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

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**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 hematolgy 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.

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

<table>
<thead>
<tr>
<th>Element</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>OC cell line</td>
</tr>
<tr>
<td>Interventions</td>
<td>OC cells-induced animal model</td>
</tr>
<tr>
<td>Comparison</td>
<td>The curcumin compound derived from <em>Curcuma longa</em> or <em>Curcuma</em> spp.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Anticancer effects and mechanisms of action</td>
</tr>
</tbody>
</table>

**Table 2** Keywords used in each database in literature searches.

<table>
<thead>
<tr>
<th>Database</th>
<th>Keywords</th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed</td>
<td>(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]))</td>
</tr>
<tr>
<td>ScienceDirect</td>
<td>Title, abstract, keywords: &quot;curcumin&quot; AND (&quot;turmeric&quot;) OR (&quot;Curcuma longa&quot;) AND (&quot;oral cancer&quot; OR &quot;oral squamous cell carcinoma&quot; OR &quot;tongue squamous cell carcinoma&quot;)</td>
</tr>
<tr>
<td>Google Scholar</td>
<td>&quot;curcumin&quot; “turmeric” “Curcuma longa” &quot;anticancer&quot; “oral cancer” “oral squamous cell carcinoma” “tongue squamous cell carcinoma&quot;</td>
</tr>
</tbody>
</table>
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
Table 3 Summary of the anticancer activity of curcumin.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study methods</th>
<th>Cell/animal model</th>
<th>Dosage</th>
<th>Duration</th>
<th>Control</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin et al. (2010)</td>
<td><strong>In vitro</strong></td>
<td>Human OSCC SAS cells</td>
<td>1, 3, 5, 7, 9, 10, 20, 25, and 30 µM</td>
<td>24 h</td>
<td>Untreated</td>
<td>Induces apoptosis. Suppresses proliferation and growth of OC.</td>
</tr>
<tr>
<td></td>
<td><strong>In vivo</strong></td>
<td>SAS cells-inoculated NOD/SCID mice</td>
<td>35 mg/kg per day, 70 mg/kg every other day, and 100 mg/kg every third day.</td>
<td>26 days</td>
<td>0.025 N NaOH</td>
<td></td>
</tr>
<tr>
<td>Liao et al. (2011)</td>
<td><strong>In vitro</strong></td>
<td>Human OSCC CAL-27 cells</td>
<td>2.5, 5, and 7.5 µM</td>
<td>24, 8, and 72 h</td>
<td>DMSO</td>
<td></td>
</tr>
<tr>
<td>Kim et al. (2012)</td>
<td><strong>In vitro</strong></td>
<td>OSCC YD10B cells</td>
<td>1, 5, 10, 20, and 40 µM</td>
<td>24 h</td>
<td>Untreated</td>
<td>Induces apoptosis through the autophagic vacuoles generation and conversion of LC3-I to LC3-II. Induces ROS production.</td>
</tr>
<tr>
<td>Moon et al. (2014)</td>
<td><strong>In vitro</strong></td>
<td>Human TSCC SCC-25 cells</td>
<td>5-50 µM</td>
<td>48 h</td>
<td>Untreated</td>
<td>Induces apoptosis via proteasome, mitochondrial, and caspase cascades. Inhibits proliferation.</td>
</tr>
<tr>
<td>Xiao et al. (2014)</td>
<td><strong>In vitro</strong></td>
<td>Human TSCC SCC-9 cells</td>
<td>20, 40, and 60 µM</td>
<td>72 h</td>
<td>Untreated</td>
<td>Inhibits proliferation. Regulates miR-9. Suppresses Wnt/β-catenin signaling.</td>
</tr>
<tr>
<td>Lee et al. (2015)</td>
<td><strong>In vitro</strong></td>
<td>OSCC SCC-25 cells</td>
<td>2.5, 5, 10, 15, and 30 µM</td>
<td>24 h</td>
<td>Untreated</td>
<td></td>
</tr>
<tr>
<td>Liao et al. (2018)</td>
<td><strong>In vitro</strong></td>
<td>Human TSCC CAL-27 and FaDu cells</td>
<td>5 and 10 µM</td>
<td>6, 12, 24, and 48 h</td>
<td>Untreated</td>
<td>Inhibits PD-L1 and p-STAT3Y705.</td>
</tr>
<tr>
<td></td>
<td><strong>In vivo</strong></td>
<td>4NQO mice</td>
<td>Not mentioned</td>
<td>4 weeks</td>
<td>DMSO</td>
<td></td>
</tr>
<tr>
<td>Elwahab et al. (2019)</td>
<td><strong>In vitro</strong></td>
<td>HNSCC HEP-2 cells</td>
<td>5-10,000 mM</td>
<td>24 h</td>
<td>Untreated</td>
<td>Inhibits proliferation. Indicates cell cycle arrest, apoptosis, and necrosis. Decreases NF-κB and COX-2 expression.</td>
</tr>
<tr>
<td>Maulina et al. (2019)</td>
<td><strong>In vivo</strong></td>
<td>OSCC-induced Sprague Dawley rats</td>
<td>80 mg/kg thrice per day</td>
<td>4 weeks</td>
<td>No curcumin use</td>
<td></td>
</tr>
<tr>
<td>Ma et al. (2020)</td>
<td><strong>In vitro</strong></td>
<td>Human TSCC CAL-27 cells</td>
<td>10, 25, 50, and 100 µM</td>
<td>6, 16, and 24 h</td>
<td>Untreated</td>
<td>Inhibits proliferation and migration. Induces apoptosis.</td>
</tr>
<tr>
<td>Ohnishi et al. (2020)</td>
<td><strong>In vitro</strong></td>
<td>Human TSCC HSC-4 and Ca9-22 cells</td>
<td>10-20 µM</td>
<td>48 h</td>
<td>FBS</td>
<td>Inhibits HGF-induced EMT and cell motility through c-Met blockade.</td>
</tr>
<tr>
<td>Liu et al. (2021)</td>
<td><strong>In vitro</strong></td>
<td>OSCC HSC-3 and CAL-33 cells</td>
<td>5-20 µM</td>
<td>24 and 48 h</td>
<td>DMSO</td>
<td>Decreases the expression of Sp1, p65, and HSF1. Decreases NF-κB activity.</td>
</tr>
<tr>
<td>Jayaraman et al. (2024)</td>
<td><strong>In vitro</strong></td>
<td>OSCC HSC-3 cells</td>
<td>25, 50, 75, 100, 125, and 150 µM</td>
<td>24 and 48 h</td>
<td>Untreated</td>
<td>Inhibits aerobic glycolysis. Regulates the cell cycle. Induces apoptosis.</td>
</tr>
</tbody>
</table>
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-STAT3Y705 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-STAT3Y705 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-\( \kappa \)B) 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-\( \kappa \)B 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 \( \mu \)M for 16 and 24 h \( (p<0.001) \), as well as at a dose of 50 \( \mu \)M 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-\( \kappa \)B (Mirzaei et al., 2022); thus, cancer therapy targeting NF-\( \kappa \)B/EMT inhibition in OC has promising potential. Related to this, a study in CAL-27 cells stated that curcumin notably suppresses NF-\( \kappa \)B 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-\( \kappa \)B \( (p<0.01) \) 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-Fabían 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 p27KIP1 protein which acts as a CDK inhibitor (Moon et al., 2014). Consequently, increasing the p27KIP1 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
Effect of curcumin on oral cancer

(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.

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**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.

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