Phytochemical-based approaches in oral cancer: Active ingredients, trends and challenges (Review)

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Abstract. Oral cancer, strongly linked to modifiable risk factors, remains a significant public health challenge. Emerging evidence suggests that phytochemicals, which are naturally occurring bioactive compounds in plants, may play a potential role in oral cancer therapy. In the present review, a narrative synthesis of the literature was conducted to examine the role of phytochemicals in oral cancer prevention and adjunctive therapy. Phytochemicals demonstrate antioxidant, anti-inflammatory and anti-proliferative properties that contribute to their anticancer potential. Current evidence indicates that phytochemicals, such as curcumin, anthocyanins, epigallocatechin-3-gallate, S-allylcysteine, quercetin, lycopene and resveratrol exert antitumor effects. However, suboptimal aqueous solubility, limited systemic bioavailability and insufficient molecular targeting frequently constrain phytochemical-based interventions. On the whole, phytochemicals exhibit promising anticancer activity in preclinical models of oral squamous cell carcinoma. Clinical validation is required to address limitations in bioavailability, rapid metabolism and heterogeneous pharmacological properties.

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1. Introduction

Oral squamous cell carcinoma (OSCC), arising from the oral mucosa, is one of the most common head and neck malignancies. Surgery remains the first-line treatment for OSCC, and advanced cases may require postoperative radiotherapy and/or chemotherapy (1). Despite the availability of advanced treatment options, such as targeted therapy or immunotherapy, the 5-year survival rate remains poor (2,3). The effectiveness of conventional treatments is limited by several factors, including systemic toxicity from chemotherapy, damage to healthy tissue caused by radiotherapy, the high cost of advanced therapies, variability in individual patient therapeutic responses leading to persistent or recurrent disease and the development of drug resistance. In addition, treatment often impairs the quality of life of patients, causing complications, such as xerostomia, mucositis and restricted jaw movement. These drawbacks highlight the need for more effective, less toxic and accessible alternatives for the management of oral cancer (4).

Dietary factors account for ~35% of cancer-related deaths, and lifestyle modifications can prevent more than two-thirds of all human cancers (5). The dietary consumption of phytochemicals may counteract some harmful effects of cancer-related risk factors, particularly oxidative stress, inflammation, and carcinogen-induced cellular damage. Recently, phytochemical-based treatments have been introduced to help mitigate the disadvantages of routine treatments and improve prognosis. Phytochemicals are small-molecule bioactive compounds naturally occurring in plants, including flavonoids, phenolic acids, carotenoids and stilbenes. These agents exhibit diverse biological activities, including antioxidant, anti-inflammatory and anticancer properties (6). They may also contribute to radiosensitization, chemosensitization and the attenuation of toxicity related to the management of cancer. Interest in the application of active ingredients of phytochemicals for oral cancer treatment is emerging. The present review aimed to analyze the literature and discuss the potential effects of isolated phytochemicals on oral cancer.

2. Literature search methods

A literature search was conducted to identify studies relevant to isolated phytochemicals and oral cancer in databases, such as PubMed and Google Scholar. The search strategy combined MeSH terms and free-text key words using Boolean operators (AND, OR). Representative search strings included were ('Phytochemicals' (MeSH) OR 'bioactive plant compounds' OR 'natural products') AND ('Oral Cancer' (MeSH) OR 'oral squamous cell carcinoma' OR 'OSCC'), ('Curcumin' OR 'Resveratrol' OR 'Epigallocatechin gallate' OR 'Quercetin' OR 'Anthocyanin') AND ('oral cancer' OR 'OSCC').

Open-access original research articles (*in vitro*, *in vivo* and clinical studies) focusing on isolated phytochemicals or purified active ingredients in oral cancer, published in English within the last 20 years (2005-2025), were included for the article analysis. Studies using crude or whole plant extracts, studies not specific to oral cancer, non-peer-reviewed sources, conference abstracts, editorials without primary data, articles without full-text, theses, conference publications, letters to the editor and articles lacking sufficient methodological detail were excluded. Reviews, systematic reviews, and meta-analyses were used only for background and were not included in analysis. Current evidence indicates that phytochemicals, such as curcumin, anthocyanins, epigallocatechin-3-gallate (EGCG), S-allylcysteine (SAC), quercetin, lycopene and resveratrol exert antitumor effects (Table I).

3. Mechanisms of action of phytochemicals

Phytochemicals are bioactive compounds derived from plants that are secondary metabolites produced by plants to defend against environmental stressors such as pathogens and UV radiation. Phytochemicals mainly consist of phenolics, carotenoids, organosulfur compounds, nitrogen-containing compounds and alkaloids (7). These compounds are found abundantly in fruits, vegetables, whole grains, herbs, spices, legumes and nuts.

Free radicals are involved in multistage carcinogenic processes. Peroxyl radicals and lipid peroxidation, in particular, can independently induce deoxyribonucleic acid (DNA) mutations that are critical for the initiation of carcinogenesis. Antioxidant phytochemicals play a vital role in regulating carcinogenic initiation by reducing oxidative stress and preserving genomic integrity. Phytochemicals also interfere with key molecular events involved in tumor initiation and promotion. They can induce apoptosis and cell-cycle arrest, modulate cell-signaling pathways, inhibit angiogenesis and suppress metastasis (Fig. 1) In addition, they can enhance innate immune surveillance and facilitate the clearance of altered cells (8).

4. Anthocyanins

Anthocyanidins, members of the flavonoid family, constitute the largest group of water-soluble pigments. The primary sources of these compounds include strawberries, raspberries, cherries and blueberries. Anthocyanins, the product of glycosylated derivatives of anthocyanidins, impart them their characteristic colors. Blueberries contain a diverse array of bioactive constituents that have demonstrated anticancer activity against various types of cancers, including oral cancer. The *in vivo* study by Baba *et al* (9) demonstrated that blueberry supplementation suppressed OSCC progression in a hamster buccal pouch model by modulating oncogenic signaling pathways, particularly TGF-β and PI3K/Akt, leading to reduced invasion and angiogenesis. Berry phytochemicals may attenuate pro-inflammatory mediators by modulating NF-κB signaling, regulating oxidative DNA damage and epithelial-mesenchymal transition (EMT)-related gene networks, and restoring immune homeostasis by promoting dendritic cell activation, antigen presentation and T-cell function. In a phase 0 clinical trial, patients with OSCC administered slow-release black raspberry troches for ~2 weeks prior to surgery exhibited significant reductions in pro-survival (EGFR) and pro-inflammatory (NFKB1) biomarkers in tumor tissues, with anthocyanin metabolites detected in resected samples and no major toxicities reported (10).

Anthocyanins have been shown to exert anti-proliferative, apoptotic and anti-metastatic effects in preclinical oral cancer models (Table II) (11,12). Anthocyanins have a very low systemic bioavailability and function primarily as dietary precursors producing downstream metabolites, such as smaller phenolic acids and microbial catabolites, rather than as directly acting bioactive circulating molecules. Hence, rather than using them as single active agents, their therapeutic efficacy can be investigated as structural scaffolds that generate multiple biologically active metabolites targeting key oncogenic pathways, such as NF-κB (13).

5. Epigallocatechin-3-gallate

Green tea is a rich source of flavonoids and other polyphenolic antioxidants that protect against cancer. EGCG is the major constituent of green tea, known to inhibit growth and interfere with the carcinogenic process in various cancer cell lines. Previous studies have indicated that EGCG suppresses both the proliferation and migratory potential of oral cancer cells, and also decreases the expression of phosphorylated EGFR *in vitro*. (Table II) (14-25). EGCG exerts anticancer effects in OSCC cell lines by triggering apoptotic pathways, arresting cell-cycle progression, downregulating the transcriptional activity of NF-κB and activator protein 1 (AP-1), and suppressing cellular migration and invasive potential (22). A large prospective study done in Japan found no association between green tea consumption and oral cancer incidence in humans (26). That study suggested that laboratory findings may not directly translate to population-level cancer prevention, highlighting the need for further research considering genetic, lifestyle and environmental factors (26).

Resveratrol in combination with EGCG have been shown to exert synergistic anti-tumorigenic effects against oral cancer (27). However, substantial clinical evidence for the use of EGCG in the treatment of oral cancer is limited. Its use is limited by its low absorption and lack of molecular targeting. Nano modification strategies, such as encapsulation, liposomes, micelles, nanoparticles and various other formulations can improve the anticancer activity of EGCG. Combining EGCG with chemotherapy can increase the susceptibility of tumors to treatment.

Table I. Phytochemicals used in oral cancer.

Phytochemical	Active compound	Natural source
Flavonoids	Anthocyanins	Berries, grapes, red cabbage
Flavonoids	Epigallocatechin-3-gallate	Green tea (*Camellia sinensis*)
Polyphenols	Curcumin	Turmeric (*Curcuma longa*)
Organosulfur	S-allylcysteine	Garlic (*Allium sativum*)
Flavonoids	Quercetin	Onions
Carotenoids	Lycopene	Tomatoes
Polyphenols	Resveratrol	Grapes, berries

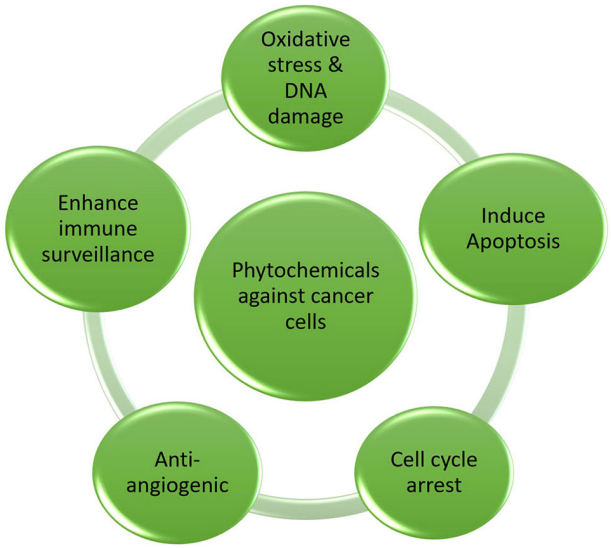


Figure 1. Mechanism of action of phytochemicals against cancer cells.

6. Curcumin

Curcumin, a polyphenolic diarylheptanoid extracted from the rhizome of *Curcuma longa*, is the principal bioactive compound in turmeric. Curcumin exerts anticancer effects through multiple molecular pathways that suppress cell proliferation, migration, invasion and EMT, while modulating cell-cycle progression and apoptotic pathways in oral cancer cells. It also inhibits key inflammatory and oncogenic transcription factors, including NF-κB and AP-1, and reduces the expression of inflammatory mediators, such as cyclooxygenase-2. Beyond its direct effects on tumor cells, curcumin has demonstrated immunomodulatory activity by reducing programmed death-ligand 1 (PD-L1) levels, thereby restoring T-cell activity and reversing tumor-induced immune suppression (Table III) (28-71). Curcumin exhibits a favorable safety profile, with clinical evidence supporting its tolerability even at high oral doses (up to 8 g/day), rendering it a viable candidate for adjunctive therapy in oncology. A previous study on 62 patients with patients with external cancerous lesions reported reductions in lesion size and pain following topical curcumin treatment in a subset of patients (72). Low systemic bioavailability, limited cellular uptake, side-effects and low patient compliance limit the clinical use of curcumin in oral cancer therapy. Nanoparticles, nanocomposite hydrogels, nanovesicles, nanofibers, exosomes, liposomes and micelles can effectively deliver curcumin, enhance drug stability, improve intracellular delivery and bypass resistance mechanisms. Curcumin-loaded nanoparticles have demonstrated the ability to bypass drug resistance by targeting multidrug resistance protein 1, providing a potential adjunctive approach with which to improve outcomes in patients with oral cancer resistant to conventional chemotherapy (35).

One of the primary challenges with nanoformulations is the cost factor and precise control of nanoparticle size for effective targeted drug delivery. The limitations of curcumin can also be overcome by using synthetic curcumin analogues, such as (3E,5E)-3,5-bis((2-fluorophenyl)methylene)-4-piperidinone (EF24), curcumin difluorinated (CDF) and FLLL12 (a synthetic diarylidenyl piperidone derivative), which have shown improved solubility and bioavailability. The randomized, placebo-controlled phase 1 trial by Basak *et al* (73), which investigated APG-157, a botanical formulation containing curcumin and related polyphenols, in patients with oral cancer, demonstrated that APG-157 achieved the systemic absorption of curcumin, reduced the levels of pro-inflammatory cytokines and inhibited tumor-associated microbes, thereby modulating both the immune response and the tumor microenvironment (73).

Current studies (Table III) have mainly focused on chemoprevention and treatment-associated complications rather than direct anticancer therapy. Further clinical trials are warranted to establish the safety and therapeutic efficacy of curcumin in the treatment of oral cancer.

7. S-allylcysteine and quercetin

The use of allium vegetables, such as garlic and onion, has been associated with a reduced risk of cancer development. SAC, a constituent of garlic, was previously demonstrated to inhibit cell proliferation and EMT in human OSCC lines and mouse models (74). SAC administration also inhibited carcinogenesis by modulating lipid peroxidation and enhancing antioxidant activity (75). Although clinical data on the optimal dosing of garlic for oral cancer prevention and therapy remain limited, no symptoms of garlic toxicity have been reported in the literature. Quercetin, a principal flavonoid compound in onions, has been shown to induce cytotoxic effects. Quercetin exerts anticancer effects in preclinical models by inducing apoptosis via mitochondrial, caspase-3, ROS, endoplasmic reticulum stress and JNK/ERK/GSK3) signaling, inhibiting metastasis through NF-κB/MMP (Matrix Metalloproteinase) and EMT suppression,

Table II. Summary of studies that employed anthocyanins or epigallocatechin-3-gallate (EGCG) as phytochemicals.

First author, year of publication	Type of study	Isolated phytochemical	Observation	Inference	(Refs.)
Fan, 2015	*In vitro* (CAL-27 cells)	Anthocyanins from black rice (*Oryza sativa* L.)	Black rice anthocyanins reduced migration and invasion, MMP-2/MMP-9 expression, and suppressed NF-κB signaling	Black rice anthocyanins exhibit anti-metastatic properties in oral cancer by targeting MMPs and NF-κB	(11)
Yue, 2019	*In vitro* (HaCaT, Tca8113 and SCC15 cell line)	Anthocyanin	Anthocyanin treatment reduced OSCC cell viability, inhibited migration/invasion, activated pyroptosis, and upregulated NLRP3, caspase-1 and IL-1β	Anthocyanins trigger pyroptosis via inflammasome activation, thereby inhibiting tumor progression	(12)
Hsu, 2005	*In vitro* (human oral carcinoma cell lines)	EGCG	EGCG induced growth arrest and apoptosis	EGCG exerts anticancer effects in oral carcinoma by activating p21WAF1	(14)
Ho, 2007	*In vitro* (human oral cancer cell lines)	EGCG - green tea polyphenol	EGCG inhibited invasion of OSCC cells, decreased production of matrix metalloproteinases and urokinase-plasminogen activator	EGCG exerts anti-invasive and anti-metastatic effects in oral cancer	(15)
Kato, 2008	*In vitro* (HSC3, HSC4, SCC9, SCC25)	EGCG	EGCG reduced methylation of the RECK gene (tumor suppressor gene), leading to its reactivation	EGCG suppresses cell invasion possibly by a demethylation effect on matrix metalloproteinase inhibitors such as RECK	(16)
Yoon, 2012	Clinical study (patients with recurrent oral neoplastic lesions)	EGCG (topical application in form of mouthwash)	Topical EGCG application reduced recurrence rates of oral neoplastic lesions	EGCG demonstrates chemopreventive potential in oral cancer	(17)
Chang, 2012	*In vitro* CAL-27	EGCG	EGCG sensitized CAL-27 cells to the anti-metastatic effects of gefitinib (Iressa). Combination treatment synergistically suppressed epidermal growth factor receptor (EGFR) and MMP-2	EGCG enhances the efficacy of gefitinib in OSCC, suggesting its potential as a chemosensitizer and anti-metastatic adjuvant	(18)
Irimie, 2015	*In vitro* (SSC-4)	EGCG	EGCG suppressed cell proliferation and promoted apoptosis and autophagy	EGCG exerts anticancer effects in oral cancer	(19)
Lee, 2015	*In vitro* (human OSCC cell lines), *in vivo* murine xenograft model	EGCG	EGCG cause cell cycle arrest and proliferation block; suppressed tumor growth in xenograft mice	EGCG exerts anticancer efficacy, acting through BTG2 induction and MAPK pathway modulation	(20)
Yoshimura, 2019	*In vitro* (HSC-3 cell line) and *in vivo* (murine xenograft model)	Epigallocatechin-3-gallate (EGCG)	EGCG inhibited OSCC cell proliferation, induced apoptosis, and suppressed tumor growth in xenografts	EGCG has therapeutic potential as an anticancer agent against OSCC	(21)

Table II. Continued.

First author, year of publication	Type of study	Isolated phytochemical	Observation	Inference	(Refs.)
Belobrov, 2019	*In vitro* (H400 and H357)	EGCG	EGCG reduced OSCC cell viability, altered molecular signaling pathways	Inhibition of cell proliferation and migration of oral cancer cells by EGCG is associated with a decrease in phosphorylated EGFR expression	(22)
López, 2019	*In vitro* (human OSCC cell lines exposed to radiation)	EGCG	EGCG + 5-Fluorouracil suppressed cell growth more effectively under radiation	EGCG enhances the chemosensitivity of 5-FU and potentiates radiotherapy effects	(23)
Chen, 2020	*In vitro* MDR oral carcinoma cells, *in vivo* KBV200 xenograft nude mice	EGCG	EGCG sensitized multidrug-resistant oral carcinoma xenografts to vincristine sulfate. Combination treatment enhanced apoptosis, reduced tumor growth, and downregulated drug resistance mechanisms	EGCG acts as a chemosensitizer, overcoming multidrug resistance and potentiating vincristine efficacy in oral cancer	(24)
Kon, 2022	*In vitro* (HSC4, HSC3, HSC2 and SAS)	EGCG	EGCG stimulated histamine production, while downregulating histamine H1 receptor expression in oral cancer cells	EGCG has a dual role in regulating the tumor microenvironment and potentially influencing cancer progression	(25)

CAL-27, human tongue squamous cell carcinoma cell line; MMP, matrix metalloproteinase; HaCaT, human keratinocyte cell line; Tca8113, human tongue squamous cell carcinoma cell line; SCC-15, SCC-9, SCC-25 and SCC-4, human oral squamous carcinoma cell lines; NLRP3, NOD-like receptor family pyrin domain containing 3; IL-1β, interleukin-1β; p21WAF1, cyclin-dependent kinase inhibitor 1A (cell cycle regulator); uPA, urokinase plasminogen activator; RECK, reversion-Inducing cysteine-rich protein with Kazal motifs (tumor suppressor gene); HSC-2, HSC-3 and HSC-4, human oral squamous carcinoma cell lines; Gefitinib (Iressa); BTG2, B-cell translocation gene 2; H400 and H357, human oral squamous carcinoma cell lines; 5-FU, 5-fluorouracil; MDR, multidrug resistance; KBV200, vincristine-resistant KB oral carcinoma xenograft model; SAS, human tongue squamous carcinoma cell line; histamine H1 receptor, histamine receptor subtype 1 involved in inflammatory signaling.

and reversing drug resistance (Table IV) (76-95). However, its clinical use is limited by its poor absorption rate and mild adverse effects in high doses, such as headaches, gastrointestinal problems, and respiratory symptoms (96). Nanotechnology-based delivery systems can overcome the pharmacokinetic limitations. Nanostructured lipid carriers can enhance the delivery and efficacy of curcumin and quercetin, providing a promising translational approach for OSCC therapy (97).

8. Resveratrol

Resveratrol is a stilbene-based polyphenolic compound biosynthesized by various plants, including *Vitis vinifera* (grapes), *Arachis hypogaea* (peanuts), and *Morus alba* (mulberries). Evidence supports the anticancer role of resveratrol in various malignancies, including those affecting the oral cavity. Resveratrol induces apoptosis via caspase-dependent pathways, modulating pro-apoptotic Bax and Bak, and anti-apoptotic Bcl-2 and Bcl-xL proteins, thereby promoting programmed cell death; it inhibits metastasis and angiogenesis by suppressing EMT, leading to reduced cell migration and invasion (Table V) (98-115). It also disrupts tumor-stroma interactions by inhibiting the CXCL-12/IL-6 axis (116). Natural compounds, including EGCG, curcumin, resveratrol and quercetin, modulate ATP-binding cassette transporters (e.g., P-glycoprotein, multidrug resistance-associated protein 1),

Table III. Summary of studies that employed curcumin as a phytochemical.

First author, year of publication	Type of study	Isolated phytochemical	Observation	Inference	(Refs.)
Sharma, 2006	*In vitro* (human oral premalignant and cancer cells exposed to smokeless tobacco)	Curcumin	Curcumin downregulates smokeless tobacco extract- or NNK-induced NF-B and COX-2 in oral premalignant and cancer cells	Curcumin suppresses tobacco-induced inflammatory and oncogenic signaling	(28)
Manoharan, 2009	*In vivo* (DMBA-induced hamster buccal pouch cancer)	Curcumin and piperine	Combined administration reduced tumor incidence, dysplasia, and progression of cancer	Curcumin and piperine exhibit synergistic chemopreventive efficacy, enhancing protective effects against oral carcinogenesis	(29)
Chakravarti, 2010	*In vitro* (normal, immortalized, and malignant oral epithelial cells)	Curcumin	Curcumin differentially inhibited protein translation machinery, with stronger suppression in malignant cells	Curcumin selectively targets malignant oral epithelial cells by disrupting protein synthesis	(30)
Balakrishnan, 2010	*In vivo* (DMBA-induced hamster buccal pouch carcinogenesis)	Curcumin and ferulic acid	p53 upregulated and Bcl-2 downregulated, reducing tumor progression	Curcumin and ferulic acid synergistically regulate apoptotic and tumor suppressor proteins	(31)
López-Jornet, 2011	*In vitro* (PECA-PJ15 human oral squamous carcinoma cell line)	Curcumin	Curcumin + irradiation reduced cell viability and enhanced apoptotic activity	Curcumin acts as a radiosensitizer	(32)
Kin, 2011	Clinical (saliva from head and neck cancer patients), *In vitro* (UM-SCC1)	Curcumin	Inhibition of IKKβ kinase activity was observed in curcumin-treated saliva samples tested on UM-SCC1 cells	Curcumin demonstrates anti-inflammatory and anti-oncogenic potential	(33)
Lin, 2012	*In vitro* (OSCC-4 and OSCC-25 cells)	Curcumin delivered via ultrasound-mediated microemulsions	Growth suppression of OSCC cells was observed	Ultrasound-mediated delivery improves curcumin's bioavailability and therapeutic efficacy	(34)
Chang, 2013	*In vitro* (cisplatin-resistant CAR human oral cancer cells)	Curcumin nanoparticles	Induced apoptosis, suppressed Multidrug resistance protein 1 (MDR1) function, and increased ROS generation in resistant oral cancer cells	Nanoparticle-based curcumin delivery can overcome cisplatin resistance	(35)
Dudás, 2014	*In vitro* (SCC-25 cells, pdl fibrobolasts)	Curcumin	Curcumin reduces fibroblast-mediated OSCC cell invasion and migration	Curcumin targets the tumor-stroma crosstalk, suppressing fibroblast-driven invasiveness in oral cancer	(36)
Zhen, 2014	*In vitro* (SCC-25 cell line)	Curcumin	Curcumin inhibited proliferation and invasion of oral cancer cells and suppressed EGFR signalling pathway	Curcumin exerts anti-proliferative and anti-invasive effects	(37)

Table III. Continued.

First author, year of publication	Type of study	Isolated phytochemical	Observation	Inference	(Refs.)
Chiang, 2014	*In vitro* (SAS/luc cells)	Curcumin	Suppressed radiation-induced NF-κB activity, leading to increased apoptosis	Curcumin acts as a radiosensitizer	(38)
Mishra, 2015	*In vitro* (HPV 16-positive oral carcinoma cells, 93VU-147T)	Curcumin	AP-1 and NF-κB transcription factors were downregulated, and HPV16 E6 oncoprotein expression was suppressed	Curcumin interferes with oncogenic signaling pathways and viral oncoproteins	(39)
Lee, 2015	*In vitro* (SCC25 cells)	Curcumin	Downregulates MMP-2 and MMP-9, and modulates the p53-E-cadherin pathway	Curcumin suppresses EMT and invasion in oral cancer	(40)
Sivanantham, 2016	*In vitro* (NT8e)	Curcumin + anti-neoplastic agent	Suppressed EGFR-ERK1/2 signaling, enhanced apoptosis, reduced cell proliferation	Curcumin synergizes with conventional anti-neoplastic agents	(41)
Beyer, 2017	*In vitro* (HN ACC 417)	Curcumin	Low concentrations of curcumin + photodynamic treatment effectively reduced OSCC cell viability	Curcumin can act as a photosensitizer in photodynamic treatment	(42)
Srivastava, 2018	*In vitro* (SCC090 SCC152)	Nanoemulsions combining 5-FU and Curcumin	Curcumin + 5-FU nanohybrid formulations enhanced cytotoxicity	Nanohybrid system improved drug uptake, triggered apoptosis, and suppressed OSCC cell proliferation	(43)
Bano, 2018	*In vitro* (HPV16+ve, HPV-ve OSCC cell lines)	Curcumin	Inhibition of cell proliferation, stemness and miRNA 21 expression on HPV^+ oral cancer stem cells	Curcumin exerts differential inhibitory activity depending on HPV status	(44)
Chen, 2018	*In vitro*, cisplatin-resistant CAR human oral cancer cells	Curcumin	Combination of curcumin and cetuximab synergistically inhibited cell growth and induced apoptosis	Curcumin enhances the efficacy of cetuximab	(45)
Hoornstra, 2018	*In vitro* (HSC-3 and SCC-25)	Fermented lingonberry juice compared with Curcumin	Both inhibited OSCC invasion	Fermented lingonberry juice demonstrates similar anti-cancer potential to curcumin	(46)
Maulina, 2019	*In vivo* study (Sprague-Dawley rat oral cancer model)	Curcumin	Curcumin reduced tumor growth and progression	Curcumin treatment demonstrated anticancer activity in OSCC-induced rats	(47)
Ma, 2020	*In vitro* (CAL 27), Bioinformatic analysis	Curcumin	Curcumin inhibited cell proliferation and induced apoptosis through modulation of apoptosis-related signaling pathways	Curcumin exerts anti-proliferative and pro-apoptotic effects in tongue cancer	(48)

Table III. Continued.

First author, year of publication	Type of study	Isolated phytochemical	Observation	Inference	(Refs.)
Ohnishi, 2020	*In vitro* (HSC-4 and Ca9-22)	Curcumin	Blocked c-Met signaling	Curcumin inhibited epithelial-mesenchymal transition (EMT) in oral cancer	(49)
Molla, 2020	*In vitro* (SCC-25 and H-357, colon-HCT-116, breast MCF-7, MCF-10A-Tr and MDA-MB-231, lung-A-549 and cervical HeLa cancer cell lines)	Curcumin	Curcumin in combination with olaparib increased the apoptosis of oral cancer cells by causing DNA damage and blocking the induction of the Base Excision Repair cascade	Curcumin acts as a DNA damage-sensitizing agent in oral cancer and when combined with PARP inhibitors, the apoptotic potential is increased	(50)
Molla, 2021	*In vitro* (H-357)	Curcumin	Curcumin + olaparib induced apoptosis by inhibition of PARP-1 trapping and indirect inhibition of chromatin remodeling	Curcumin acts as a DNA damage-sensitizing agent	(51)
Saleh, 2020	*In vivo* (OSCC chemically induced in hamsters)	Green tea extract and Curcumin	Combined administration reduced tumor incidence and progression	Green tea and curcumin exhibit synergistic effect	(52)
de Souza Ferreira, 2020	*In vitro* (Cal27), *in vivo* (porcine oral mucosa)	Emulgel systems containing curcumin	Formulation demonstrated stability, strong mucoadhesion, and cytotoxicity against OSCC tissue-engineered models	Mucoadhesive emulgel systems act as a localized delivery platform for curcumin	(53)
Liu, 2021	*In vitro* (HSC3 and CAL33)	Curcumin	Suppressed OSCC cell proliferation via inhibition of Specificity protein 1 (SP1) and NF-κB-dependent signaling	Curcumin exerts anti-proliferative effects	(54)
Chatterjee, 2021	*In vitro* (H357)	Curcumin + PARP inhibitor veliparib	Veliparib enhanced curcumin's anti-angiogenic potential by deregulating NECTIN-4 and modulating nitric oxide signaling	This combination augments anti-angiogenic and apoptotic effects	(55)
Liu, 2021	*In vitro* HNSCC cell lines, *in vivo* oral cancer xenograft mouse model	Curcumin	Curcumin restored T cell activity and reduced tumor growth in oral cancer model	Curcumin acts as an immunomodulatory agent, restoring T cell function and reducing immune evasion	(56)
Kumbar, 2022	*In vitro* (cisplatin-resistant oral cancer sublines)	Curcumin encapsulated in nanomicelles	Curcumin-encapsulated nanomicelles enhanced cellular uptake and significantly increased cytotoxicity compared to free curcumin	Nanomicelle-based delivery improves bioavailability and therapeutic efficacy of curcumin	(57)

Table III. Continued.

First author, year of publication	Type of study	Isolated phytochemical	Observation	Inference	(Refs.)
Fazli, 2022	*In vitro* (KB oral cancer cells and human umbilical vein endothelial cells), *in vivo* (rat)	Curcumin niosome, injectable form of mouthwash	Curcumin-loaded niosome was effective in preventing severe dysplasia. Curcumin-loaded niosome in the form of injection (as a systemic use) was shown to be more effective than the form of mouthwash (as a topical use)	Curcumin-loaded niosome was effective in preventing the development of severe dysplasia and the inhibition of the growth of cancer cells	(58)
Chatterjee, 2022	*In vitro* (oral cancer cell line H-357 and SCC-9, breast cancer cell line MCF-7)	Curcumin	Curcumin exhibited maximum DNA damaging capacity in comparison to Resveratrol and 5-Fluorouracil	Combination of talazoparib and olaparib (PARP inhibitors) enhanced curcumin-mediated apoptosis	(59)
Azizi, 2023	*In vitro* (OCC-02)	Curcumin + *Dorema aucheri* extract (co-encapsulated in nanoliposomes)	Co-encapsulation enhanced cytotoxicity, promoted apoptosis induction, and significantly inhibited EGFR gene expression	Nanoliposomal co-delivery provides synergistic anticancer effects	(60)
Siyuan, 2023	*In silico*/ bioinformatics analysis	Curcumin	Curcumin targeted cell cycle regulation, apoptosis, immune modulation, and inflammatory signaling	Curcumin exerts multi-targeted anti-cancer effects	(61)
Hussein, 2023	*In vitro* (HGF normal cells and TSCCF cancer cells)	Curcumin	Curcumin induced apoptosis in oral cancer cells without affecting normal cells	Curcumin demonstrates selective apoptotic activity compared to conventional chemotherapeutics like paclitaxel	(62)
Udompatanakorn, 2024	*In vitro* (SCC-9)	Curcumin + *Lactobacillus rhamnosus* GG cell-free supernatant	Combination inhibited cell viability, induced apoptosis, and showed selective cytotoxicity	Curcumin synergizes with probiotic cell free supernatant to enhance anticancer efficacy	(63)
Rezaei, 2024	*In vitro* (CAL-27 cells)	Curcumin (niosomal nanoparticle formulation, combined with cisplatin)	Anticancer activity was enhanced, cellular uptake and cytotoxicity were improved, and drug resistance was reduced compared to cisplatin alone	Niosome-based co-delivery of curcumin and cisplatin overcomes resistance and improves therapeutic outcomes	(64)
Saeidi, 2024	*In vitro*	Curcumin liposomal co-formulation with carboplatin and cisplatin	Enhanced cytotoxic effects compared to platinum drugs alone	Curcumin strengthens the efficacy of platinum-based chemotherapy when co-delivered in liposomes	(65)

Table III. Continued.

First author, year of publication	Type of study	Isolated phytochemical	Observation	Inference	(Refs.)
Ziaei, 2024	*In vitro* (CAL-27 cell line)	Curcumin combined with paclitaxel, methotrexate, vincristine	Co-administration enhanced cytotoxicity and apoptosis	Curcumin acts as a chemosensitizer	(66)
Moravedeh, 2025	*In vitro* (SCC-9 and HN-5)	Liposomal nanoparticle formulation of curcumin	Enhanced cellular uptake and cytotoxicity	Liposomal nanoparticle delivery improves the therapeutic potential of curcumin	(67)
Senthil, 2025	*In vitro* (OSCC cells)	Curcumin [integrative nanoformulation with paclitaxel and ruthenium (II)]	Enhanced suppression of oral cancer cell growth compared to individual agents	Multi-agent nanoformulation demonstrates synergistic anticancer potential	(68)
Saberian, 2025	*In vitro* (OECM-1 cells)	Niosomal nanoparticle curcumin formulation, combined with cisplatin	Enhanced anticancer efficacy, improved drug delivery, and reduced resistance compared to cisplatin alone	Niosome-based combination therapy of curcumin and cisplatin provides synergistic anticancer effects	(69)
Ramos, 2025	*In vitro* (HSC3 cells), *in vivo* (OSCC xenograft model)	Curcumin	Curcumin exhibits cytotoxic activity in the spheroid model, and inhibits OSCC growth in mice	Curcumin exerts anti-metastatic and pro-apoptotic effects in oral cancer	(70)
Dash, 2025	*In vitro* (peripheral blood mononuclear cells from OSCC patients)	Curcumin	Curcumin reduced the levels of PD-1 and PD-L1 in peripheral blood mononuclear cell lysates	Curcumin demonstrates immunomodulatory potential, reversing tumor-induced immune suppression in OSCC patients	(71)

DMBA, 7,12-dimethylbenz(a)anthracene; PECA-PJ15 human tongue squamous cell carcinoma cell line; UM-SCC1, University of Michigan squamous cell carcinoma 1; OSCC, oral squamous cell carcinoma; MDR1, multidrug resistance protein 1; ROS, reactive oxygen species; HPV, human papillomavirus; AP-1, activator protein 1; MMP, matrix metalloproteinase; PDT, photodynamic therapy; 5-FU, 5-fluorouracil; c-Met, mesenchymal-epithelial transition factor; EMT, epithelial-mesenchymal transition; PARP, poly(ADP-ribose) polymerase; SP1, specificity protein 1; NECTIN4, nectin cell adhesion molecule 4; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

breast cancer resistance protein and solute carrier transporters, thereby influencing drug uptake, efflux, and sensitivity in oral cancer cells. Natural compounds can overcome drug resistance in oral cancer (117).

Resveratrol is generally considered safe; however, high doses may cause side-effects, such as diarrhea. Despite the evidence of its effectiveness against cancer, its instability and unfavorable pharmacokinetic properties (short half-life, non-stability, low water solubility and low bioavailability) hinder its clinical use. It was previously demonstrated that the encapsulation of resveratrol in nanostructured carriers ensured sustained release, inhibited metastasis and angiogenesis *in vitro* by reducing inflammatory cytokines and specifically targeting tumor-associated macrophages, which are key mediators of tumor progression and immune evasion (118). Mechanistically targeted formulations, such as resveratrol-copper can overcome the limitations of single-agent phytochemicals, providing translational potential. The RESCU 004 exploratory clinical study demonstrated that the resveratrol-copper complex downregulated hallmarks of cancer and suppressed immune checkpoint expression in patients with advanced-stage OSCC (113). The direct

Table IV. Summary of studies that employed S-allylcysteine or quercetin as phytochemicals.

First author, year of publication	Type of study	Isolated phytochemical	Observation	Inference	(Refs.)
Pai, 2012	*In vivo* mouse xenograft model	S-Allylcysteine	Inhibited tumor progression and suppressed epithelial-mesenchymal transition markers	S-allylcysteine demonstrates therapeutic potential in oral cancer	(76)
Haghiac, 2005	*In vitro* (SCC-9)	Quercetin	Induced both necrosis and apoptosis	Quercetin demonstrates dual cytotoxic mechanisms	(77)
Kang, 2010	*In vitro* (SCC-1483 and SCCQLL1)	Kaempferol and quercetin	Induced caspase-3-dependent apoptosis	Kaempferol and quercetin trigger intrinsic apoptotic pathways	(78)
Chen, 2012	*In vitro* (SCC25 drug-resistant oral cancer spheres) and *in vivo* (xenograft mouse model)	Quercetin	Suppressed drug-resistant spheres via p38 MAPK-Hsp27 apoptotic pathway; reduced tumor growth	Quercetin overcomes drug resistance and induces apoptosis	(79)
Lai, 2013	*In vitro* (SAS human oral cancer cell line)	Quercetin	Inhibited migration and invasion of OSCC cells via suppression of NF-κB and downregulation of MMP-2/-9 signaling pathways	Quercetin exhibits anti-metastatic potential	(80)
Chen, 2013	*In vitro* (SCC-25)	Quercetin	Exhibited cytotoxicity, induced apoptosis, and modulated signaling pathways	Quercetin produced dose-dependent cell cycle arrest accompanied by mitochondria-mediated apoptosis	(81)
Droguett, 2015	*In vivo* (chemically induced murine oral cancer model)	Quercetin	Reduced tumor incidence and progression	Quercetin has chemopreventive and therapeutic efficacy *in vivo*	(82)
Zhang, 2017	*In vivo* (DMBA-induced hamster oral cancer model)	Quercetin	Induced apoptosis through modulation of NF-κB signaling	Quercetin reduced tumor incidence and progression *in vivo*	(83)
Ma, 2018	*In vitro* (SAS human oral cancer cell line)	Quercetin	Induced apoptosis via mitochondrial dysfunction and endoplasmic reticulum stress-mediated signaling pathways	Quercetin exhibit pro-apoptotic potential in oral cancer	(84)
Zhang, 2019	*In vitro* (hNOK, Tca8113), *in vivo* (murine xenograft model), clinical samples (50 patients with OSCC)	Quercetin	Inhibited cell viability and induced apoptosis; inhibited the growth of OSCC xenograft tumors by inducing miR-22 expression and repressing the WNT1/β-catenin pathway	Quercetin exerts anticancer effects through modulation of microRNA-mediated WNT/β-catenin pathway	(85)
Li, 2019	*In vitro* (Tca-8113 and SCC-15)	Quercetin + cisplatin	Enhanced apoptosis in by downregulating xIAP through NF-κB pathway suppression	Quercetin synergizes with cisplatin to potentiate apoptosis, overcoming resistance mechanisms	(86)

Table IV. Continued.

First author, year of publication	Type of study	Isolated phytochemical	Observation	Inference	(Refs.)
Kim, 2020	*In vitro* (OSC20, SAS, and HN22 cells)	Quercetin	Inhibited cell survival and suppressed epithelial-mesenchymal transition (EMT) pathway	Quercetin interferes with EMT-mediated signaling, reducing OSCC progression and metastasis	(87)
Singh, 2020	*In vitro* (Cal-33 and SCC-15)	Quercetin	Caused cell growth inhibition, DNA damage, cell cycle arrest, and apoptosis	Synergistic effect of resveratrol and quercetin enhances anticancer efficacy	(88)
Chen, 2021	*In vitro* (CAL-27)	Quercetin	Suppressed cell survival and invasion via modulation of the miR-1254/CD36 cascade	Quercetin exerts anticancer activity by targeting microRNA-mediated regulation of CD36	(89)
Huang, 2022	*In vitro* (tongue SCC-derived cell line SAS)	Quercetin	Induced apoptosis via JNK activation-regulated ERK/GSK-3α/β-mediated mitochondria-dependent apoptotic signaling pathway	Quercetin promotes mitochondria-dependent apoptosis	(90)
Son, 2023	*In vitro* (YD10B and YD38)	Quercetin	Induced cell cycle arrest and apoptosis	Quercetin inhibits proliferation and triggers programmed cell death in oral cancer cells	(91)
Chan, 2023	*In vitro* (HSC-3, OECM-1, and SAS with acquired erlotinib resistance)	Quercetin	Induced sensitivity in erlotinib-resistant cells by targeting pyruvate kinase M2, leading to apoptosis and growth inhibition	Quercetin can overcome acquired resistance to EGFR inhibitors (erlotinib)	(92)
Tubtimsri, 2025	*In vitro* (KON cancer cell line)	Quercetin oral	Triggered ROS-mediated apoptosis, induced S-phase and G2/M-phase cell cycle arrest	Quercetin exerts anticancer effects via oxidative stress-mediated apoptosis and disruption of cell cycle progression	(93)
Thakore, 2025	Computational docking, *in vitro* (CAL-27)	Kaempferol and quercetin	Both showed strong binding affinity to MMP1 and inhibited MMP1 activity	Kaempferol and quercetin act as potential inhibitors of MMP1	(94)
Guo, 2025	Network pharmacology analysis, *in vitro* (nicotine-induced transformed oral epithelial cells and SAS)	Quercetin	Identified multiple molecular targets (including PKM2, EGFR, apoptosis regulators); Quercetin induced apoptosis and inhibited proliferation	Quercetin exerts multi-targeted anticancer effects in nicotine-related OSCC	(95)

OSCC, oral squamous cell carcinoma; SCC, squamous cell carcinoma (oral cancer cell lines such as SCC-9, SCC-15, SCC-25, SCC-1483, SCCQLL1); EMT, epithelial-mesenchymal transition; Hsp27, heat shock protein 27; MMP, matrix metalloproteinase; ROS, reactive oxygen species; GSK-3, glycogen synthase kinase 3; miR, microRNA (e.g., miR-22 and miR-1254); WNT, wingless/integrated signaling pathway; β-catenin, β-catenin (transcriptional co-activator in WNT signaling); xIAP, X-linked inhibitor of apoptosis protein; PKM2, pyruvate kinase M2 isoform; HSC-3, human squamous cell carcinoma cell line 3; OECM-1, oral epidermoid carcinoma cell line 1; CAL-27, human tongue squamous cell carcinoma cell line; DMBA, 7,12-dimethylbenz(a)anthracene.

Table V. Summary of studies that employed Resveratrol as a phytochemical.

First author, year of publication	Type of study	Isolated phytochemical	Observation	Inference	(Refs.)
Shan, 2014	*In vitro* (KB cell)	Resveratrol	Inhibited proliferation and induced apoptosis	Resveratrol exerts direct cytotoxic effects on OSCC cells	(98)
Atienzar, 2014	*In vitro* (PE/CA-PJ15)	Resveratrol	Resveratrol + irradiation enhanced cytotoxicity, reduced cell viability, and induced apoptosis	Resveratrol can act as a radiosensitizer	(99)
Chang, 2015	*In vitro* (OC2 human oral cancer cells)	Resveratrol	Induced changes in cytosolic free Ca^{2+} concentrations, leading to disruption of calcium homeostasis and reduced cell viability	Resveratrol triggers Ca^{2+}-mediated signaling pathways contributing to apoptosis and growth inhibition	(100)
Shrotriya, 2015	*In vitro* (4-nitroquinoline-1-oxide-induced oral cancer murine model)	Resveratrol and grape seed extract	prevented oral tumorigenesis by activating AMPK; reduced tumor incidence and progression in mice	Chemopreventive efficacy of resveratrol and grape seed extract confirmed	(101)
Chang, 2017	*In vitro* (cisplatin-resistant CAR oral cancer cells)	Resveratrol	Induced both autophagy and apoptosis via AMPK activation and Akt/mTOR pathway suppression	Resveratrol overcomes cisplatin resistance by triggering autophagy-apoptosis crosstalk	(102)
Kim, 2018	*In vitro* (CAL-27, SCC15, and SCC25)	Resveratrol	Induced mitochondrial apoptosis and inhibited epithelial-mesenchymal transition (EMT)	Resveratrol demonstrates dual anticancer mechanisms	(103)
Kim, 2018	*In vitro* (YD-10B)	Resveratrol	Suppressed lysophosphatidic acid-induced invasion of OSCC cells; reduced migratory and invasive capacity	Resveratrol can counteract pro-metastatic stimuli	(104)
Lin, 2019	*In vitro* (OEC-M1 cells, SCC-25 cells)	Resveratrol	Antagonized thyroid hormone-induced expression of checkpoint and proliferative genes	Resveratrol counteracts thyroid hormone-driven tumorigenic signaling	(105)
Uzawa, 2019	*In vitro* (SAS, Sa3, and HSC-3)	Resveratrol	Resveratrol targeted urokinase-type plasminogen activator receptor (uPAR) expression, reducing invasive potential and restoring sensitivity to cetuximab in resistant OSCC cells	Resveratrol can overcome cetuximab resistance	(106)
Singh, 2020	*In vitro* (Cal-33 and SCC-15 oral cancer cell lines)	Resveratrol + quercetin	Cell growth inhibition, DNA damage, cell cycle arrest, and apoptosis observed	Combination of resveratrol and quercetin exerts synergistic anticancer effects	(88)
Kim, 2020	*In vitro* (OSCC cell lines YD-9 and YD-38)	Resveratrol	Suppressed Rab coupling protein-induced invasion of OSCC cells by inhibiting Zeb1 expression	Resveratrol reduces invasive potential in OSCC	(107)

Table V. Continued.

First author, year of publication	Type of study	Isolated phytochemical	Observation	Inference	(Refs.)
Park, 2020	*In vitro* (YD-10B)	Resveratrol	Inhibited cell growth by downregulating Bmi-1 expression, leading to reduced proliferation and impaired oncogenic signaling	Bmi-1 pathway is a critical target of resveratrol	(108)
Shang, 2021	*In vitro* (CAL-27)	Resveratrol	Inhibited proliferation of OSCC cells by modulating MAGEA12/Akt signaling	MAGEA12/Akt axis is a novel target of resveratrol	(109)
Bang, 2021	*In vitro* (Ca9-22 and CAL-27)	Polydatin (resveratrol-3-O-β-mono-D-glucoside)	Induced apoptosis via mitochondrial pathways and inhibited metastasis by downregulating EMT-related markers	Polydatin retains and enhances resveratrol's anticancer properties	(110)
Xiao, 2021	*In vitro* (CAL-27)	Resveratrol	Suppressed malignant progression by inducing ZNF750 expression and modulating RAC1 signaling	ZNF750/RAC1 axis is a novel pathway through which resveratrol inhibits OSCC progression	(111)
Fukuda, 2022	*In vitro* (HSC-2, HSC-3, HSC-4, Ca9-22 and SAS)	Resveratrol	Inhibited proliferation and induced autophagy by blocking SREBP1 expression	Resveratrol suppresses tumor growth and promotes autophagy through lipid metabolism regulation	(112)
Pilankar, 2022	Clinical (25 advanced OSCC patients)	Resveratrol + copper	Down-regulated hallmarks of cancer and immune checkpoints; reduced inflammatory and tumor-promoting signaling	A pro-oxidant resveratrol-copper combination shows translational promise in advanced OSCC	(113)
de Jesús Valle, 2024 (115)	*In vitro* (TR146 cell line)	Resveratrol (nanotechnology-based buccal delivery system)	Liposomal buccal formulation showed enhanced permeation, retention, and controlled release; improved stability and bioavailability compared to free resveratrol	Liposomal buccal delivery can overcome pharmacokinetic limitations	(114)
Mao, 2024	*In vitro* (CAL-27/ SCC-9)	Resveratrol	Induced ferroptosis mediated by the p53/SLC7A11 axis; downregulation of SLC7A11 promoted lipid peroxidation and iron-dependent cell death	Establishes ferroptosis as a novel anticancer mechanism of resveratrol in OSCC	(115)

OSCC, oral squamous cell carcinoma; KB cell, human oral carcinoma cell line KB; PE/CA-PJ15, human oral squamous carcinoma cell line; OC2, human oral cancer cell line OC2; Ca^{2+}, calcium ion; AMPK, AMP-activated protein kinase; CAL-27, human tongue squamous cell carcinoma cell line; SCC15 and SCC25, human oral squamous carcinoma cell lines; EMT, epithelial-mesenchymal transition; YD-10B, YD-9 and YD-38, human oral squamous carcinoma cell lines; OEC-M1, oral epidermoid carcinoma cell line 1; uPAR, urokinase-type plasminogen activator receptor; cetuximab, EGFR monoclonal antibody; Rab coupling protein (RCP), endosomal trafficking protein; Zeb1, zinc finger E-box binding homeobox 1 transcription factor; Bmi-1, B lymphoma Mo-MLV insertion region 1 proto-oncogene; MAGEA12, melanoma antigen gene A12; polydatin, resveratrol-3-O-β-mono-D-glucoside; ZNF750, zinc finger protein 750; RAC1, Ras-related C3 botulinum toxin substrate 1; HSC-2, HSC-3 and HSC-4, human oral squamous carcinoma cell lines; Ca9-22, human gingival squamous carcinoma cell line; SREBP1, sterol regulatory element-binding protein 1; TR146, human buccal carcinoma cell line; p53, tumor suppressor protein p53; SLC7A11, solute carrier family 7 member 11 (cystine/glutamate antiporter).

delivery of resveratrol onto the oral cavity can also improve its bioavailability. Localized delivery systems have also been explored *in vivo*, particularly for the treatment of skin cancers such as melanoma, to enhance tissue retention and therapeutic

Table VI. Summary of studies that employed lycopene or Aloe-emodin as phytochemicals.

First author, year of publication	Type of study	Isolated phytochemical	Observation	Inference	(Refs.)
El-Rouby, 2011	*In vivo* murine model (4- nitroquinoline-1-oxide induced tongue carcinogenesis) with histological and immunohistochemical evaluation	Lycopene	Lycopene administration reduced dysplastic changes and malignant progression in tongue epithelium; immunohistochemistry showed decreased proliferative markers and enhanced apoptotic activity	Lycopene can exert chemoprotective effects through reduction in cell proliferation and enhanced cellular adhesion	(122)
Wang, 2020	*In vitro* (CAL-27 and SCC-9), *in vivo* (mouse model)	Lycopene	Inhibited EMT and promoted apoptosis via suppression of PI3K/Akt/mTOR signaling; reduced proliferation and invasiveness; suppressed tumor growth	Lycopene dual anti-cancer efficacy confirmed	(123)
Tao A, 2021	*In vitro* (CAL-27 and WSU-HN6), *in vivo* (CAL-27 cells)	Lycopene	Inhibited OSCC cell growth by suppressing the IGF1 signaling pathway; reduced tumor volume and downregulated IGF1 pathway components	Lycopene regulates OSCC cell growth by inhibiting the IGF1 pathway	(124)
Rasheed, 2024	*In vitro* (OSCC cell line)	Lycopene	Inhibited cancer cell growth, reduced proliferation, and promoted apoptosis	Lycopene exerts anticancer potential	(125)
Chen, 2010	*In vitro* (SCC 4)	Emodin, aloe-emodin, Rhein	Induced DNA damage, inhibited the expression of DNA repair genes	Anthraquinones exhibit genotoxic and DNA repair inhibitory activity	(126)
Chen, 2010	*In vitro* (SCC 4)	Emodin, aloe-emodin, Rhein	Inhibited migration and invasion, suppressed MMP-9 gene expression	Anthraquinones (emodin, aloe-emodin, rhein) exhibit anti-metastatic potential in oral cancer	(127)
Liu, 2018	*In vitro* and *in vivo* study (human oral mucosa carcinoma cell lines and xenograft mouse model)	Aloe-emodin	Aloe-emodin combined with photodynamic therapy (PDT) significantly inhibited proliferation of oral carcinoma cells, induced apoptosis, and suppressed tumor growth in xenograft mice	Aloe-emodin acts as an effective photosensitizer in PDT	(128)

Table VI. Continued.

First author, year of publication	Type of study	Isolated phytochemical	Observation	Inference	(Refs.)
Li, 2018	*In vitro* (SCC 15)	Aloe-emodin	Inhibited cell viability, induced apoptosis, and triggered caspase activation	Aloe-emodin exerts direct pro-apoptotic effects on OSCC cells	(129)
Suluvoy, 2024	*In vitro* (KB 3-1)	Aloe emodin	Reduced OSCC cell viability, induced apoptosis, and showed dose-dependent cytotoxicity	Aloe emodin exerts direct anticancer activity	(130)
El Said, 2024	*In vitro* (SCC 25, normal WI-38 fibroblasts)	Emodin compared with 5-fluorouracil (5-FU)	A lower concentration of 5-FU was more cytotoxic to normal cells than emodin; emodin + 5-FU combinations (both high and low doses) had synergistic cytotoxicity	Emodin demonstrates anticarcinogenic potential with selective safety for normal cells. When combined with 5-FU, it acts as a chemo-sensitizer	(131)

OSCC, oral squamous cell carcinoma; CAL-27, human tongue squamous cell carcinoma cell line; SCC-9, SCC-4, SCC-15 and SCC-25, human oral squamous carcinoma cell lines; WSU-HN6, human oral squamous carcinoma cell line derived from tongue carcinoma; WI-38, normal human lung fibroblast cell line; kb 3-1, human oral carcinoma cell line; EMT, epithelial-mesenchymal transition; igf1, insulin-Like Growth Factor 1; MMP, matrix metalloproteinase; PDT, photodynamic therapy; 5-FU, 5-fluorouracil.

efficacy, supporting the potential value of site-specific resveratrol administration in oral cancer (119,120)

9. Lycopene

Lycopene, a lipophilic carotenoid with potent antioxidant properties, is primarily obtained from tomatoes and tomato-derived products. Additional sources include red-pigmented fruits, such as apricots, cranberries, grapes, pink grapefruit, guavas, papayas, peaches and watermelons. Lycopene administration has been shown to inhibit oral carcinogenesis by modulating lipid peroxidation and upregulating key enzymatic activities within the glutathione redox cycle (121). *In vitro* studies have demonstrated its anticancer effect in OSCC cell lines (122-125). Lycopene exhibits high tolerability and a low incidence of treatment-related toxicity. However, further mechanistic investigations and robust clinical trials are essential before it can be employed clinically in routine management.

10. Aloe-emodin

Polysaccharides, such as acemannan, found in the gel of *Aloe vera* leaves, are chiefly responsible for its immunomodulatory, wound-healing and anti-inflammatory effects. Aloe-emodin, an anthraquinone, has been shown to inhibit the growth and proliferation of oral cancer cells. Aloe-emodin-mediated photodynamic therapy blocks cell proliferation and migration, and promotes the apoptosis of oral cancer cells both *in vitro* and *in vivo* (Table VI) (126-131).

To date, only a limited number of studies have investigated the effects of phytochemicals, such as isothiocyanates, thymoquinone, genistein and naringenin on oral cancer cells. Benzyl isothiocyanate, a compound with chemopreventive potential, is commonly found in cruciferous vegetables such as broccoli, cabbage and watercress. Thymoquinone, a polyphenol found in *Nigella sativa*, can induce oxidative stress in oral cancer cells (132). Genistein is an isoflavone found in soybeans, their derivatives, and some legumes and cereals. Genistein inhibits the viability, proliferation, adhesion, and migration of tongue cancer cells (133). Flavonoids, such as myricetin and naringenin, suppress the cell cycle progression and migration of OSCC cell lines (134).

11. Conclusion and future perspectives

Poor aqueous solubility, low bioavailability and inadequate tissue-specific targeting frequently limit the use of natural compounds. Consequently, the development of nanoformulations can overcome these pharmacokinetic and pharmacodynamic barriers. Their efficacy can also be improved by developing drug delivery systems specifically designed for the oral mucosa. These systems provide targeted and efficient drug delivery, while remaining self-administrable and well-accepted by

patients. Buccal delivery systems loaded with natural anticancer compounds and drugs (e.g., 5-fluorouracil) have been studied *in vitro*. Although a number of studies have investigated the effects of phytochemicals on oral cancer cell lines and animal models, human clinical trials have rarely been conducted. Future studies are warranted to focus on human clinical trials.

In conclusion, compounds, such as curcumin, EGCG, quercetin and resveratrol have demonstrated potent antitumor effects in pre-clinical studies, which cannot be directly extrapolated to therapeutic efficacy in patients with established OSCC. Their clinical utility is constrained by poor bioavailability, rapid metabolism and variability in pharmacological properties. Innovative delivery platforms, such as nanoparticles, buccal films and phytochemical conjugates may help overcome these barriers; however, their effectiveness and safety remain to be validated in well-designed clinical trials. At present, phytochemicals should be regarded as agents with potential adjunctive therapeutic agents rather than substitutes for established OSCC therapies.

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Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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