.; Chhokar, A.; Thakur, K.; Aggarwal, N.; Pragya, P.; Yadav, J.; Tripathi, T.; Jadli, M.; Bhat, A.; Gupta, P.; et al. Targeting Aberrant Expression of STAT3 and AP-1 Oncogenic Transcription Factors and HPV Oncoproteins in Cervical Cancer by Berberis Aquifolium. *Front. Pharmacol.* **2021**, *12*, 757414. [CrossRef] [PubMed]
169. Lukoceviciute, M.; Zupancic, M.; Kostopoulou, O.N.; Holzhauser, S.; Dalianis, T. Curcumin Alone and Combined With PI3K Inhibitors Elicits Positive Effects on Oropharyngeal Cancer Cell Lines Regardless of HPV Status. *Anticancer Res.* **2024**, *44*, 1863–1876. [CrossRef] [PubMed]
170. Divya, C.S.; Pillai, M.R. Antitumor Action of Curcumin in Human Papillomavirus Associated Cells Involves Downregulation of Viral Oncogenes, Prevention of NFkB and AP-1 Translocation, and Modulation of Apoptosis. *Mol. Carcinog.* **2006**, *45*, 320–332. [CrossRef] [PubMed]
171. Ji, M.; Lv, Y.; Chen, C.; Xing, D.; Zhou, C.; Zhao, J.; Qi, Y.; Zhang, J.; Wang, Y.; Ma, X.; et al. Metformin Inhibits Oral Squamous Cell Carcinoma Progression through Regulating RNA Alternative Splicing. *Life Sci.* **2023**, *315*, 121274. [CrossRef] [PubMed]
172. Lindsay, C.; Kostiuk, M.; Conrad, D.; O'Connell, D.A.; Harris, J.; Seikaly, H.; Biron, V.L. Antitumor Effects of Metformin and Curcumin in Human Papillomavirus Positive and Negative Head and Neck Cancer Cells. *Mol. Carcinog.* **2019**, *58*, 1946–1959. [CrossRef] [PubMed]
173. Peraza-Labrador, A.; Buitrago, D.M.; Coy-Barrera, E.; Perdomo-Lara, S.J. Antiproliferative and Pro-Apoptotic Effects of a Phenolic-Rich Extract from Lycium Barbarum Fruits on Human Papillomavirus (HPV) 16-Positive Head Cancer Cell Lines. *Molecules* **2022**, *27*, 3568. [CrossRef] [PubMed]
174. 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*, 3371–3378. [PubMed]
175. Pourhajibagher, M.; Bahador, A. Bioinformatics Analysis of Photoexcited Natural Flavonoid Glycosides as the Inhibitors for Oropharyngeal HPV Oncoproteins. *AMB Express* **2024**, *14*, 29. [CrossRef] [PubMed]
176. Agarwal, A.; Kansal, V.; Farooqi, H.; Prasad, R.; Singh, V.K. Epigallocatechin Gallate (EGCG), an Active Phenolic Compound of Green Tea, Inhibits Tumor Growth of Head and Neck Cancer Cells by Targeting DNA Hypermethylation. *Biomedicines* **2023**, *11*, 789. [CrossRef] [PubMed]
177. King, M.; Chatelain, K.; Farris, D.; Jensen, D.; Pickup, J.; Swapp, A.; O'Malley, S.; Kingsley, K. Oral Squamous Cell Carcinoma Proliferative Phenotype Is Modulated by Proanthocyanidins: A Potential Prevention and Treatment Alternative for Oral Cancer. *BMC Complement. Altern. Med.* **2007**, *7*, 22. [CrossRef] [PubMed]

178. Souza, R.P.; Bonfim-Mendonça, P.d.S.; Gimenes, F.; Ratti, B.A.; Kaplum, V.; Bruschi, M.L.; Nakamura, C.V.; Silva, S.O.; Maria-Engler, S.S.; Consolaro, M.E.L. Oxidative Stress Triggered by Apigenin Induces Apoptosis in a Comprehensive Panel of Human Cervical Cancer-Derived Cell Lines. *Oxid. Med. Cell. Longev.* **2017**, *2017*, 1512745. [CrossRef] [PubMed]
179. Osailan, R.; Habeeb, T.; Khalafalla, M.A.H.; Bashal, A.H. Molecular Dynamics and Electronic Structure Insights into Chloroquine, Quercetin, and Luteolin Binding to HPV-16 E2 Protein. *J. Steroid Biochem. Mol. Biol.* **2026**, *256*, 106899. [CrossRef] [PubMed]
180. Ham, S.; Kim, K.H.; Kwon, T.H.; Bak, Y.; Lee, D.H.; Song, Y.S.; Park, S.-H.; Park, Y.S.; Kim, M.S.; Kang, J.W.; et al. Luteolin Induces Intrinsic Apoptosis via Inhibition of E6/E7 Oncogenes and Activation of Extrinsic and Intrinsic Signaling Pathways in HPV-18-Associated Cells. *Oncol. Rep.* **2014**, *31*, 2683–2691. [CrossRef] [PubMed]
181. Dunjic, M.; Turini, S.; Nejkovic, L.; Sulovic, N.; Cvetkovic, S.; Dunjic, M.; Dunjic, K.; Dolovac, D. Comparative Molecular Docking of Apigenin and Luteolin versus Conventional Ligands for TP-53, PRb, APOBEC3H, and HPV-16 E6: Potential Clinical Applications in Preventing Gynecological Malignancies. *Curr. Issues Mol. Biol.* **2024**, *46*, 11136–11155. [CrossRef] [PubMed]
182. Cherry, J.J.; Rietz, A.; Malinkevich, A.; Liu, Y.; Xie, M.; Bartolowits, M.; Davisson, V.J.; Baleja, J.D.; Androphy, E.J. Structure Based Identification and Characterization of Flavonoids That Disrupt Human Papillomavirus-16 E6 Function. *PLoS ONE* **2013**, *8*, e84506. [CrossRef] [PubMed]
183. 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. [CrossRef] [PubMed]
184. 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. [CrossRef] [PubMed]
185. 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 Sov. Med. Counc.* **2022**, *2022*, 151–159. [CrossRef]
186. 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. [CrossRef] [PubMed]
187. 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*, 3055. [CrossRef] [PubMed]
188. Abdullah, M.Z.; Bakar, L.M.; Othman, N.; Taher, M.; Rasad, M.S.B.A.; Foong, F.H.N.; Ichwan, S.J.A. Anti-Cancer Activities of β-Mangostin Against Oral Squamous Cell Carcinoma. *J. Int. Dent. Med. Res.* **2022**, *15*, 81–86. [CrossRef] [PubMed]
189. Rizqiawan, A.; Mulyawan, I.; Ta, T.T.; Ashari, A.F.; Soleh, A.R.; Busri, A.M.H.; Artha, D.A.; Shavia, C.; El Fadhlallah, P.M. Viability Test of α-Mangostin against Oral Squamous Cell Carcinoma. *Malays. J. Med. Health Sci.* **2022**, *18*, 41–44. [CrossRef]
190. 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. [CrossRef] [PubMed]
191. 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*, 512. [CrossRef] [PubMed]
192. Bosch-Barrera, J.; Menendez, J.A. Silibinin and STAT3: A Natural Way of Targeting Transcription Factors for Cancer Therapy. *Cancer Treat. Rev.* **2015**, *41*, 540–546. [CrossRef] [PubMed]
193. Wang, Y.; Yuan, A.-J.; Wu, Y.-J.; Wu, L.-M.; Zhang, L. Silymarin in Cancer Therapy: Mechanisms of Action, Protective Roles in Chemotherapy-Induced Toxicity, and Nanoformulations. *J. Funct. Foods* **2023**, *100*, 105384. [CrossRef]
194. IRCT2015050622132N1 Evaluation of Oral Nano-Silymarin Formulation Efficacy on Prevention of Radiotherapy Induced Mucositis: A Randomized, Double-Blinded, Placebo-Controlled Clinical Trial. Available online: https://www.researchgate.net/publication/345365778_939P_Evaluation_of_oral_nano-silymarin_formulation_efficacy_on_prevention_of_blinded_placebo-controlled_clinical_trial (accessed on 13 May 2026).
195. Thyagarajan, S.; Subramanian, K.; Rasul, H.O.; Mohammed, O.S.; Salgado, M.G.; Gerli Candia, L. AMulti-Target in Silico Profiling of Silymarin Derivatives against Oncogenic Pathways: Integration of Docking, DFT, ADMET, and Molecular Dynamics. *Biochem. Biophys. Res. Commun.* **2025**, *786*, 152675. [CrossRef] [PubMed]
196. Einbond, L.S.; Zhou, J.; Huang, K.; Castellanos, M.R.; Mbazor, E.; Balick, M.; Ma, H.; DeVoti, J.A.; Redenti, S.; Wu, H. Plant Compounds Inhibit the Growth of W12 Cervical Precancer Cells Containing Episomal or Integrant HPV DNA; Tanshinone IIA Synergizes with Curcumin in Cervical Cancer Cells. *Viruses* **2024**, *17*, 55. [CrossRef] [PubMed]
197. Zhao, X.; Zhang, R.; Song, Z.; Yang, K.; He, H.; Jin, L.; Zhang, W. Curcumin Suppressed the Proliferation and Apoptosis of HPV-positive Cervical Cancer Cells by Directly Targeting the E6 Protein. *Phytother. Res.* **2024**, *38*, 4967–4981. [PubMed]
198. Chen, Y.-H.; Wu, J.-X.; Yang, S.-F.; Hsiao, Y.-H. Synergistic Combination of Luteolin and Asiatic Acid on Cervical Cancer In Vitro and In Vivo. *Cancers* **2023**, *15*, 548. [CrossRef] [PubMed]

199. Wang, G.; Wang, J.; Momeni, M.R. Epigallocatechin-3-Gallate and Its Nanoformulation in Cervical Cancer Therapy: The Role of Genes, MicroRNA and DNA Methylation Patterns. *Cancer Cell Int.* **2023**, *23*, 335. [CrossRef] [PubMed]
200. Yap, J.K.W.; Kehoe, S.T.; Woodman, C.B.J.; Dawson, C.W. The Major Constituent of Green Tea, Epigallocatechin-3-Gallate (EGCG), Inhibits the Growth of HPV18-Infected Keratinocytes by Stimulating Proteasomal Turnover of the E6 and E7 Oncoproteins. *Pathogens* **2021**, *10*, 459. [CrossRef] [PubMed]
201. Clemente-Soto, A.; Salas-Vidal, E.; Milan-Pacheco, C.; Sánchez-Carranza, J.; Peralta-Zaragoza, O.; González-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*, 2097–2106. [CrossRef] [PubMed]
202. 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*, 39. [CrossRef] [PubMed]
203. Munagala, R.; Aqil, F.; Jeyabalan, J.; Gupta, R.C. Tanshinone IIA Inhibits Viral Oncogene Expression Leading to Apoptosis and Inhibition of Cervical Cancer. *Cancer Lett.* **2015**, *356*, 536–546. [CrossRef] [PubMed]
204. Lee, C.-H.; Ying, T.-H.; Chiou, H.-L.; Hsieh, S.-C.; Wen, S.-H.; Chou, R.-H.; Hsieh, Y.-H. Alpha-Mangostin Induces Apoptosis through Activation of Reactive Oxygen Species and ASK1/P38 Signaling Pathway in Cervical Cancer Cells. *Oncotarget* **2017**, *8*, 47425–47439. [CrossRef] [PubMed]
205. Shin, H.J.; Han, J.M.; Choi, Y.S.; Jung, H.J. Pterostilbene Suppresses Both Cancer Cells and Cancer Stem-Like Cells in Cervical Cancer with Superior Bioavailability to Resveratrol. *Molecules* **2020**, *25*, 228. [CrossRef] [PubMed]
206. Ambreen, G.; Duse, L.; Tariq, I.; Ali, U.; Ali, S.; Pinnapireddy, S.R.; Bette, M.; Bakowsky, U.; Mandic, R. Sensitivity of Papilloma Virus-Associated Cell Lines to Photodynamic Therapy with Curcumin-Loaded Liposomes. *Cancers* **2020**, *12*, 3278. [CrossRef] [PubMed]
207. Roschenko, V.; Ayoub, A.M.; Engelhardt, K.; Schäfer, J.; Amin, M.U.; Preis, E.; Mandic, R.; Bakowsky, U. Lipid-Coated Polymeric Nanoparticles for the Photodynamic Therapy of Head and Neck Squamous Cell Carcinomas. *Pharmaceutics* **2023**, *15*, 2412. [CrossRef] [PubMed]
208. Kang, T.H.; Lee, J.H.; Song, C.K.; Han, H.D.; Shin, B.C.; Pai, S.I.; Hung, C.-F.; Trimble, C.; Lim, J.-S.; Kim, T.W.; et al. Epigallocatechin-3-Gallate Enhances CD8+ T Cell–Mediated Antitumor Immunity Induced by DNA Vaccination. *Cancer Res.* **2007**, *67*, 802–811. [CrossRef] [PubMed]
209. Chuang, C.-M.; Monie, A.; Wu, A.; Hung, C.-F. Combination of Apigenin Treatment with Therapeutic HPV DNA Vaccination Generates Enhanced Therapeutic Antitumor Effects. *J. Biomed. Sci.* **2009**, *16*, 49. [CrossRef] [PubMed]
210. Kawish, S.M.; Sharma, S.; Gupta, P.; Ahmad, F.J.; Iqbal, M.; Alshabrmi, F.M.; Anwer, M.K.; Fathi-karkan, S.; Rahdar, A.; Aboudzadeh, M.A. Nanoparticle-Based Drug Delivery Platform for Simultaneous Administration of Phytochemicals and Chemotherapeutics: Emerging Trends in Cancer Management. *Part. Part. Syst. Charact.* **2024**, *41*, 1105–1121. [CrossRef]
211. 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. [CrossRef] [PubMed]
212. Jafernik, K.; Ładniak, A.; Blicharska, E.; Czarnek, K.; Ekiert, H.; Wiącek, A.E.; Szopa, A. Chitosan-Based Nanoparticles as Effective Drug Delivery Systems—A Review. *Molecules* **2023**, *28*, 1963. [CrossRef] [PubMed]
213. Karimi, M.; Parsania, M.; Motakef Kazemi, N.; Qomi, M.; Hadipour Jahromy, M. Curcumin Nanoemulsion Suppresses HPV Oncogenes and Inhibits Cervical Cancer Progression: In Vitro and in Vivo Study. *Virol. J.* **2025**, *22*, 165. [CrossRef] [PubMed]
214. Gupta, T.; Singh, J.; Kaur, S.; Sandhu, S.; Singh, G.; Kaur, I.P. Enhancing Bioavailability and Stability of Curcumin Using Solid Lipid Nanoparticles (CLEN): A Covenant for Its Effectiveness. *Front. Bioeng. Biotechnol.* **2020**, *8*, 879. [CrossRef] [PubMed]
215. Hazzah, H.A.; Farid, R.M.; Nasra, M.M.A.; EL-Massik, M.A.; Abdallah, O.Y. Lyophilized Sponges Loaded with Curcumin Solid Lipid Nanoparticles for Buccal Delivery: Development and Characterization. *Int. J. Pharm.* **2015**, *492*, 248–257. [CrossRef] [PubMed]
216. Jacob, S.; Rao, R.; Gorain, B.; Boddu, S.H.S.; Nair, A.B. Solid Lipid Nanoparticles and Nanostructured Lipid Carriers for Anticancer Phytochemical Delivery: Advances, Challenges, and Future Prospects. *Pharmaceutics* **2025**, *17*, 1079. [CrossRef] [PubMed]
217. Hao, X.; Sun, X.; Zhu, H.; Xie, L.; Wang, X.; Jiang, N.; Fu, P.; Sang, M. Hydroxypropyl-β-Cyclodextrin-Complexed Resveratrol Enhanced Antitumor Activity in a Cervical Cancer Model: In Vivo Analysis. *Front. Pharmacol.* **2021**, *12*, 573909. [CrossRef] [PubMed]
218. Santiago, L.R.; Asevedo, E.A.; de Oliveira, M.E.J.; Pereira, K.C.; da Silva Trindade, M.F.; Oliveira, A.G.S.; Rocha, M.A.; Kang, S.; Rani, A.; Park, M.N.; et al. Artificial Intelligence-Based Screening of Phytochemicals for Targeted Cancer Therapy. *Nat. Prod. Bioprospect.* **2026**, *16*, 55. [CrossRef] [PubMed]
219. Garcia, F.A.R.; Cornelison, T.; Nuño, T.; Greenspan, D.L.; Byron, J.W.; Hsu, C.-H.; Alberts, D.S.; Chow, H.-H.S. Results of a Phase II Randomized, Double-Blind, Placebo-Controlled Trial of Polyphenon E in Women with Persistent High-Risk HPV Infection and Low-Grade Cervical Intraepithelial Neoplasia. *Gynecol. Oncol.* **2014**, *132*, 377–382. [CrossRef] [PubMed]

220. Puviani, M.; Galluzzo, M.; Talamonti, M.; Mazzilli, S.; Campione, E.; Bianchi, L.; Milani, M.; Luppino, I.; Micali, G. Efficacy of Sinecatechins 10% as Proactive Sequential Therapy of External Genital Warts after Laser CO 2 Ablative Therapy: The PACT Study (Post-Ablation Immunomodulator Treatment of Condylomata with Sinecatechins): A Randomized, Masked Outcome Assessment, Multicenter Trial. *Int. J. STD AIDS* **2019**, *30*, 131–136. [PubMed]
221. 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. *Obstet. Gynecol.* **2008**, *111*, 1371–1379. [CrossRef] [PubMed]
222. Bhatia, N. Overview of HPV-Related Dermatoses and Applications of Sinecatechins Ointment. *Curr. Dermatol. Rep.* **2012**, *1*, 161–167. [CrossRef]
223. Gaspari, V.; Cinotti, E.; Puviani, M.; Trovato, E.; Campoli, M.; Milani, M. Assessment of Sinecatechins 10% Ointment Used as Proactive Sequential Therapy in Recurrence Rate of Genital Warts Lesions after Cryotherapy. The PACT-II Trial (Postablation Immunomodulator Treatment of Condylomata with Sinecatechins): A Prospective Assessor-Blinded, Multicenter, Pilot Trial. *Ital. J. Dermatol. Venereol.* **2022**, *157*, 72–77. [CrossRef] [PubMed]
224. 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. *Ann. Oncol.* **2016**, *27*, ix115–ix116. [CrossRef]
225. 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. *Ann. Oncol.* **2020**, *31*, S672. [CrossRef]
226. Ghodousi, M.; Karbasforooshan, H.; Arabi, L.; Elyasi, S. Silymarin as a Preventive or Therapeutic Measure for Chemotherapy and Radiotherapy-Induced Adverse Reactions: A Comprehensive Review of Preclinical and Clinical Data. *Eur. J. Clin. Pharmacol.* **2023**, *79*, 15–38. [PubMed]
227. 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. [CrossRef]
228. 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. *Phytother. Res.* **2016**, *30*, 1879–1885. [CrossRef] [PubMed]
229. 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. [CrossRef] [PubMed]
230. Doğan, D.; Meydan, İ.; Kömüroğlu, A.U. Protective Effect of Silymarin and Gallic Acid against Cisplatin-Induced Nephrotoxicity and Hepatotoxicity. *Int. J. Clin. Pract.* **2022**, *2022*, 6541026. [CrossRef] [PubMed]
231. Kiselev, V.I.; Ashrafyan, L.A.; Muyzhnek, E.L.; Gerfanova, E.V.; Antonova, I.B.; Aleshikova, O.I.; Sarkar, F.H. A New Promising Way of Maintenance Therapy in Advanced Ovarian Cancer: A Comparative Clinical Study. *BMC Cancer* **2018**, *18*, 904. [CrossRef] [PubMed]
232. Kia, S.J.; Basirat, M.; Saedi, H.S.; Arab, S.A. Effects of Nanomicelle Curcumin Capsules on Prevention and Treatment of Oral Mucosits in Patients under Chemotherapy with or without Head and Neck Radiotherapy: A Randomized Clinical Trial. *BMC Complement. Med. Ther.* **2021**, *21*, 232. [CrossRef] [PubMed]
233. Ramezani, V.; Ghadirian, S.; Shabani, M.; Boroumand, M.A.; Daneshvar, R.; Saghafi, F. Efficacy of Curcumin for Amelioration of Radiotherapy-Induced Oral Mucositis: A Preliminary Randomized Controlled Clinical Trial. *BMC Cancer* **2023**, *23*, 354. [CrossRef] [PubMed]
234. Chen, Z.-X.; Qin, Y.-S.; Shi, B.-H.; Gao, B.-Y.; Tao, R.-C.; Yong, X.-Z. Effects of Curcumin on Radiation/Chemotherapy-Induced Oral Mucositis: Combined Meta-Analysis, Network Pharmacology, Molecular Docking, and Molecular Dynamics Simulation. *Curr. Issues Mol. Biol.* **2024**, *46*, 10545–10569. [CrossRef] [PubMed]
235. Bardy, J.; Molassiotis, A.; Ryder, W.D.; Mais, K.; Sykes, A.; Yap, B.; Lee, L.; Kaczmarski, E.; Slevin, N. A Double-Blind, Placebo-Controlled, Randomised Trial of Active Manuka Honey and Standard Oral Care for Radiation-Induced Oral Mucositis. *Br. J. Oral Maxillofac. Surg.* **2012**, *50*, 221–226. [CrossRef] [PubMed]
236. Jen, S.-C.; Chen, Y.-W.; Tsai, J.-T.; Kuo, C.-C.; Ting, L.-L.; Huang, W.-Y.; Huang, T.-W.; Chen, J.-H.; Gautama, M.S.N. Effects of Honey and Taiwanese Green Propolis on Oral Mucositis and Quality of Life in Head and Neck Cancer Patients Undergoing Radiotherapy: A Randomized Controlled Trial. *Food Funct.* **2025**, *16*, 4958–4969. [CrossRef] [PubMed]
237. Pawar, D.; Neve, R.S.; Kalgane, S.; Riva, A.; Bombardelli, E.; Ronchi, M.; Petrangolini, G.; Morazzoni, P. SAMITAL® Improves Chemo/Radiotherapy-Induced Oral Mucositis in Patients with Head and Neck Cancer: Results of a Randomized, Placebo-Controlled, Single-Blind Phase II Study. *Support. Care Cancer* **2013**, *21*, 827–834.
238. Fasanaro, E.; Del Bianco, P.; Groff, E.; Riva, A.; Petrangolini, G.; Busato, F.; Stritoni, P.; Scarzello, G.; Loreggian, L.; De Salvo, G.L. Role of SAMITAL in the Prevention and Treatment of Chemo-Radiotherapy-Induced Oral Mucositis in Head and Neck

Carcinoma: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Clinical Trial (ROSAM). *Cancers* **2022**, *14*, 6192. [CrossRef] [PubMed]
239. Najafizade, N.; Dehkordi, R.M.; Hemati, S. Investigating the Effect of Aloe Vera on the Prevention and Treatment of Radiotherapy-Induced Oral Mucositis in Patients with Head-and-Neck Cancer. *J. Res. Med. Sci.* **2024**, *29*, 16. [CrossRef] [PubMed]
240. Momeni, A. Effect of Silymarin in the Prevention of Cisplatin Nephrotoxicity, a Clinical Trial Study. *J. Clin. Diagn. Res.* **2015**, *9*, OC11–OC13. [CrossRef]
241. Fallah, M.; Soleimani, A.; Nouri, A.; Fallah, M.; Haghighi, A.; Dehpour, A.R.; Zendehdel, A.; Ebrahimpour-Koujan, S. Resveratrol for Cancer Radio-Sensitization: Ready for Prime Time or Future Perspective. *Food Sci. Nutr.* **2026**, *14*, e71579. [CrossRef] [PubMed]
242. Bostan, M.; Petrică-Matei, G.G.; Radu, N.; Hainarosie, R.; Stefanescu, C.D.; Diaconu, C.C.; Roman, V. The Effect of Resveratrol or Curcumin on Head and Neck Cancer Cells Sensitivity to the Cytotoxic Effects of Cisplatin. *Nutrients* **2020**, *12*, 2596. [CrossRef] [PubMed]
243. Saberian, E.; Jenčová, J.; Jenča, A.; Jenča, A.; Petrášová, A.; Jenča, J.; Akbarzadehkhayavi, A. Combination Therapy of Curcumin and Cisplatin Encapsulated in Niosome Nanoparticles for Enhanced Oral Cancer Treatment. *Indian J. Clin. Biochem.* **2025**, *40*, 59–66. [PubMed]
244. Quimby, A.E.; Hogan, D.; Khalil, D.; Hearn, M.; Nault, C.; Johnson-Obaseki, S. Coconut Oil as a Novel Approach to Managing Radiation-Induced Xerostomia: A Primary Feasibility Study. *Int. J. Otolaryngol.* **2020**, *2020*, 1–6. [CrossRef] [PubMed]
245. Stockfleth, E.; Beti, H.; Orasan, R.; Grigorian, F.; Mescheder, A.; Tawfik, H.; Thielert, C. Topical Polyphenon ® E in the Treatment of External Genital and Perianal Warts: A Randomized Controlled Trial. *Br. J. Dermatol.* **2008**, *158*, 1329–1338. [CrossRef] [PubMed]
246. Calcagno, M.; Incocciati, B.; Di Fraia, L.; Unfer, V. Counteracting HPV Cervical and Anal Infection through Dietary Supplementation of EGCG, Folic Acid, Vitamin B12 and Hyaluronic Acid: Clinical Case Reports. *J. Clin. Med.* **2024**, *13*, 3597. [CrossRef] [PubMed]
247. Giampieri, F.; Cianciosi, D.; Forbes-Hernández, T.Y. Myrtle (*Myrtus Communis* L.) Berries, Seeds, Leaves, and Essential Oils: New Undiscovered Sources of Natural Compounds with Promising Health Benefits. *Food Front.* **2020**, *1*, 276–295. [CrossRef]
248. Basu, P.; Dutta, S.; Begum, R.; Mittal, S.; Dutta, P.D.; Bharti, A.C.; Panda, C.K.; Biswas, J.; Dey, B.; Talwar, G.P.; et al. Clearance of Cervical Human Papillomavirus Infection by Topical Application of Curcumin and Curcumin Containing Polyherbal Cream: A Phase II Randomized Controlled Study. *Asian Pac. J. Cancer Prev.* **2013**, *14*, 5753–5759. [CrossRef] [PubMed]
249. Wang, E.; Kuhn, T.; Lahiri, C.; Nguyen, M.; Ofotokun, I.; Abraham, R.; Easley, K.; Mosunjac, M.; Tadros, T.; Finneran, C.; et al. 4553 An Investigation into the Use of Curcumin, a Topical Herbal Agent, for the Treatment of Cervical Intraepithelial Neoplasia. *J. Clin. Transl. Sci.* **2020**, *4*, 122–123. [CrossRef]
250. Gençtürk, N.; Karaahmet, A.Y.; Cömert, D. The Impact of Herbal Treatments on Cervicovaginal Human Papillomavirus Infection: A Systematic Review and Meta-Analysis. *Rev. Assoc. Med. Bras.* **2024**, *70*, e20240141. [CrossRef] [PubMed]
251. Rosen, C.A.; Woodson, G.E.; Thompson, J.W.; Hengesteg, A.P.; Bradlow, H.L. Preliminary Results of the Use of Indole-3-Carbinol for Recurrent Respiratory Papillomatosis. *Otolaryngol.—Head Neck Surg.* **1998**, *118*, 810–815. [CrossRef] [PubMed]
252. Rosen, C.A.; Bryson, P.C. Indole-3-Carbinol for Recurrent Respiratory Papillomatosis: Long-Term Results. *J. Voice* **2004**, *18*, 248–253. [CrossRef] [PubMed]
253. Shady, N.H.; Mokhtar, F.A.; Abdullah, H.S.; Abdel-Aziz, S.A.; Mohamad, S.A.; Imam, M.S.; El Afify, S.R.; Abdelmohsen, U.R. In Vitro and Randomized Controlled Clinical Study of Natural Constituents' Anti-HPV Potential for Treatment of Plantar Warts Supported with In Silico Studies and Network Analysis. *Pharmaceuticals* **2024**, *17*, 759. [CrossRef] [PubMed]
254. Zupancic, M.; Kostopoulou, O.N.; Holzhauser, S.; Lukoseviciute, M.; Jylhä, C.; Marklund, L.; Näsman, A.; Sivars, L.; Dalianis, T. Human Papillomavirus (HPV) Load Is Higher in HPVDNA/P16 Positive than in HPVDNA Positive/P16 Negative Oropharyngeal Squamous Cell Carcinoma but Does Not Differ Significantly between Various Subsites or Correlate to Survival. *Oral Oncol.* **2024**, *151*, 106749. [CrossRef] [PubMed]

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