Current Biomedicine
p-ISSN: 2962-8490, e-ISSN: 2985-4784

Ridho *et al.*, Jul 2024, 2(2): 101-115
https://doi.org/10.29244/currbiomed.2.2.101-115
Available at https://journal.ipb.ac.id/index.php/currbiomed

Review OPEN ACCESS

In vitro and *in vivo* effects of curcumin on oral cancer: a systematic review

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Received: 04 April 2024 | **Revised:** 22 May 2024 | **Accepted:** 23 May 2024
Published online: 15 June 2024

Abstract

Current therapy for oral cancer (OC) patients, including surgery, radiotherapy, and chemotherapy, still has many shortcomings. Therefore, the discovery of natural products to prevent and treat cancer is receiving increasing attention, including curcumin. Curcumin (diferuloylmethane) is a polyphenolic compound found in turmeric (*Curcuma longa*), and it has been widely used as a herbal medicine because of its effects on health, one of which is as an anticancer agent. This study aimed to systematically and comprehensively review and summarize the anticancer effects and action mechanisms involving curcumin on OC cells. A systematic review methodology adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to review and summarize previous studies published in databases, including PubMed, ScienceDirect, and Google Scholar. The final results included 14 articles, both *in vitro* and *in vivo* studies. Based on several preclinical studies regarding the effects of curcumin on OC cells, we highlight that curcumin has a strong potential to inhibit OC cells through exerted effects such as immunomodulatory and anti-inflammatory effects, inhibition of cell proliferation, invasion, migration, and angiogenesis, as well as through the induction of apoptosis and autophagy. The systematic review presented in this paper concludes that curcumin possesses the potential to inhibit the development of OC cells through several mechanisms of action related to immunomodulatory effects, anti-inflammatory effects, cell proliferation, invasion and migration, angiogenesis, apoptosis, and autophagy.

Keywords: anticancer | curcumin | oral cancer | oral squamous cell carcinoma | turmeric

Introduction

Oral cancer (OC) is a malignancy that can be found in several areas, including the inner lips, gingiva, buccal mucosa, palate, floor of the mouth, dorsal of the tongue, and other non-specific parts of the oral cavity (Rivera, 2015; Sarode *et al.*, 2020). OC is a multifactorial disease and can be prevented, where smoking or tobacco alongside alcohol consumption represent primary risk factors that contribute to 90% of OC cases (Leite *et al.*, 2021). Apart from these two major factors, human papillomavirus (HPV) is correlated with the incidence of oral and oropharyngeal cancer (Kim, 2016; Giraldi *et al.*, 2021) and exposure to ultraviolet radiation is linked with the incidence of lip cancer (Alhabbab & Johar, 2022). Furthermore, other factors, including genetics (Ali *et al.*, 2017), HIV/AIDS infection (Speicher *et al.*, 2016), severe and chronic periodontitis (Kavarthapu & Gurumoorthy, 2021; Komlós *et al.*, 2021), chronic trauma to the buccal

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mucosa and tongue (Gupta *et al.*, 2021), poor oral hygiene (Mathur *et al.*, 2019), chewing betel and areca nut (Song *et al.*, 2015; Yang *et al.*, 2021), malnutrition due to unhealthy lifestyle and diet (Zhang *et al.*, 2019), and diabetes (Ramos-Garcia *et al.*, 2021) contribute to the incidence of OC.

Based on the statistical findings provided by WHO in 2020, it was observed that there were 377,713 newly diagnosed cases of OC, and an associated incidence rate of OC was 4,1 per 100,000 population. The reported death in 2020 due to OC was 177,757 people worldwide, with a mortality rate of 1.2 per 100,000 population (WHO, 2020). This data has an increasing trend compared to 2018 (Sarode *et al.*, 2020). Thus, OC has become a crucial global problem and must be addressed.

The primary modalities of OC therapy currently include surgical treatment, chemotherapy, and radiotherapy, either alone or in combination (Deng *et al.*, 2011; Nandini *et al.*, 2020). However, some adverse side effects exist from these therapies and have an influence on the patient's well-being and quality of life. Surgery effects difficulties in swallowing, changes or loss of taste, nerve pain, aesthetic damage due to tissue loss, and limited movement or function if a neck dissection occurs (Nandini *et al.*, 2020). Side effects that arise due to radiotherapy include nausea, vomiting, odynophagia, dysphagia, orofacial pain, mucositis, dermatitis, subcutaneous fibrosis, trismus, salivary gland disorders, xerostomia, caries, change or loss of taste sensation, hoarseness, osteoradionecrosis, thyroid dysfunction, telangiectasia, carotid artery rupture, post-radiotherapy pigmentation, and radiation-related neoplasms (Tolentino *et al.*, 2011; Brook, 2021; Rocha *et al.*, 2022). Meanwhile, nausea, vomiting, mucositis, oral ulcers, enamel erosion, alopecia, skin rashes, neuropathy, infection, bone marrow suppression, and toxicity to the kidneys, lungs, ears, neurology, and hematology are the adverse effects of chemotherapy (Poulopoulos *et al.*, 2017; Nandini *et al.*, 2020; Sharma *et al.*, 2023; Śledzińska *et al.*, 2023).

In light of the adverse side effects of current OC treatments, research related to exploring and discovering alternative medicines, including herbal natural products, continues to be conducted excessively. One natural compound with many health benefits is curcumin, which has an anticancer potential (Ahsan *et al.*, 2020).

Curcumin, also called diferuloylmethane, constitutes the primary compound identified in the turmeric plant (*Curcuma longa*) as well as others *Curcuma* spp. and has received particular attention due to its bioactivity in various diseases, one of which is its anticancer potential (Rathore *et al.*, 2020). Curcumin has been well-documented to modulate immunity and downregulate growth factors, oncogenic molecules, protein kinases, as well as numerous signaling pathways related to growth inhibition in various cancers (Zoi *et al.*, 2021). In addition, several studies highlight that curcumin triggers inhibition of cancer cells through autophagy and apoptosis pathways, antiproliferative, angiogenesis inhibition, inhibition of invasion, migration, and metastasis, etc., through inhibition of various pathways (Shakeri *et al.*, 2019; Shakeri *et al.*, 2019; Davoodvandi *et al.*, 2021; Joshi *et al.*, 2021; Kusuma *et al.*, 2022).

However, research on the inhibition of OC cells by curcumin is rarely summarized comprehensively. Since OC remains a pervasive global health concern and alternative treatments using natural products are still being carried out to prevent the adverse side effects caused by current cancer therapy, we sought to systematically and comprehensively review and summarize the curcumin effects and mechanisms of action involved on OC cells, encompassing both at the *in vitro* and *in vivo* studies.

Methods

Research question

The present systematic review adhered to the guidelines delineated in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020. The main question in the present study was "What is the effect of curcumin on oral cancer cells?". To answer the research question, we applied the population, intervention, comparison, and outcomes (PICO) framework shown in **Table 1**.

Information sources

Three databases, such as PubMed, ScienceDirect, and Google Scholar, were utilized in the initial literature search performed in December 2023 and subsequently repeated in February 2024.

Search terms

We systematically and comprehensively conducted a literature search in a predetermined database using a combination of keywords, as presented in **Table 2**.

Study selection

We included research articles that reported the anticancer effects of curcumin on OC. In the study selection process, inclusion and exclusion criteria were applied, which generally refer to the PICO criteria. The inclusion criteria were preclinical studies (*in vitro* and/or *in vivo*), English or Indonesian, peer-reviewed, and only full-text or open-access articles.

Exclusion criteria were all types of review articles, mini reviews, short communications, editorials, preclinical studies that only reported cytotoxicity analysis and did not analyze the mechanism of anticancer action, articles discussing curcumin derivatives, and studies involving combination treatment of curcumin with other compounds or agents. All research published up to February 2024 was considered for review in this study, and no publication year restrictions were applied.

Data extraction

Data extraction was carried out using tables to summarize the necessary information regarding several aspects, including author, year of publication, research methods, study sample (type of OC cell line and animal model used), intervention (curcumin dose and duration of curcumin administration), type of control, and mechanism of action. Then, we performed a qualitative analysis covering the mechanism of action of curcumin on OC cells. In-depth and careful discussions were carried out to resolve differences of opinion.

Results

The 863 articles were obtained after duplicates were removed. A total of 828 reports were eliminated

Table 1 The population, intervention, comparison, and outcomes (PICO) framework.

Element	Details
Population	OC cell line OC cells-induced animal model
Intervention	The curcumin compound derived from *Curcuma longa* or *Curcuma* spp.
Comparison	Cell line or animal model with placebo control or without any treatment Standard cancer treatment
Outcomes	Anticancer effects and mechanisms of action

Table 2 Keywords used in each database in literature searches.

Database	Keywords
PubMed	(curcumin[Title/Abstract]) AND ((turmeric[Title/Abstract]) OR (Curcuma longa[Title/Abstract])) AND ((anticancer[Title/Abstract]) OR (oral cancer[Title/Abstract]) OR (oral squamous cell carcinoma[Title/Abstract]) OR (tongue squamous cell carcinoma[Title/Abstract]))
ScienceDirect	Title, abstract, keywords: "curcumin" AND ("turmeric") OR ("Curcuma longa") AND ("oral cancer" OR "oral squamous cell carcinoma" OR “tongue squamous cell carcinoma”)
Google Scholar	“curcumin” “turmeric” “Curcuma longa” “anticancer” “oral cancer” “oral squamous cell carcinoma” “tongue squamous cell carcinoma”

from consideration due to their lack of relevance to this study, and 35 articles remain. After conducting an eligibility assessment, the final result was 14 articles, which were included for review. The entire study selection process is depicted in **Figure 1**. All articles included eleven *in vitro* studies, one *in vivo* study, and two *in vitro* and *in vivo* studies, and the characteristics of all articles are presented in **Table 3**.

Discussion

Immunomodulatory effects

Myeloid-derived suppressor cells (MDSCs) are involved in diminishing interleukin (IL)-12 secretion, which causes reduced CD8+ T cell infiltration. Thus, cancer therapy by reducing MDSCs accumulation at the tumor site is important for improving adaptive T cell immunotherapy (Maimela *et al.*, 2019). In this case, curcumin has an important influence on the number of MDSCs in mouse spleens, as proven in *in vivo* studies. The study also concluded that curcumin effectively increased CD8+ T cells (Liao *et al.*, 2018). Evidence suggests that CD8+ T cells constitute a vital element of tumor immunity and control cancer growth (Shimizu *et al.*, 2019). Another investigation indicated that OC patients with low CD8+ T cell index show larger tumors, nodal metastases, and advanced clinical stages (Santos *et al.*, 2019).

Additionally, a significant reduction in the regulatory T cells (Tregs) frequency was observed in the mice peripheral blood compared to controls (Liao *et al.*, 2018). In OC, Tregs are integral in the regulation and preservation of immune homeostasis and tolerance (Liu *et al.*, 2016). Tregs suppress the host immune response and enhance angiogenesis and tissue remodeling in the cancer development and expansion (Kouketsu *et al.*, 2019). In this *in vivo* study, a decrease in Tregs in mice after being given curcumin therapy was reported. Thus, it can be inferred that curcumin impeded the growth of

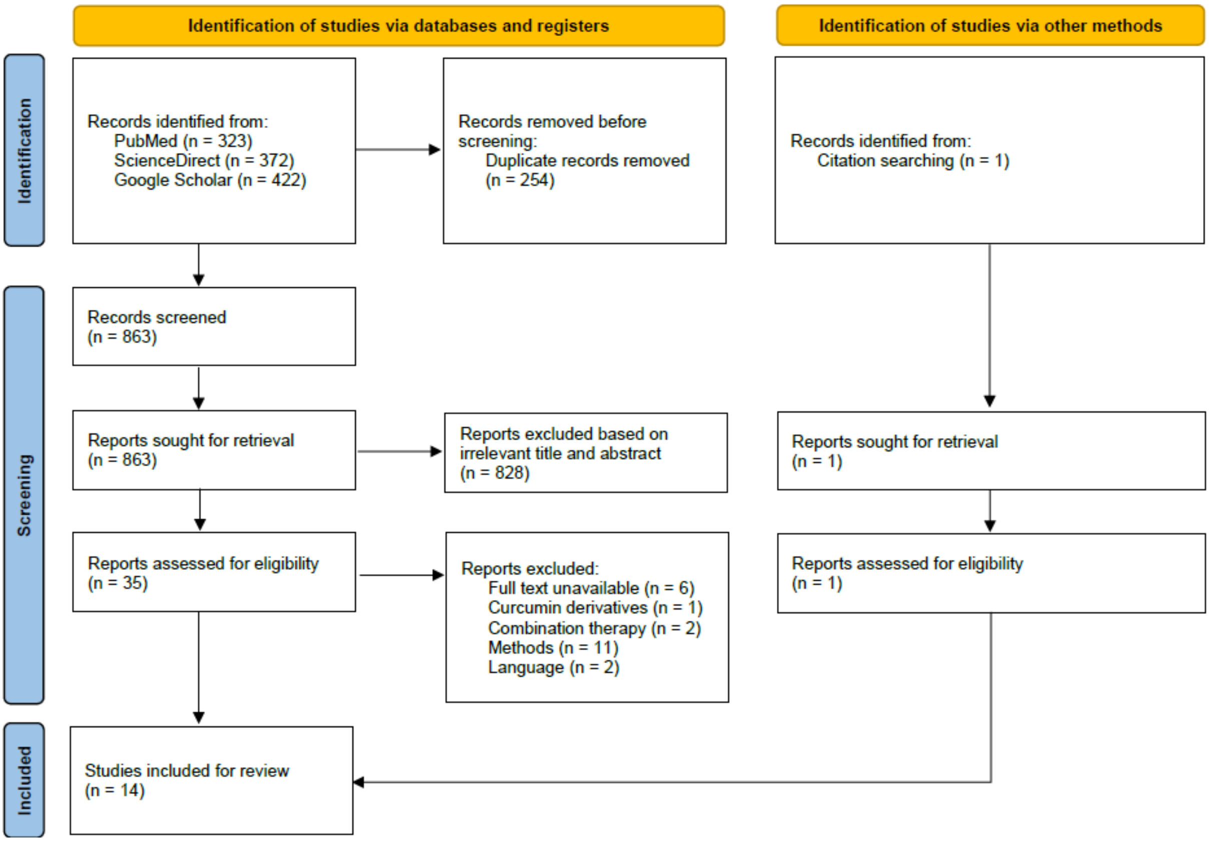

Figure 1 Study selection process adhering to the PRISMA guidelines.

Table 3 Summary of the anticancer activity of curcumin.

Reference	Study methods	Cell/animal model	Dosage	Duration	Control	Mechanism of action
Lin *et al.* (2010)	*In vitro*	Human OSCC SAS cells	1, 3, 5, 7, 9, 10, 20, 25, and 30 µM	24 h	Untreated	Induces apoptosis. Suppresses proliferation and growth of OC.
	In vivo	SAS cells-inoculated NOD/SCID mice	35 mg/kg per day, 70 mg/kg every other day, and 100 mg/kg every third day.	26 days	0.025 N NaOH	
Liao *et al.* (2011)	*In vitro*	Human OSCC CAL-27 cells	2.5, 5, and 7.5 µM	24, 8, and 72 h	DMSO	Induces apoptosis. Suppresses cell growth and invasion through Notch-1 and NF-κB downregulation.
Kim *et al.* (2012)	*In vitro*	OSCC YD10B cells	1, 5, 10, 20, and 40 µM	24 h	Untreated	Induces autophagy through the autophagic vacuoles generation and conversion of LC3-I to LC3-II. Induces ROS production.
Moon *et al.* (2014)	*In vitro*	Human TSCC SCC-25 cells	5-50 µM	48 h	Untreated	Induces apoptosis via proteasome, mitochondrial, and caspase cascades. Inhibits proliferation.
Xiao *et al.* (2014)	*In vitro*	Human TSCC SCC-9 cells	20, 40, and 60 µM	72 h	Untreated	Inhibits proliferation. Regulates miR-9. Suppresses Wnt/β-catenin signaling.
Zhen *et al.* (2014)	*In vitro*	Human OSCC SCC-25 cells	10, 20, 40, and 80 µmol/L	24 and 48 h	Untreated	Inhibits proliferation and invasion through impeding EGFR phosphorylation and its downstream signaling molecules.
Lee *et al.* (2015)	*In vitro*	OSCC SCC-25 cells	2.5, 5, 10, 15, and 30 µM	24 h	Untreated	Decreases MMP-2 and -9 expression. Modulates Snail, Twist, and E-cadherin expression. Induces p53 expression.
Liao *et al.* (2018)	*In vitro*	Human TSCC CAL-27 and FaDu cells	5 and 10 µM	6, 12, 24, and 48 h	Untreated	Inhibits PD-L1 and p-STAT3Y^{705}.
	In vivo	4NQO mice	Not mentioned	4 weeks	DMSO	Reduces the number of cancer cells and tumor volume. Inhibits tumor proliferation. Reduces the population of immunosuppressive cells.
Elwahab *et al.* (2019)	*In vitro*	HNSCC HEP-2 cells	5-10,000 mM	24 h	Untreated	Inhibits proliferation. Induces cell cycle arrest, apoptosis, and necrosis.
Maulina *et al.* (2019)	*In vivo*	OSCC-induced Sprague Dawley rats	80 mg/kg thrice per day	4 weeks	No curcumin use	Decreases NF-κB and COX-2 expression.
Ma *et al.* (2020)	*In vitro*	Human TSCC CAL-27 cells	10, 25, 50, and 100 µM	6, 16, and 24 h	Untreated	Inhibits proliferation and migration. Induces apoptosis.
Ohnishi *et al.* (2020)	*In vitro*	Human TSCC HSC-4 and Ca9-22 cells	10-20 µM	48 h	FBS	Inhibits HGF-induced EMT and cell motility through c-Met blockade.
Liu *et al.* (2021)	*In vitro*	OSCC HSC-3 and CAL-33 cells	5-20 µM	24 and 48 h	DMSO	Decreases the expression of Sp1, p65, and HSF1. Decreases NF-κB activity.
Jayaraman *et al.* (2024)	*In vitro*	OSCC HSC-3 cells	25, 50, 75, 100, 125, and 150 µM	24 and 48 h	Untreated	Inhibits aerobic glycolysis. Regulates the cell cycle. Induces apoptosis.

OC cells by regulating tumor immunity.

Anti-inflammatory effects

Maulina *et al.* (2019) reported that curcumin significantly decreases cyclooxygenase-2 (COX-2) expression. COX-2, an inflammatory mediator, is expressed in various cancer cells, and it has an essential relationship between chronic inflammation and carcinogenesis (Hashemi Goradel *et al.*, 2019). In OC, overexpressed COX-2 causes the release of prostaglandin (PG) E2, leading to cancer cell progression and enhancing migration and metastasis (Nasry *et al.*, 2018). In addition, COX-2 promotes cell proliferation, enhances angiogenesis, suppresses apoptosis, and augments the metastatic propensity of cancer cells (Desai *et al.*, 2018). Therefore, inhibition of COX-2 in cancer makes cancer cells sensitive to cancer treatment and inhibits cancer cell growth. The findings from the reviewed articles indicate that curcumin possesses the potential to inhibit COX-2 expression.

Cell proliferation

Several *in vitro* and *in vivo* studies reported that curcumin significantly inhibits the proliferation and growth of OC compared to controls (Lin *et al.*, 2010; Xiao *et al.*, 2014; Zhen *et al.*, 2014; Liao *et al.*, 2018; Ma *et al.*, 2020). Other studies also suggest that curcumin inhibited colony formation in several OC cells (Moon *et al.*, 2014; Liu *et al.*, 2021).

A decrease in glucose absorption, lactate production, and lactate dehydrogenase A (LDHA) enzyme activity in HSC-3 cells occurred after curcumin administration (Jayaraman *et al.*, 2024). This study highlighted that curcumin has a strong potential for inhibiting aerobic glycolysis in OC cells. As widely recognized, changes in aerobic glycolysis represent a hallmark of cancer cell energy metabolism, commonly referred to as the Warburg effect (Wu *et al.*, 2020). By inhibiting aerobic glycolysis activity in OC due to the administration of curcumin, cancer cells cannot take up glucose for their growth and proliferation needs (Ganapathy-Kanniappan, 2018). Ultimately, curcumin inhibits proliferation by targeting metabolic processes that are essential for the OC cell survival and proliferation.

Curcumin downregulates Notch-1 expression in CAL-17 cells (Liao *et al.*, 2011). Notch-1 is believed to be crucial in regulating cancer proliferation and invasion, including OC cells (Yoshida *et al.*, 2013). Therapy targeting Notch-1 inhibition can diminish cell proliferation, invasion, and migration and promote apoptosis (Gan *et al.*, 2018). At least one study stated that curcumin was effective in downregulating Notch-1 expression, which, among other things, could inhibit cell proliferation in OC.

The expression of microRNA (miR)-9 increased significantly ($p<0.05$) in SCC-9 cells after administration of curcumin (Xiao *et al.*, 2014). In OC, increased expression of miR-9 is considered a promising target for cancer therapy because miR-9 directly targets the CXCR4 gene and correlates with constitutive activation of β-catenin (Yu *et al.*, 2014). Additionally, Xiao *et al.* also documented that curcumin also interferes with the Wnt/β-catenin (Xiao *et al.*, 2014), where this signaling pathway is integral in regulating growth, differentiation, migration, and proliferation (Goñi *et al.*, 2021). As a result, targeting miR-9 in cancer therapy is promising, and since curcumin is effective in increasing miR-9 expression, OC cell proliferation can be inhibited.

Liao *et al.* reported that curcumin effectively decreases the programmed death-ligand 1 (PD-L1) and p-STAT3^{Y705} expression (Liao *et al.*, 2018). PD-L1 is a protein produced by cancer cells and overexpressed in several types of cancer, which interacts with PD-1 and suppresses activated T cells from interacting with cancer cells. An increase in PD-L1 contributes to cancer resistance to anticancer therapy and is also instrumental in promoting cell proliferation (Yang *et al.*, 2019). Meanwhile, signal transducer and activator of transcription 3 (STAT3) are pivotal in survival, proliferation, invasion, metastasis, and unfavorable prognosis in OC

(Khatoon *et al.*, 2022). Furthermore, in the same study, curcumin effectively reduced the number of tongue cancers and decreased tumor volume, which was reported in *in vivo* testing (Liao *et al.*, 2018). Hence, a study reporting a reduction in PD-L1 and p-STAT3^{Y705} expression after administration of curcumin makes curcumin a promising anticancer agent for attenuating the proliferation and development of OC cells through this mechanism.

Based on an examination by Liu *et al.*, curcumin effectively downregulates specificity protein 1 (Sp1), a p65, and heat shock factor 1 (HSF1) transcription factor. Furthermore, the expression of p65 and HSF1 also exhibits a notable reduction following administration of curcumin ($p<0.001$). Apart from that, administration of curcumin also decreased nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activity by 88.2% in HSC-3 cells and 95.4% in CAL-33 cells (Liu *et al.*, 2021). Finally, curcumin inhibited the proliferation and activity of NF-κB through the Sp1 regulation in OC cells.

Invasion and migration

OC cell invasion and migration were effectively inhibited by curcumin, as in the assay by Lee *et al.*, which documented reducing the invasion of SCC-25 cells by up to 95% (Lee *et al.*, 2015). Ohnishi *et al.* also reported the invasion and migration inhibition by curcumin in HSC-4 cells ($p<0.05$) (Ohnishi *et al.*, 2020). Furthermore, inhibition of CAL-27 cell migration also occurred after administration of curcumin at a dose of 100 µM for 16 and 24 h ($p<0.001$), as well as at a dose of 50 µM for 24 h ($p<0.01$) (Ma *et al.*, 2020).

Curcumin inhibits matrix metalloproteinase (MMP)-9 (Liao *et al.*, 2011; Zhen *et al.*, 2014; Lee *et al.*, 2015; Ohnishi *et al.*, 2020) and MMP-2 (Zhen *et al.*, 2014; Lee *et al.*, 2015), enzymes involved in the proteolytic processes associated with invasion and migration. As is known, the latent, active, and total forms, as well as the activation ratio of MMP-2 and -9, are remarkably increased in malignant tissue compared to normal tissue, and MMP itself is a factor contributing to the process of invasion and metastasis, also predicting prognosis in cancer (Patel *et al.*, 2007; Aparna *et al.*, 2015). Findings in several research showed that curcumin effectively inhibits invasion and migration through inhibiting MMP-2 and -9.

Curcumin significantly downregulated the urokinase-type plasminogen activator (uPA) and uPA receptor (uPAR) expression (Zhen *et al.*, 2014). A study states that uPA and uPAR contribute to cancer development involving in migration, invasion, survival, and angiogenesis (Masucci *et al.*, 2022). Therefore, inhibition of uPA/uPAR in OC cells also appears promising because the expression of uPAR is elevated in cancerous tissues but remains low in normal tissues. In addition, uPA/uPAR inhibition also has an impact on inhibiting invasion, migration, and cell proliferation (Zhai *et al.*, 2022).

Additionally, curcumin effectively inhibits epithelial-mesenchymal transition (EMT), as supported by decreased levels of Snail and Twist, alongside increased in E-cadherin expression (Lee *et al.*, 2015). Furthermore, there was also an elevation in the p53 protein, which is crucial in regulating the EMT process. In another investigation conducted by Ohnishi *et al.*, it was documented that curcumin effectively impeded HGF-induced EMT by suppressing the c-Met and extracellular signal-regulated kinase (ERK) activation, increasing E-cadherin, as well as decreasing vimentin (Ohnishi *et al.*, 2020). One of the molecular pathways that regulate the EMT mechanism is NF-κB (Mirzaei *et al.*, 2022); thus, cancer therapy targeting NF-κB/EMT inhibition in OC has promising potential. Related to this, a study in CAL-27 cells stated that curcumin notably suppresses NF-κB DNA-binding activity (Liao *et al.*, 2011). Maulina *et al.* (2019) conducted research indicating that, in an *in vivo* study on Sprague Dawley rats, curcumin significantly decreased NF-κB ($p<0.01$) compared to controls. Accordingly, NF-κB/EMT inhibition in OC will impact on inhibiting cell invasion and migration.

A study by Zhen *et al.* (2014) documented that there was inhibition of the protein kinase B (AKT), ERK1/2, and STAT3 pathways, which are epidermal growth factor receptor (EGFR) downstream signaling molecules, in SCC-25 cells. EGFR is a pathway intricately engaged in the processes of cell differentiation, proliferation, and, of course, invasion and migration. More specifically, in OC, EGFR activation impacts the stimulation of signaling pathways such as phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) and Janus kinase (JAK)/STAT pathways, resulting in invasion and metastasis induction (Huang *et al.*, 2023). Consequently, the effect of curcumin on inhibiting downstream signaling molecules from EGFR will have an impact on inhibiting tumor invasion through several signaling pathways that have been mentioned.

Angiogenesis

Several studies have documented the impact of curcumin on angiogenesis, such as that by Liao *et al.* (2011), which states that curcumin is effective in inhibiting vascular endothelial growth factor (VEGF). A recent study examining curcumin on angiogenesis reported that there was significant suppression of the hypoxia-inducible factor 1-alpha (HIF-1α), VEGF, and STAT3 expression in HSC-3 cells after administration of curcumin (Jayaraman *et al.*, 2024). As is known, these genes are markers related to hypoxia and angiogenesis in cancer. One factor that regulates angiogenesis is VEGF; one factor that mediates hypoxic conditions to support angiogenesis is HIF-1α (Rajabi & Mousa, 2017; Herrera-Vargas *et al.*, 2021). On the other hand, the role of STAT3 here is to inhibit proteasomal degradation, which impacts the accumulation of HIF-1α (Jung *et al.*, 2005). Interestingly, evidence suggests that the transcription of VEGF is facilitated by STAT3 and HIF-1α (Carbajo-Pescador *et al.*, 2013). Curcumin disrupts MMP-3, another important factor promoting angiogenesis during cancer development (Quintero-Fabián *et al.*, 2019). These results suggest that curcumin possesses a strong potential to interfere with several factors related to angiogenesis so that cancer cells can be inhibited by interfering with angiogenesis.

Apoptosis

Curcumin increases apoptosis in the sub-G1 phase (Lin *et al.*, 2010) and induces cell accumulation in the G2/M phase fraction, which elevated from 5.5% to 13.6% in CAL-27 cells (Liao *et al.*, 2011). Meanwhile, in HEP-2 cells, curcumin induces apoptosis by decreasing the G0/G1 phase (Elwahab *et al.*, 2019). In addition, curcumin was reported to have the potential to inhibit cyclin D expression in CAL-27 cells (Liao *et al.*, 2011). Furthermore, curcumin effectively reduce the expression of cyclin D1 and D3 and cyclin-dependent kinase (CDK)2/4, which regulate the G0/G1 phase (Moon *et al.*, 2014). These components are crucial for controlling the cell cycle in cancer (Musgrove *et al.*, 2011; Choi *et al.*, 2012). Related to this, curcumin has also been documented to elevate the $p27^{KIP1}$ protein which acts as a CDK inhibitor (Moon *et al.*, 2014). Consequently, increasing the $p27^{KIP1}$ protein by curcumin can inhibit cyclin/CDK activity (Lee & Kim, 2009). Based on these findings, curcumin influences the induction of apoptosis in the cell cycle phase and through components that regulate the cell cycle.

Apoptosis consists of intrinsic and extrinsic pathways, which are regulated by various proteins, including pro-apoptotic, BH3-specific pro-apoptotic, and anti-apoptotic proteins (Chota *et al.*, 2021). Regarding pro-apoptotic proteins, curcumin increases Bax expression, as evidenced by the research results (Moon *et al.*, 2014). Meanwhile, curcumin effectively inhibits Bcl-2 expression for anti-apoptotic proteins, based on findings in two studies

(Liao *et al.*, 2011; Moon *et al.*, 2014). Furthermore, the Bcl-2/Bax ratio was significantly decreased by curcumin, as reported by an *in vitro* investigation (Ma *et al.*, 2020). The findings from multiple studies indicated that curcumin has a strong potential to induce apoptosis by increasing pro-apoptotic proteins while suppressing anti-apoptotic proteins.

In addition, therapeutic targeting of cancer can be achieved through the caspase pathway. Caspases themselves are divided into two groups, namely initiator caspases, which include caspase-2, -8, -9, and -10, and executor caspases, which consist of caspase-3, -6, and -7 (Boice & Bouchier-Hayes, 2020). Two studies reported that administration of curcumin caused increased caspase-3 cleavage (Kim *et al.*, 2012; Ma *et al.*, 2020). Curcumin also induces the degradation of caspase-9 and -6 (Moon *et al.*, 2014). Finally, curcumin can activate the caspase cleavage of both initiator caspases, including caspase-9, and executor caspases, namely caspase-3 and -6.

Autophagy

Autophagy begins with the formation of the autophagosome; currently, microtubule-associated protein 1A/1B-light chain 3 (LC3) is a protein identified on the inner membrane of the autophagosome (Zhang *et al.*, 2015). The potential of curcumin to influence the autophagy process in OC cells was reported, indicated by autophagic vacuoles formation and increasing the conversion of LC3-I to LC3-II and the LC3 protein total concentration in YD10B cells after administration of curcumin (Kim *et al.*, 2012). The conversion of LC3-I to LC3-II, indicative of active autophagosome formation, is thought to be correlated with heightened autophagic activity (Lee *et al.*, 2013). Additionally, at a dose of 10 μM, curcumin significantly increases reactive oxygen species (ROS) generation, and it induces JNK activation and NF-κB reduction, indicating that the possibility of this molecule is involved in ROS generation and autophagy resulting from curcumin administration (Kim *et al.*, 2012). These findings suggested that curcumin possesses the potency to initiate autophagy in OC by promoting autophagic vacuole formation and conversion of LC3-I to LC3-II, as well as ROS generation.

According to the findings of both *in vitro* and *in vivo* studies, the mechanism of action of curcumin exhibits considerable potential in inhibiting OC cells through its immunomodulation, anti-inflammation, inhibition of cell proliferation, invasion and migration, angiogenesis, apoptosis, and autophagy induction. The schematic of main effects and mechanism of action of curcumin on inhibition of OC cells is shown in **Figure 2**.

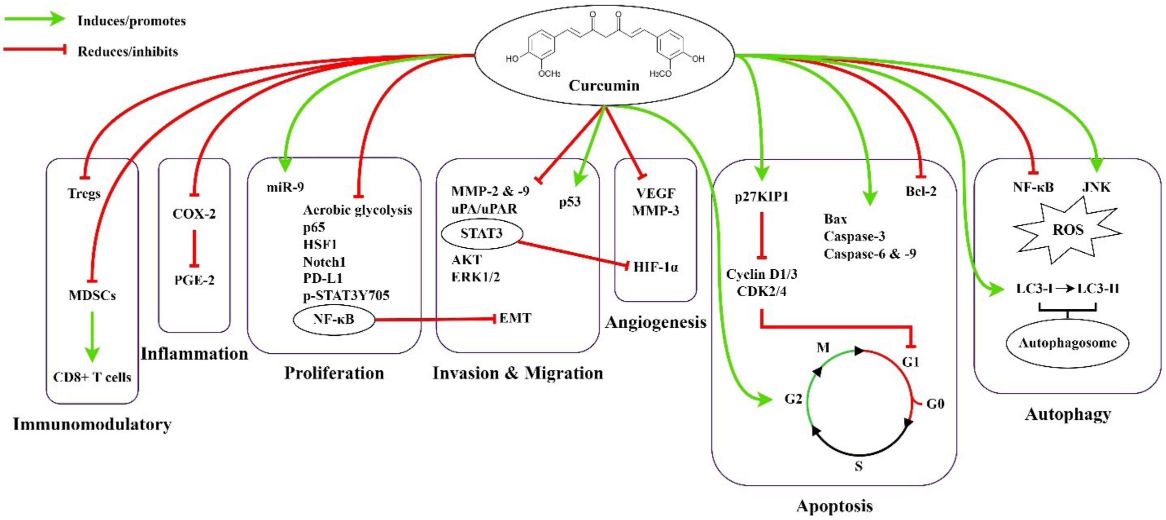

Figure 2 The main effects and mechanism of action of curcumin on OC cells.

Conclusion

Curcumin, also called diferuloylmethane, is a polyphenol product that can be found in turmeric and has biological and medicinal properties in certain diseases, including OC cells. *In vitro* and *in vivo* studies showed curcumin exhibits inhibiting OC cells through its immunomodulatory and anti-inflammatory effects, inhibition of cell proliferation, invasion and migration, and angiogenesis, as well as through apoptosis and autophagy induction. However, future research is strongly needed regarding evaluating the effects of curcumin on humans to ascertain the potential to influence the development of OC cells. Research regarding the impact of curcumin on combinations of conventional cancer treatments such as radiotherapy and chemotherapy may also be warranted to evaluate whether there is an effect of curcumin on reducing the side effects caused by radiotherapy and chemotherapy. Furthermore, future research related to the synthesis of curcumin and the development of formulations such as nanoparticles, liposomes, or complexation with other substances that can increase the stability and bioavailability of curcumin needs to be conducted.

Acknowledgments: The authors would like to acknowledge that no external assistance or funding was received for this research.

Funding: None.

Competing interests: The authors have declared that there was no conflict of interest in the research.

Author contributions: FMR and AJS designed the study; FMR and AJS collected the data; FMR, AJS, and PF analyzed the data; FMR, PF, and AN wrote the original draft; NN and NSL wrote the paper.

References

Ahsan R, Arshad M, Khushtar M, Ahmad MA, Muazzam M, Akhter MS, Gupta G, Muzahid M. 2020. A comprehensive review on physiological effects of curcumin. *Drug Research*, 70(10): 441–447. DOI: 10.1055/a-1207-9469.

Alhabbab R, Johar R. 2022. Lip cancer prevalence, epidemiology, diagnosis, and management: A review of the literature. *Advances in Oral and Maxillofacial Surgery*, 6: 100276. DOI: 10.1016/j.adoms.2022.100276.

Ali J, Sabiha B, Jan HU, Haider SA, Khan AA, Ali SS. 2017. Genetic etiology of oral cancer. *Oral Oncology*, 70: 23–28. DOI: 10.1016/j.oraloncology.2017.05.004.

Aparna M, Rao L, Kunhikatta V, Radhakrishnan R. 2015. The role of MMP-2 and MMP-9 as prognostic markers in the early stages of tongue squamous cell carcinoma. *Journal of Oral Pathology & Medicine*, 44(5): 345–352. DOI: 10.1111/jop.12245.

Boice A, Bouchier-Hayes L. 2020. Targeting apoptotic caspases in cancer. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research*, 1867(6): 118688. DOI: 10.1016/j.bbamcr.2020.118688.

Brook I. 2021. Early side effects of radiation treatment for head and neck cancer. *Cancer/Radiothérapie*, 25(5): 507–513. DOI: 10.1016/j.canrad.2021.02.001.

Carbajo-Pescador S, Ordoñez R, Benet M, Jover R, García-Palomo A, Mauriz JL, González-Gallego J. 2013. Inhibition of VEGF expression through blockade of Hif1α and STAT3 signalling mediates the anti-angiogenic effect of melatonin in HepG2 liver cancer cells. *British Journal of Cancer*, 109(1): 83–91. DOI: 10.1038/bjc.2013.285.

Choi YJ, Li X, Hydbring P, Sanda T, Stefano J, Christie AL, Signoretti S, Look AT, Kung AL, von Boehmer H, Sicinski P. 2012. The requirement for cyclin D function in tumor maintenance. *Cancer Cell*, 22(4): 438–451. DOI: 10.1016/j.ccr.2012.09.015.

Chota A, George BP, Abrahamse H. 2021. Interactions of multidomain pro-apoptotic and anti-apoptotic proteins in cancer cell death. *Oncotarget*, 12(16): 1615–1626. DOI: 10.18632/oncotarget.28031.

Davoodvandi A, Farshadi M, Zare N, Akhlagh SA, Alipour Nosrani E, Mahjoubin-Tehran M, Kangari P, Sharafi SM, Khan H, Aschner M, Baniebrahimi G, Mirzaei H. 2021. Antimetastatic effects of curcumin in oral and gastrointestinal cancers. *Frontiers in Pharmacology*, 12: 668567. DOI: 10.3389/fphar.2021.668567.

Deng H, Sambrook P, Logan R. 2011. The treatment of oral cancer: an overview for dental professionals. *Australian Dental Journal*, 56(3): 244–252. DOI: 10.1111/j.1834-7819.2011.01349.x.

Desai SJ, Prickril B, Rasooly A. 2018. Mechanisms of phytonutrient modulation of cyclooxygenase-2 (COX-2) and inflammation related to cancer. *Nutrition and Cancer*, 70(3): 350–375. DOI: 10.1080/01635581.2018.1446091.

Elwahab IMA, El Azab SM, El Bolok AHM, Gamal HE. 2019. Effect of curcumin and nanocurcumin on squamous cell carcinoma cell line (An-in vitro study). *Egyptian Dental Journal*, 65(3): 27–33.

Gan RH, Wei H, Xie J, Zheng DP, Luo EL, Huang XY, Xie J, Zhao Y, Ding LC, Su BH, Lin LS, Zheng DL, Lu YG. 2018. Notch1 regulates tongue cancer cells proliferation, apoptosis and invasion. *Cell Cycle*, 17(2): 216–224. DOI: 10.1080/15384101.2017.1395534.

Ganapathy-Kanniappan S. 2018. Molecular intricacies of aerobic glycolysis in cancer: current insights into the classic metabolic phenotype. *Critical Reviews in Biochemistry and Molecular Biology*, 53(6): 667–682. DOI: 10.1080/10409238.2018.1556578.

Giraldi L, Collatuzzo G, Hashim D, Franceschi S, Herrero R, Chen C, Schwartz SM, Smith E, Kelsey K, McClean M, Gillison M, Boccia S, Hashibe M, Amy Lee YC, Boffetta P. 2021. Infection with human papilloma virus (HPV) and risk of subsites within the oral cancer. *Cancer Epidemiology*, 75: 102020. DOI: 10.1016/j.canep.2021.102020.

Goñi FJ, Peña-Oyarzún D, Torres VA, Reyes M. 2021. Expression profile of components of the β-catenin destruction complex in oral dysplasia and oral cancer. *Medicina Oral Patología Oral y Cirugia Bucal*, 26(6): e729–e737. DOI: 10.4317/medoral.24528.

Gupta AA, Kheur S, Varadarajan S, Parveen S, Dewan H, Alhazmi YA, Raj TA, Testarelli L, Patil S. 2021. Chronic mechanical irritation and oral squamous cell carcinoma: A systematic review and meta-analysis. *Bosnian Journal of Basic Medical Sciences*, 21(6): 647–658. DOI: 10.17305/bjbms.2021.5577.

Hashemi Goradel N, Najafi M, Salehi E, Farhood B, Mortezaee K. 2019. Cyclooxygenase-2 in cancer: A review. *Journal of Cellular Physiology*, 234(5): 5683–5699. DOI: 10.1002/jcp.27411.

Herrera-Vargas AK, García-Rodríguez E, Olea-Flores M, Mendoza-Catalán MA, Flores-Alfaro E, Navarro-Tito N. 2021. Pro-angiogenic activity and vasculogenic mimicry in the tumor microenvironment by leptin in cancer. *Cytokine & Growth Factor Reviews*, 62: 23–41. DOI: 10.1016/j.cytogfr.2021.10.006.

Huang J, Yang JG, Ren JG, Xia HF, Chen GH, Fu QY, Zhang LZ, Liu HM, Wang KM, Xie QH, Chen G. 2023. Overexpression of RAB27A in oral squamous cell carcinoma promotes tumor migration and invasion via modulation of EGFR membrane stability. *International Journal of Molecular Sciences*, 24(17): 13103. DOI: 10.3390/ijms241713103.

Jayaraman S, Veeraraghavan VP, Natarajan SR, Jasmine S. 2024. Exploring the therapeutic potential of curcumin in oral squamous cell carcinoma (HSC-3 cells): Molecular insights into hypoxia-mediated angiogenesis. *Pathology-Research and Practice*, 254: 155130. DOI: 10.1016/j.prp.2024.155130.

Joshi P, Joshi S, Semwal D, Bisht A, Paliwal S, Dwivedi J, Sharma S. 2021. Curcumin: An Insight into molecular pathways involved in anticancer activity. *Mini-Reviews in Medicinal Chemistry*, 21(17): 2420–2457. DOI: 10.2174/

1389557521666210122153823.

Jung JE, Lee HG, Cho IH, Chung DH, Yoon SH, Yang YM, Lee JW, Choi S, Park JW, Ye SK, Chung MH. 2005. STAT3 is a potential modulator of HIF-1-mediated VEGF expression in human renal carcinoma cells. *The FASEB Journal*, 19(10): 1296–1298. DOI: 10.1096/fj.04-3099fje.

Kavarthapu A, Gurumoorthy K. 2021. Linking chronic periodontitis and oral cancer: A review. *Oral Oncology*, 121: 105375. DOI: 10.1016/j.oraloncology.2021.105375.

Khatoon E, Hegde M, Kumar A, Daimary UD, Sethi G, Bishayee A, Kunnumakkara AB. 2022. The multifaceted role of STAT3 pathway and its implication as a potential therapeutic target in oral cancer. *Archives of Pharmacal Research*, 45(8): 507–534. DOI: 10.1007/s12272-022-01398-y.

Kim JY, Cho TJ, Woo BH, Choi KU, Lee CH, Ryu MH, Park HR. 2012. Curcumin-induced autophagy contributes to the decreased survival of oral cancer cells. *Archives of Oral Biology*, 57(8): 1018–1025. DOI: 10.1016/j.archoralbio.2012.04.005.

Kim SM. 2016. Human papilloma virus in oral cancer. *Journal of the Korean Association of Oral and Maxillofacial Surgeons*, 42(6): 327. DOI: 10.5125/jkaoms.2016.42.6.327.

Komlós G, Csurgay K, Horváth F, Pelyhe L, Németh Z. 2021. Periodontitis as a risk for oral cancer: a case–control study. *BMC Oral Health*, 21(1): 640. DOI: 10.1186/s12903-021-01998-y.

Kouketsu A, Sato I, Oikawa M, Shimizu Y, Saito H, Tashiro K, Yamashita Y, Takahashi T, Kumamoto H. 2019. Regulatory T cells and M2-polarized tumour-associated macrophages are associated with the oncogenesis and progression of oral squamous cell carcinoma. *International Journal of Oral and Maxillofacial Surgery*, 48(10): 1279–1288. DOI: 10.1016/j.ijom.2019.04.004.

Kusuma SMW, Utomo DH, Susanti R. 2022. Molecular mechanism of inhibition of cell proliferation: An in silico study of the active compounds in *Curcuma longa* as an anticancer. *Journal of Tropical Biodiversity and Biotechnology*, 7(3): 74905. DOI: 10.22146/jtbb.74905.

Lee AY, Fan CC, Chen YA, Cheng CW, Sung YJ, Hsu CP, Kao TY. 2015. Curcumin Inhibits invasiveness and epithelial-mesenchymal transition in oral squamous cell carcinoma through reducing matrix metalloproteinase 2, 9 and modulating p53-E-cadherin pathway. *Integrative Cancer Therapies*, 14(5): 484–490. DOI: 10.1177/1534735415588930.

Lee J, Kim SS. 2009. The function of p27 KIP1 during tumor development. *Experimental and Molecular Medicine*, 41(11): 765. DOI: 10.3858/emm.2009.41.11.102.

Lee YJ, Hah YJ, Kang YN, Kang KJ, Hwang JS, Chung WJ, Cho KB, Park KS, Kim ES, Seo HY, Kim MK, Park KG, Jang BK. 2013. The Autophagy-related marker LC3 can predict prognosis in human hepatocellular carcinoma. *PLoS ONE*, 8(11): e81540. DOI: 10.1371/journal.pone.0081540.

Leite RB, Marinho AC, Costa BL, Laranjeira MB, Araújo KD, Cavalcanti A. 2021. The influence of tobacco and alcohol in oral cancer: literature review. *Jornal Brasileiro de Patologia e Medicina Laboratorial*, 57: 1–5. DOI: 10.5935/1676-2444.20210001.

Liao F, Liu L, Luo E, Hu J. 2018. Curcumin enhances anti-tumor immune response in tongue squamous cell carcinoma. *Archives of Oral Biology*, 92: 32–37. DOI: 10.1016/j.archoralbio.2018.04.015.

Liao S, Xia J, Chen Z, Zhang S, Ahmad A, Miele L, Sarkar FH, Wang Z. 2011. Inhibitory effect of curcumin on oral carcinoma CAL-27 cells via suppression of Notch-1 and NF-κB signaling pathways. *Journal of Cellular Biochemistry*, 112(4): 1055–1065. DOI: 10.1002/jcb.23019.

Lin YC, Chen HW, Kuo YC, Chang YF, Lee YJ, Hwang JJ. 2010. Therapeutic efficacy evaluation of curcumin on human oral squamous cell carcinoma xenograft using multimodalities of molecular imaging. *The American Journal of Chinese Medicine*, 38(02): 343–358. DOI: 10.1142/S0192415X10007890.

Liu S, Liu D, Li J, Zhang D, Chen Q. 2016. Regulatory T cells in oral squamous cell carcinoma. *Journal of Oral Pathology & Medicine*, 45(9): 635–639. DOI: 10.1111/jop.12445.

Liu T, Long T, Li H. 2021. Curcumin suppresses the proliferation of oral squamous cell carcinoma through a specificity protein 1/nuclear factor-κB-dependent pathway. *Experimental and Therapeutic Medicine*, 21(3): 202. DOI: 10.3892/etm.2021.9635.

Ma C, Zhuang Z, Su Q, He J, Li H. 2020. Curcumin has anti-proliferative and pro-apoptotic effects on tongue cancer in vitro: A Study with bioinformatics analysis and in vitro experiments. *Drug Design, Development and Therapy*, 14: 509–518. DOI: 10.2147/DDDT.S237830.

Maimela NR, Liu S, Zhang Y. 2019. Fates of CD8+ T cells in tumor microenvironment. *Computational and Structural Biotechnology Journal*, 17: 1–13. DOI: 10.1016/j.csbj.2018.11.004.

Masucci MT, Minopoli M, Di Carluccio G, Motti ML, Carriero MV. 2022. Therapeutic strategies targeting urokinase and its receptor in cancer. *Cancers*, 14(3): 498. DOI: 10.3390/cancers14030498.

Mathur R, Singhavi HR, Malik A, Nair S, Chaturvedi P. 2019. Role of Poor oral hygiene in causation of oral cancer—a review of literature. *Indian Journal of Surgical Oncology*, 10(1): 184–195. DOI: 10.1007/s13193-018-0836-5.

Maulina T, Hadikrishna I, Hardianto A, Sjamsudin E, Pontjo B, Yusuf HY. 2019. The therapeutic activity of curcumin through its anti-cancer potential on oral squamous cell carcinoma: A study on Sprague Dawley rat. *SAGE Open Medicine*, 7: 205031211987598. DOI: 10.1177/2050312119875982.

Mirzaei S, Saghari S, Bassiri F, Raesi R, Zarrabi A, Hushmandi K, Sethi G, Tergaonkar V. 2022. NF-κB as a regulator of cancer metastasis and therapy response: A focus on epithelial–mesenchymal transition. *Journal of Cellular Physiology*, 237(7): 2770–2795. DOI: 10.1002/jcp.30759.

Moon JB, Lee KH, Kim IR, Kim GC, Kwak HH, Park BS. 2014. Mechanism Underlying curcumin-induced apoptosis and cell cycle arrest on SCC25 Human tongue squamous cell carcinoma cell line. *International Journal of Oral Biology*, 39(1): 23–33. DOI: 10.11620/IJOB.2014.39.1.023.

Musgrove EA, Caldon CE, Barraclough J, Stone A, Sutherland RL. 2011. Cyclin D as a therapeutic target in cancer. *Nature Reviews Cancer*, 11(8): 558–572. DOI: 10.1038/nrc3090.

Nandini DB, Rao RS, Hosmani J, Khan S, Patil S, Awan KH. 2020. Novel therapies in the management of oral cancer: An update. *Disease-a-Month*, 66(12): 101036. DOI: 10.1016/j.disamonth.2020.101036.

Nasry W, Rodriguez-Lecompte J, Martin C. 2018. Role of COX-2/PGE2 mediated inflammation in oral squamous cell carcinoma. *Cancers*, 10(10): 348. DOI: 10.3390/cancers10100348.

Ohnishi Y, Sakamoto T, Zhengguang L, Yasui H, Hamada H, Kubo H, Nakajima M. 2020. Curcumin inhibits epithelial-mesenchymal transition in oral cancer cells via c-Met blockade. *Oncology Letters*, 19(6): 4177–4182. DOI: 10.3892/ol.2020.11523.

Patel BP, Shah SV, Shukla SN, Shah PM, Patel PS. 2007. Clinical significance of MMP-2 and MMP-9 in patients with oral cancer. *Head & Neck*, 29(6): 564–572. DOI: 10.1002/hed.20561.

Poulopoulos A, Papadopoulos P, Andreadis D. 2017. Chemotherapy: oral side effects and dental interventions. A review of the literature. *Stomatological Disease and Science*, 1: 35–49. DOI: 10.20517/2573-0002.2017.03.

Quintero-Fabián S, Arreola R, Becerril-Villanueva E, Torres-Romero JC, Arana-Argáez V, Lara-Riegos J, Ramírez-Camacho MA, Alvarez-Sánchez

ME. 2019. Role of matrix metalloproteinases in angiogenesis and cancer. *Frontiers in Oncology*, 9: 1370. DOI: 10.3389/fonc.2019.01370.

Rajabi M, Mousa S. 2017. The role of angiogenesis in cancer treatment, *Biomedicines*, 5(4): 34. DOI: 10.3390/biomedicines5020034.

Ramos-Garcia P, Roca-Rodriguez MDM, Aguilar-Diosdado M, Gonzalez-Moles MA. 2021. Diabetes mellitus and oral cancer/oral potentially malignant disorders: A systematic review and meta-analysis. *Oral Diseases*, 27(3): 404–421. DOI: 10.1111/odi.13289.

Rathore S, Mukim M, Sharma P, Devi S, Nagar JC, Khalid M. 2020. Curcumin: A review for health benefits. *International Journal of Research and Review*, 7(1): 273–290.

Rivera C. 2015. Essentials of oral cancer. *International Journal of Clinical and Experimental Pathology*, 8(9): 11884–11894.

Rocha PHP, Reali RM, Decnop M, Souza SA, Teixeira LAB, Júnior AL, Sarpi MO, Cintra MB, Pinho MC, Garcia MRT. 2022. Adverse radiation therapy effects in the treatment of head and neck tumors. *RadioGraphics*, 42(3): 806–821. DOI: 10.1148/rg.210150.

Santos EM, Rodrigues de Matos F, Freitas de Morais E, Galvão HC, de Almeida Freitas R. 2019. Evaluation of Cd8+ and natural killer cells defense in oral and oropharyngeal squamous cell carcinoma. *Journal of Cranio-Maxillofacial Surgery*, 47(4): 676–681. DOI: 10.1016/j.jcms.2019.01.036.

Sarode G, Maniyar N, Sarode SC, Jafer M, Patil S, Awan KH. 2020. Epidemiologic aspects of oral cancer. *Disease-a-Month*, 66(12): 100988. DOI: 10.1016/j.disamonth.2020.100988.

Shakeri A, Ward N, Panahi Y, Sahebkar A. 2019. Anti-angiogenic activity of curcumin in cancer therapy: A narrative review. *Current Vascular Pharmacology*, 17(3): 262–269. DOI: 10.2174/1570161116666180209113014.

Shakeri A, Cicero AFG, Panahi Y, Mohajeri M, Sahebkar A. 2019. Curcumin: A naturally occurring autophagy modulator. *Journal of Cellular Physiology*, 234(5): 5643–5654. DOI: 10.1002/jcp.27404.

Sharma K, Jasuja S, Jain M, Singh Y. 2023. Assessment of adverse drug reactions in oral cancer patients receiving chemotherapy treatment at tertiary care centres in North-Western India. *Scripta Medica*, 54(1): 45–51. DOI: 10.5937/scriptamed54-42967.

Shimizu S, Hiratsuka H, Koike K, Tsuchihashi K, Sonoda T, Ogi K, Miyakawa A, Kobayashi J, Kaneko T, Igarashi T, Hasegawa T, Miyazaki A. 2019. Tumor-infiltrating CD8 $^+$ T-cell density is an independent prognostic marker for oral squamous cell carcinoma. *Cancer Medicine*, 8(1): 80–93. DOI: 10.1002/cam4.1889.

Śledzińska A, Śledzińska P, Bebyn M, Komisarek O. 2023. Chemotherapy-induced oral complications and prophylaxis strategies. *Cancer Investigation*, 41(5): 432–455. DOI: 10.1080/07357907.2023.2188558.

Song H, Wan Y, Xu YY. 2015. Betel quid chewing without tobacco: A meta-analysis of carcinogenic and precarcinogenic effects. *Asia Pacific Journal of Public Health*, 27(2): NP47–NP57. DOI: 10.1177/1010539513486921.

Speicher DJ, Ramirez-Amador V, Dittmer DP, Webster-Cyriaque J, Goodman MT, Moscicki AB. 2016. Viral infections associated with oral cancers and diseases in the context of HIV: a workshop report. *Oral Diseases*, 22(S1): 181–192. DOI: 10.1111/odi.12418.

Tolentino Ede S, Centurion BS, Ferreira LH, Souza AP, Damante JH, Rubira-Bullen IR. 2011. Oral adverse effects of head and neck radiotherapy: literature review and suggestion of a clinical oral care guideline for irradiated patients. *Journal of applied oral science: revista FOB*, 19(5): 448–454. DOI: 10.1590/s1678-77572011000500003.

WHO [World Health Organization] (2020) *Oral Health*. Link: https://www.who.int/news-room/

fact-sheets/detail/oral-health. Download: 11 December 2023.

Wu Z, Wu J, Zhao Q, Fu S, Jin J. 2020. Emerging roles of aerobic glycolysis in breast cancer', *Clinical and Translational Oncology*, 22(5): 631–646. DOI: 10.1007/s12094-019-02187-8.

Xiao C, Wang L, Zhu L, Zhang C, Zhou J. 2014. Curcumin inhibits oral squamous cell carcinoma SCC-9 cells proliferation by regulating miR-9 expression. *Biochemical and Biophysical Research Communications*, 454(4): 576–580. DOI: 10.1016/j.bbrc.2014.10.122.

Yang J, Wang ZY, Huang L, Yu TL, Wan SQ, Song J, Zhang BL, Hu M. 2021. Do betel quid and areca nut chewing deteriorate prognosis of oral cancer? A systematic review, meta-analysis, and research agenda. *Oral Diseases*, 27(6): 1366–1375. DOI: 10.1111/odi.13456.

Yang YSH, Li ZL, Shih YJ, Bennett JA, Whang-Peng J, Lin HY, Davis PJ, Wang K. 2019. Herbal Medicines attenuate PD-L1 expression to induce anti-proliferation in obesity-related cancers. *Nutrients*, 11(12): 2979. DOI: 10.3390/nu11122979.

Yoshida R, Nagata M, Nakayama H, Niimori-Kita K, Hassan W, Tanaka T, Shinohara M, Ito T. 2013. The pathological significance of Notch1 in oral squamous cell carcinoma. *Laboratory Investigation*, 93(10): 1068–1081. DOI: 10.1038/labinvest.2013.95.

Yu T, Liu K, Wu Y, Fan J, Chen J, Li C, Yang Q, Wang Z. 2014. MicroRNA-9 inhibits the proliferation of oral squamous cell carcinoma cells by suppressing expression of CXCR4 via the Wnt/β-catenin signaling pathway. *Oncogene*, 33(42): 5017–5027. DOI: 10.1038/onc.2013.448.

Zhai BT, Tian H, Sun J, Zou JB, Zhang XF, Cheng JX, Shi YJ, Fan Y, Guo DY. 2022. Urokinase-type plasminogen activator receptor (uPAR) as a therapeutic target in cancer', *Journal of Translational Medicine*, 20(1): 135. DOI: 10.1186/s12967-022-03329-3.

Zhang FF, Cudhea F, Shan Z, Michaud DS, Imamura F, Eom H, Ruan M, Rehm CD, Liu J, Du M, Kim D, Lizewski L, Wilde P, Mozaffarian D. 2019. Preventable Cancer burden associated with poor diet in the United States. *JNCI Cancer Spectrum*, 3(2): pkz034. DOI: 10.1093/jncics/pkz034.

Zhang N, Li L, Wang J, Cao M, Liu G, Xie G, Yang Z, Li Y. 2015. Study of autophagy-related protein light chain 3 (LC3)-II expression levels in thyroid diseases. *Biomedicine & Pharmacotherapy*, 69: 306–310. DOI: 10.1016/j.biopha.2014.12.021.

Zhen L, Fan D, Yi X, Cao X, Chen D, Wang L. 2014. Curcumin inhibits oral squamous cell carcinoma proliferation and invasion via EGFR signaling pathways. *International Journal of Clinical and Experimental Pathology*, 7(10): 6438–6446.

Zoi V, Galani V, Lianos GD, Voulgaris S, Kyritsis AP, Alexiou GA. 2021. The Role of Curcumin in Cancer Treatment. *Biomedicines*, 9(9): 1086. DOI: 10.3390/biomedicines9091086.