Pathology - Research and Practice 275 (2025) 156227

Contents lists available at ScienceDirect

Pathology - Research and Practice

journal homepage: www.elsevier.com/locate/prp

Review

Mechanistic signaling pathways of flavonoid-induced oral squamous cell carcinoma therapy: Clinical evidence and therapeutic application

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ARTICLE INFO

Keywords:
Flavonoids
Oral squamous cell carcinoma
Cancer
Clinical application

ABSTRACT

Flavonoids, a class of plant-derived polyphenolic chemicals, are being explored as potential candidates for oral squamous cell carcinoma (OSCC) therapy due to their anti-cancer properties. The review explores flavonoids' potential therapeutic applications and their impact on OSCC, evaluating clinical evidence and investigating flavonoid-induced therapy mechanisms. Recent research focusing on experimental and clinical investigations has been thoroughly analyzed to understand the flavonoid mechanisms of action in OSCC. The review also evaluated the efficacy and safety of flavonoid therapy in treating angiogenesis, invasion, apoptosis, and cell proliferation through clinical trials and case studies. Flavonoids exhibit anti-cancer actions in OSCC by modulating essential cell growth and survival signaling pathways like PI3K/Akt, MAPK, and NF-κB. Furthermore, the study suggests that targeting matrix metalloproteinases and other factors can prevent cancer cell invasion and metastasis and induce apoptosis through intrinsic and extrinsic pathways. Flavonoids are promising therapies for treating OSCC due to their diverse modes of action, safety profile, and ability to impact critical cancer pathways. They can reduce side effects and improve patient outcomes. However, clinical trials reveal varied outcomes, necessitating further research to enhance patient selection, dosage, and formulation. Further mechanistic studies and clinical trials are needed to enhance their therapeutic efficacy.

1. Introduction

Oral squamous cell carcinoma (OSCC) (Fig. 1) is the most prevalent oral cancer, affecting 95 % of all malignancies in the oral cavity. Men are twice as affected as women, especially those older than 50. The oral cavity floor and tongue lesions affect the retromolar triangle, palate, and gingiva. The five-year survival rate varies from 20 % to 60 %. Early diagnosis is challenging due to low detection rates and difficulty

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https://doi.org/10.1016/j.prp.2025.156227
Received 5 June 2025; Received in revised form 24 August 2025; Accepted 8 September 2025
Available online 9 September 2025

distinguishing between reactive and metastatic lymph nodes. Imaging studies are used to study OSCC, but early interpretation can be challenging [1]. Over 90 % of oral cancer cases are classified as OSCC. Oral cancer is a prevalent global issue, with over 500,000 new cases reported annually. OSCC, a condition affecting the lower lip, mouth floor, and the lateral edge of the tongue, can manifest in various anatomical features of the oral cavity. Various risk factors, such as prolonged tobacco use and heavy alcohol consumption, influence the development of OSCC. Genetic mutations in epithelial cells lead to the formation of neoplastic sites in the oral cavity or, in most cases, the growth of precancerous lesions. Healthcare professionals utilize the TNM classification system for oral cancer staging to diagnose and conduct routine clinical evaluations. This classification provides essential information about the treatment mode, which can be invasive (like surgery) or noninvasive (like radiotherapy) [2]. Oral cancer is a significant health concern in many countries, as it is the primary cause of death from oral disorders. In 2018, 177,384 deaths and 354,864 new cases occurred worldwide [3]. Alcohol and tobacco addiction are prevalent risk factors for oral cancer. Conventional OSCC, a prevalent head and neck malignancy, is increasing globally, particularly in younger age groups [4,5]. One of the most significant global risk factors for early death is tobacco use. Tobacco has over 60 hazardous substances that can infiltrate the body's different systems. More than 90 % of oral cancers are of the pathogenic kind known as OSCC. Tobacco use is linked to OSCC, with complex carcinogenic pathways suggested by various scientific, clinical, and epidemiological evidence [6]. A study on OSCC found that inflammatory bacterial features were enriched in the tissues. The study used 27 fibroepithelial polyps (FEP) controls from Sri Lanka and 25 OSCC patients. Lower species richness and diversity were found in OSCC tissues, with higher abundances of proinflammatory bacterial characteristics. The functional level of the bacteriome linked to OSCC was consistent, suggesting that the bacteriome linked to OSCC is inflammatory. The study highlights the importance of considering functional redundancy in microbiome studies on oral cancer [7]. Flavonoids in plants like tea, wine, fruits, cereals, nuts, and vegetables have been linked to long-term mortality effects. They have therapeutic biological effects and are currently being researched for their potential in cancer prevention. Studies show flavonoids significantly impact chemotherapy and chemoprevention, making them a reliable substitute for current therapeutic approaches [8]. Plant-based flavonoids are polyphenolic chemicals with a wide range of biological properties, such as anti-inflammatory and anti-cancer effects. They prevent various forms of cancer through mechanisms like apoptosis activation, cell cycle inhibition, and intracellular pathway modification. Over the past decade, significant research has explored flavonoids as potential anticancer therapy candidates due to their diverse biological activity and safe toxicological profile. Studies have shown that flavonoids have varying effects depending on their target cancer cell type [9]. Another study aimed to identify and relocate medications harmful to treatment-resistant OSCC. Luteolin, when combined with metixene hydrochloride and nitazoxanide, was found to be a potent cytotoxic agent against oral cancer cells. Its low toxicity and excellent efficacy make it a potential cytotoxic and adjuvant therapy for oral cancer [10].

OSCC is linked to oxidative damage. Researchers studied quercetin's effectiveness as a chemoprotective drug against 4 NQO-induced OSCC in mice. Doses of 10 and 100 mg/kg/day were administered, and tumor markers mutant p53 and proliferating cell nuclear antigen were evaluated [11]. Kim et al. investigated the anticancer properties of quercetin on OSCC cell lines using various tests. Quercetin inhibited OSCC cell survival by causing a cell cycle arrest at the G2/M phase, inhibiting cell migration via EMT and MMP, and reducing TGF-β1-induced EMT in HaCaT cells. It may offer a novel pharmaceutical strategy for managing OSCCs [12]. Furthermore, Fan et al. found that S100A7, a protein in cancer cells, might stimulate EMT signaling and promote tumor cell metastasis. Quercetin and luteolin can lower S100A7, p-Src, and p-Stat3 levels in A431-III cells. Treatment with inhibitors and flavonoids reduced EMT indicators, such as Twist and E-cad protein levels. Treatment with S3I-201, luteolin, and quercetin in zebrafish larvae reduced

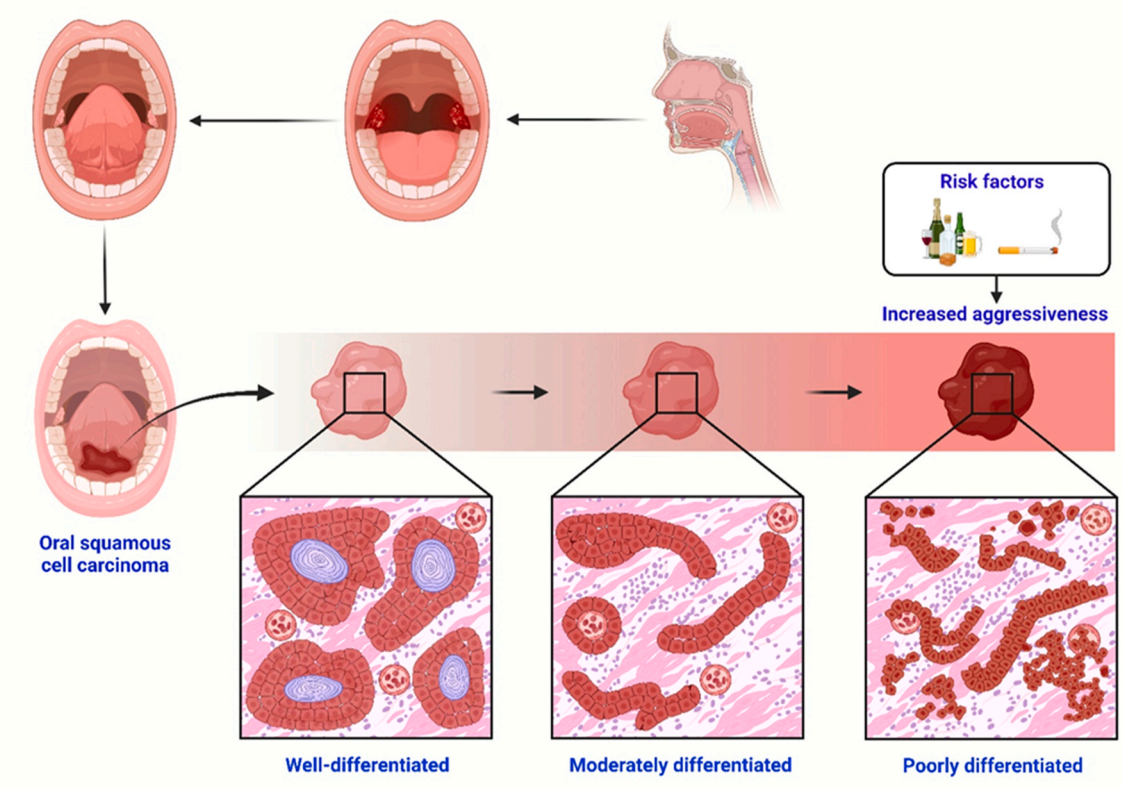

Fig. 1. Illustration of the histopathology of oral squamous cell carcinoma.

tumor cell metastasis, suggesting that luteolin and quercetin may suppress Src/Stat3/S100A7 signaling [13]. In addition, Zhang et al. investigated the impact of quercetin on OSCC chemoprevention. The research involved hamsters exposed to DMBA, which caused cancer, and quercetin administration. Quercetin significantly decreased OSCC incidence and severity of dysplasia and hyperplasia, caused apoptosis, and reduced NF-κB p50, p65, and Bcl-2 gene expression. It also reduces body weight loss. It has potential as an OSCC chemoprevention strategy [14]. Fisetin therapy reduced proliferation and apoptosis in OSCC cells by repressing PAK4 expression and inhibiting signaling pathways. This could offer a treatment approach for human OSCC, potentially inhibiting differentiation and cell death via PAK4 signaling pathways [15]. Isoorientin inhibits JAK/STAT3 and Wnt/β-catenin signaling in OSCC cell lines, attenuating cell stemness and epithelial-mesenchymal transition potential. It decreased β-catenin colocalization and increased the cytotoxic effects of cisplatin. Combining isoorientin with cisplatin therapies may enhance the anticancer impact. Isoorientin's ability to disrupt the Wnt/β-catenin/STAT3 signaling pathway may be useful for halting OSCC recurrence and metastasis while improving long-term survival [16]. EGCG has been shown to inhibit cancer cell growth. This study assessed EGCG's therapeutic potential for treating OSCC in vivo and in vitro. EGCG significantly inhibited HSC-3 cell survival, increased apoptotic cells, and decreased mouse tumor size. It could be a unique oral cancer treatment strategy [17].

Moreover, Pei et al. investigated the impact of apigenin in combination with low OXA concentrations on OSCC. Apigenin inhibits the protumor metastatic effect of low OXA concentrations by downregulating the expression of LINC00857 [18]. Another study found that hesperidin, a drug that inhibits the expression of programmed death-L1 (PD-L1) in oral cancer cells, significantly reduces cell migration and proliferation. This is achieved by phosphorylating STAT1 and STAT3, which lowers PD-L1 protein expression. Hesperidin could be used as an adjuvant treatment for oral cancer, potentially enhancing cancer cell survival and evasion of anti-tumor immunity [19]. Additionally, Kawaguchi et al. investigated the role of CD169 + macrophages in OSCC and the anti-tumor effects of naringenin, which activates these cells. Results show that higher CD169 + macrophage levels in local lymph nodes and higher CD8 + cell counts within tumor sites are associated with better prognosis and higher CD8 + cell counts. Naringenin administration inhibits tumor growth and increases CD169, IL-12, and CXCL10 mRNA levels [20]. Furthermore, Silibinin is cytotoxic to SCC-25 cells, primarily due to its activation of the mitochondrial pathway, including caspases 9 and 3, and cytochrome c. It can be a viable medication for treating oral squamous carcinoma [21]. The review highlights flavonoids' potential therapeutic applications in treating OSCC, evaluating clinical evidence, and flavonoid-induced therapy mechanisms. Flavonoids are promising therapeutic agents for treating OSCC, modulating cell growth, survival, and preventing invasion, metastasis, and causing apoptosis, demonstrating diverse modes of action and safety.

2. Etiology and risk factors

In the Western world, alcohol and tobacco use are the biggest risk factors for oral cancer [22,23]. The majority of oral cancer cases are linked to tobacco use. Smokers are six times more likely to develop mouth cancer compared to non-smokers. Additionally, alcohol drinkers have a six-fold increased risk of developing oral cancer compared to non-drinkers. The combination of alcohol and tobacco increases the risk of oral cancer fifteen times for users compared to non-users [24]. Drinking and smoking are the primary risk factors, but ethnic differences, like eating betel quid, should also be considered. Chewing betel quid is a common habit among Taiwanese and Indian communities, and it is linked to a markedly elevated risk of oral cancer [25–27]. The use of cannabis, areca nuts, and opioids has also been linked to an increased risk of mouth cancer [28]. The most prevalent form of OSCC is observed in older men, individuals from lower socioeconomic backgrounds, and ethnic minority groups. Some immune deficiencies include reduced DNA repair, carcinogen breakdown, trace elements, and deficiencies in vitamins A, E, and C. An insufficient immune response may predispose to the development of cancer. Kaposi's sarcoma is the most prevalent oral cancer among HIV-positive people. B-cell Hodgkin lymphoma patients have a high prevalence. Patients with HIV, those awaiting organ transplants, and those on immunosuppressive medication have a higher risk of developing OSCC [29–31]. Over 100 different HPV varieties have been identified based on their oncogenic potential and classified as low or high-hazard viruses. The most common virus type in most investigations was HPV16. The detection of HPV was more common in tonsils and oropharyngeal OSCCs than in other head and neck locations. Research on the role of HPV in mouth carcinogenesis has formed contradicting results. The reported range of infected neoplastic cell percentages is 0–90 %. Some studies suggest that HPV has a short-term role, while others suggest it's involved in the early stages of carcinogenesis. The viral protein E6 is believed to bind to p53 and initiate its degradation. The protein E7 interacts with the tumor suppressor retinoblastoma protein and inhibits its function. Oral cancer is a condition characterized by the abnormal functioning of essential oncosuppressive substances, leading to uncontrolled cell proliferation and disruptions. Currently, HPV-infected oral mucosal cells are believed to undergo malignant transformation only after exposure to chemical carcinogens like benzopyrene [32–36]. Infectious mononucleosis is known to be caused by the Epstein-Barr virus. The role of this substance in the malignant transformation of B cells is well-established, but its role in the pathophysiology of OSCC remains unknown. Oral epithelium malignant cells express the major oncoprotein of the latent phase (LMP-1) [35,37,38]. The HCV (hepatitis C virus) infection is more prevalent in individuals with the virus, leading to the development of OSCC. A Japanese study found a strong correlation between HCV infection and the development of primary OSCC and multiple primary carcinomas [39]. The risk factors of OSCC are depicted in Fig. 2.

3. Flavonoid in oral squamous cell carcinoma treatment: molecular mechanism of action

Flavonoids are utilized to prevent and treat OSCC (Table 1).

3.1. Quercetin

Quercetin (Fig. 3) can potentially treat OSCC by controlling the miR-22/WNT1/β-catenin pathway. This study aimed to explore its antitumor properties in OSCC. Quercetin therapy reduced cell viability and increased apoptosis in OSCC cells. It increased miR-22 expression and decreased WNT1 and β-catenin expression in OSCC cells. MiR-22 deletion reduced quercetin-mediated viability suppression and apoptosis. This provides insight into quercetin's molecular targets for OSCC treatment [40]. A study investigated the anticancer properties of quercetin on OSCC cell lines through various tests. Quercetin significantly reduced OSCC cell survival by causing a G2/M phase cell cycle arrest, preventing EMT and MMP cell migration, and reducing TGF-β1-induced EMT in HaCaT cells. It can potentially provide a novel pharmaceutical approach for managing OSCCs [12]. Researchers investigated quercetin's efficacy as a chemoprotective drug against 4 NQO-induced OSCC in mice, highlighting its potential in treating common head and neck cancer. The study evaluated mutant p53 and proliferating cell nuclear antigen tumor markers using 10 and 100 mg/kg/day doses [11]. Chen et al. found the influence of quercetin on OSCC growth and invasion and its impact on the miR-1254/CD36 signaling pathway. It significantly inhibited OSCC growth and invasion by up-regulating miR-1254 and down-regulating CD36, but overexpression of miR-1254 improved its ability to prevent CAL-27 cell invasion and survival [41]. OSCC is the most prevalent head and neck cancer, with minimal side effects. A study found that quercetin has anticancer effects in OSCC cells. In YD10B and YD38 OSCC cells,

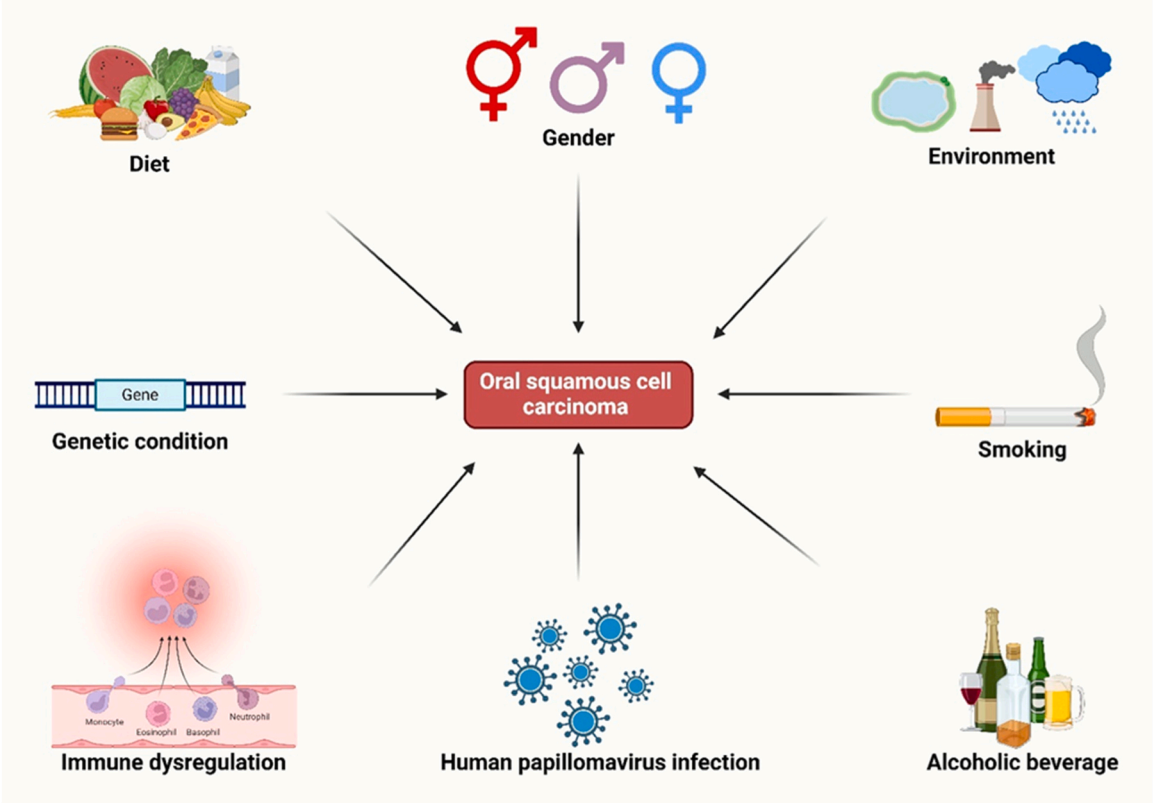

Fig. 2. Demonstration of the risk factors of oral squamous cell carcinoma.

quercetin reduced cell viability and caused G1 cell cycle arrest. The substance increased the annexin-V-positive cells and activated the p38 MAPK signaling pathway. Quercetin may offer a novel quercetin-based therapeutic approach for OSCC [57]. Additionally, Zhang et al. investigated the impact of flavonoid quercetin on OSCC chemoprevention. The research involved hamsters exposed to DMBA, which caused cancer, and quercetin administration. Quercetin significantly reduced the incidence and severity of hyperplasia and dysplasia in OSCC. It also caused apoptosis and reduced NF-κB p50, p65, and Bcl-2 gene expression. At high doses, quercetin raised Bax gene mRNA and protein expression. It also decreases body weight loss. Quercetin has potential as an OSCC chemoprevention strategy [14]. Chan et al. aimed to overcome erlotinib resistance in OSCC by identifying intracellular molecules and adjuvant chemicals. Two erlotinib-resistant cell lines were formed, ERL-R5 and ERL-R10. These lines showed increased proliferation, glucose usage, invasiveness, and EMT. Quercetin was sensitive to ERL-R cells and prevented cellular invasiveness. PKM2 is crucial in quercetin sensitivity and erlotinib resistance [58]. A mouse tumor model study found that quercetin, a flavonoid in various foods and plants, has anti-cancer properties. Quercetin inhibits NF-κB, which causes cisplatin-induced apoptosis in human OSCC cells. It also enhances apoptosis by activating caspase-8 and caspase-9. The findings support using cisplatin and quercetin in OSCC treatment [59].

Furthermore, Hu et al. explored the role of GTPase-activating protein SH3 domain-binding protein 1 (G3BP1) in developing OSCC. Overexpressing G3BP1 significantly increased glucose absorption, glycolysis, cell division, and YWHAZ production in CAL27 cells. Quercetin treatment also affected the activity of hexokinase, pyruvate kinase, lactate dehydrogenase, and proteins involved in glucose uptake, glycolysis, and lactate production. Quercetin blocks the G3BP1/YWHAZ axis, preventing glycolysis and cell growth [60]. A study using OSCC cell lines found that quercetin inhibited tumor growth by promoting ferroptosis, which depended on the mTOR/S6KP70 axis activity. It inhibited SLC7A11 expression, lipid peroxidation, and GSH levels while suppressing cell proliferation by targeting the mTOR/S6KP70 cascade [61]. Radi et al. assessed quercetin's chemopreventive effect on squamous cell cancer in male Syrian hamsters using Caspase-3. Five groups received different dosages of quercetin, with the highest mean area percent value (23.64) in Group V and the lowest mean percent (10.23) in Group III. The results showed that quercetin demonstrated apoptotic potential, indicating its potential as a useful chemopreventive drug to counteract carcinogenesis caused by DMBA in animal models [62]. OSCC is a potentially fatal condition that requires chemotherapy and radiation treatment. Herbal ingredients like piperine and quercetin can be utilized to treat oral cancer by encapsulating them into lipid matrix-mediated nanostructured lipid carriers (NLCs). These NLCs have shown promising results in encapsulating drugs with high efficiency and enhanced drug release. The dual drug-loaded NLCs exhibited higher IC50 concentrations than pure drug solutions and improved apoptosis. Optimized dual drug-loaded NLCs could be an improved method for combating oral cancer [63].

Moreover, Dong et al. explored the role of quercetin in oral cancer through molecular docking and network pharmacology analysis. 8971 targets were identified, with 190 quercetin action targets. 172 potential therapeutic targets were analyzed, yielding six core targets for quercetin treatment. The drug targets AKT1, HIF1A, HSP90AA1, MYC, PIK3R1, and SRC, with molecular docking scores below −0.7, indicating good compatibility with small molecules. This research offers new strategies for treating oral cancer and suggests quercetin as a multitarget drug [64]. Additionally, Tubtimsri et al. investigated the anti-growth, anti-migrative, and anti-invasive properties of quercetin. The study focused on treating KON oral cancer cells with quercetin and evaluating their vitality and morphology. Quercetin reduced cell viability, increased ROS production, and impacted cell stability and structure, thereby delaying the migration and invasion of KON cells. The study discovered that apoptosis and metastasis are triggered by upregulating BAX expression and inhibiting it by downregulating BCL-2/BCL-XL expression. The expression of MMP-2 and MMP-9 was found to be downregulated, while

Table 1
Flavonoids are used to prevent and treat OSCC.

Flavonoids	Signaling pathways	Findings	Ref.
Quercetin	microRNA−22/WNT1/β-catenin axis	Inhibited OSCC tumor growth by controlling the miR−22/WNT1/β-catenin pathway.	[40]
	EMT-mediated	Inhibited the survival and metastatic ability of OSCC cells through the EMT-mediated pathway.	[12]
	miR−1254/CD36 cascade	Impacted the growth and invasion of OSCC and the activity of the miR−1254/CD36 signaling pathway.	[41]
Epigallocatechin gallate	–	Reduced cell proliferation in vitro and in vivo by impacting apoptosis and cell cycle development.	[17]
	MAPK	Reduced invasion and migration of CAL−27 cells reduced MMP−2 protein expression and inhibited cell spread by lowering phosphorylated ERK, JNK, p38, and AKT proteins.	[42]
	–	Reduced RhoA activation in RhoA N19 and Q63E cells inhibited their invasive capability.	[43]
Luteolin	DNA damage	Potential cytotoxic and adjuvant therapy for treatment-resistant OSCC.	[10]
	Mitochondrial	Inhibited OSCC invasion and migration by suppressing transcription factors induced by the EMT and promoting apoptosis via the mitochondrial pathway.	[44]
Apigenin	–	Inhibited OSCC growth in vitro by causing cell cycle arrest and apoptosis.	[45]
	–	Inhibited LINC00857 levels, suppressing OSCC cancer cell metastasis induced by low-dose OXA.	[18]
Hesperidin	STAT1 and STAT3	Reduced the induction of PD-L1 protein in both cell lines by inactivating STAT1 and STAT3 signaling molecules.	[19]
	Apoptosis and inflammatory signaling-mediated mechanisms	Investigated the anticancer potential of hesperidin on human oral cancer cells by observing its ability to modulate pro-inflammatory and apoptotic signaling mechanisms.	[46]
Naringenin	ROS-mediated Bid and Bcl-xl	Promised treatment for oral cancer by inducing apoptotic cell death through modulation of the Bid and Bcl-xl signaling pathways.	[47]
Chrysin	Oxidative DNA damage	Stimulated cytotoxic activity causes increased ROS levels and oxidative DNA damage, intensifying cell death in OSCC cells when combined.	[48]
Kaempferol	ERK1/2 and the Activator Protein−1	Demonstrated anti-metastatic effect by suppressing SCC4 cell migration and invasion, reducing MMP−2 and TIMP−2 mRNA and protein levels, and inhibiting ERK1/2 phosphorylation.	[49]
Isorhamnetin	ERK/MAPK	Triggered proptosis, suggesting a potential therapeutic approach for OSCC.	[50]
Silibinin	Mitochondrial	Demonstrated to trigger apoptosis in human OSCC cells, suggesting its potential for treatment.	[21]
	JNK/c-Jun	Reduced oral cancer cell development by inducing apoptosis, G0/G1 arrest, ROS generation, and activating the JNK/c-Jun pathway.	[51]
Fisetin	PAK4	Showed a potential therapeutic strategy for human OSCC by targeting PAK4 signaling pathways.	[15]
	Met/Src	Inhibited tumor cell proliferation and induced apoptosis in human OSCC cells.	[52]
Baicalein	Sp1/NF-κB-dependent mechanism	Decreased NF-κB activity in OSCC cells and also inhibited the Sp1/NF-κB-dependent pathway, arresting the cell cycle in the G0/G1 phase.	[53]
	ERK-FAK	Demonstrated anti-proliferation effect and the ERK-FAK signal pathway in OSCC.	[54]
Genistein	MAP Kinase and Akt	Inhibited cell growth and decreased ERK and Akt phosphorylation.	[55]
Anthocyanins	–	Activated pyroptosis promotes the death of OSCC cells and inhibits tumor progression.	[56]

TIMP-1 expression was found to be elevated. Quercetin has the potential to be a co-chemotherapeutic and prophylactic treatment for oral cancer patients, potentially eliminating oral cancer cells [65]. Abnormal activation of the epidermal growth factor receptor in head and neck squamous cell carcinomas often leads to low survival and poor prognosis. Quercetin has antitumorigenesis properties, with FOXO1 playing a critical role in quercetin-induced growth suppression. Treatment with quercetin inhibited EGFR-overexpressing oral cancer cells, causing G2 arrest and death. FOXO1 knockdown mitigated effects on p21 and FasL expression [66]. Quercetin, known for its antioxidant, immunomodulatory, antiviral, antihistamine, and anti-inflammatory properties, was tested on KB/VCR oral cancer cells to assess its anticancer efficacy. It inhibited cell migration and invasion, suppressed proliferation, and stimulated Bcl-2 and Caspase-3 expression. It also inhibited P-gp expression, reversing MDR. Combining quercetin with vincristin increased apoptosis and decreased proliferation, suggesting quercetin as a potential treatment for various malignancies [67].

In addition, Ma et al. explored the impact of quercetin on apoptosis in human oral cancer cells through various techniques. Despite no evidence supporting quercetin's ability to cause apoptosis, the results show that quercetin increases cell death rates with treatment duration. Western blotting revealed that quercetin increases the expression of apoptotic proteins, while confocal microscopy showed that quercetin increases apoptotic pathways-related genes. Quercetin has the potential to be a novel anti-cancer drug for treating oral cancer, a leading global cause of cancer-related death [68]. Another study on dietary

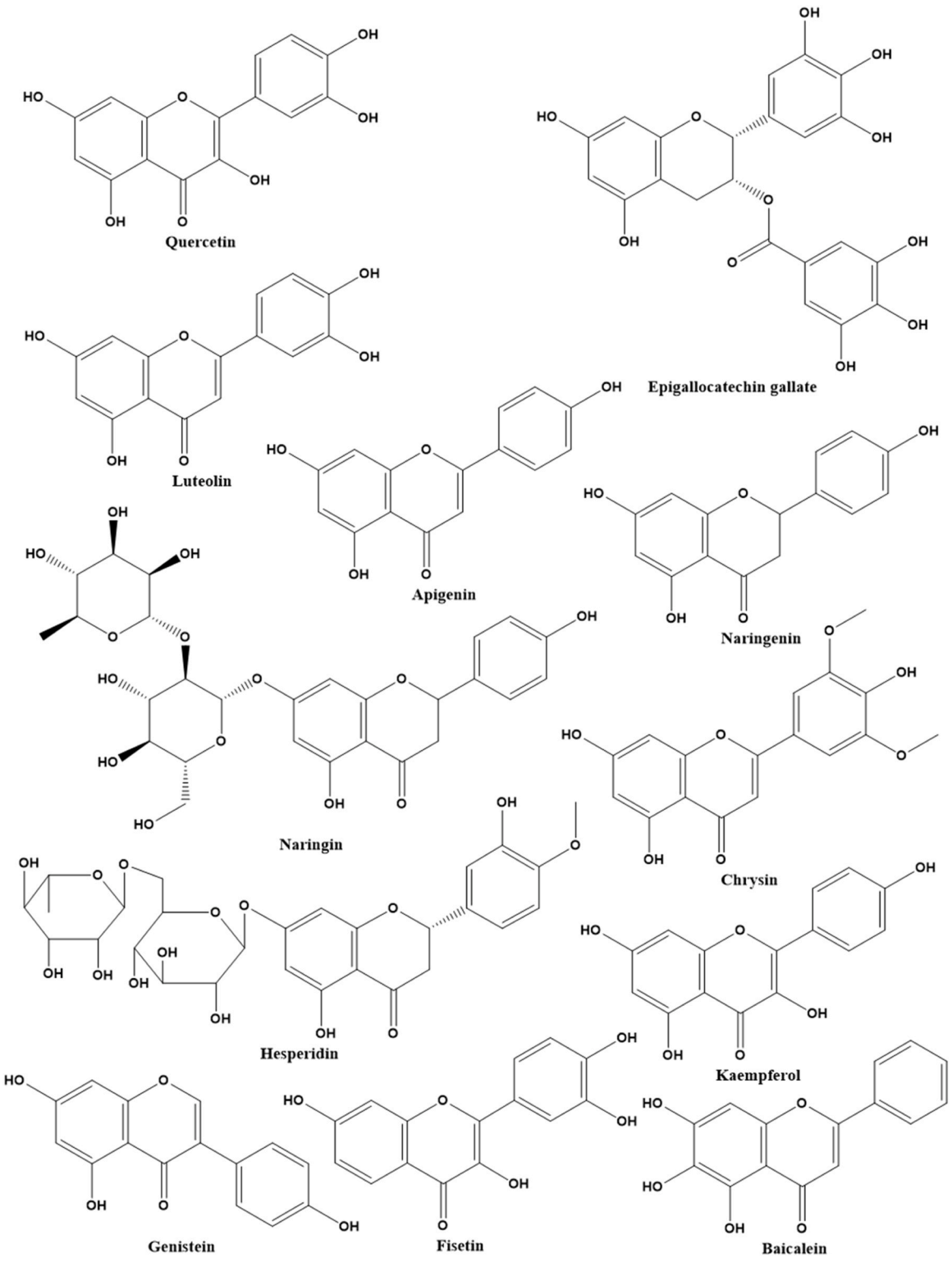

Fig. 3. Chemical structures of flavonoids that are used to treat OSCC.

polyphenols on oral cancer cells, specifically flavonoids. Quercetin inhibits cell growth, DNA synthesis, and cell cycle regulation in human oral squamous carcinoma SCC-9 cells. It caused necrosis at 24 and 48 h and apoptosis at 72 h. It also inhibited thymidylate synthase (TS), a crucial S-phase enzyme, leading to cell death. The findings support quercetin's potential for oral cancer protection [69]. Furthermore, Huang et al. found the pharmacological effects of quercetin, a polyphenolic flavonoid found in Chinese herbal medicine, on the apoptosis of the tongue SCC-derived SAS cell line. The study demonstrated quercetin's impact on SAS cell survival, mitochondrial-dependent apoptotic signals, and increased apoptosis-related Annexin V-FITC fluorescence and caspase-3 activity. The substance increased protein production in SAS cells, which was reduced by pretreatment with a JNK inhibitor, SP600125. However, inhibitors PD98059 and LiCl were able to stop quercetin-induced phosphorylation, suggesting quercetin can trigger the death of tongue SCC cells [70]. Quercetin is used to prevent and treat

OSCC (Fig. 4).

3.2. Epigallocatechin gallate

OSCC is treated with traditional methods like radiation, chemotherapy, and surgery. However, high death rates persist. Natural substances like genistein from soybeans and catechin from green tea show potential anti-cancer effects. Genistein inhibits the proliferation and invasion of OSCC cells, while catechin induces apoptosis and cell cycle arrest. Cordycepin, an adenosine receptor agonist, inhibits OSCC cell growth [71]. A study investigated the pro-oxidant properties of green tea polyphenol EGCG, which is thought to be an antioxidant. However, EGCG may also have pro-oxidant properties, producing ROS when exposed to oxygen and transition metals. It regulates antioxidant-related genes in normal cells while down-regulating superoxide dismutase 2/3 and thioredoxin reductase 2 in cancer cells. It also inhibits the transcriptional factor of SIRT3, estrogen-related receptor α (ERRα), in cancer cells. It may control SIRT3's mRNA expression in distinct ways through ERRα. It also stimulates antioxidant responses in normal cells while inducing oxidative stress and death in oral cancer cells. MT and SIRT3 are the molecular mediators of the distinct pro-oxidant effects of EGCG in oral cells. The study suggests a potential interaction between SIRT3 and MT signaling, which MTF1 may facilitate. EGCG differs from the normal cells' pro-oxidant effects on oral cancer [72]. OSCC is a prevalent oral cancer with a low survival rate despite modern treatments. EGCG has effectively inhibited cancer cell growth. This study assessed EGCG's therapeutic potential for treating OSCC in vivo and in vitro. It significantly inhibited HSC-3 cell survival, increased apoptotic cells, and decreased mouse tumor size. It could also be a unique oral cancer treatment strategy [17]. EGCG effectively inhibits SSC-4 human OSCC growth, suggesting potential medicinal use for OSCC patients through autophagy and apoptosis based on its dose- and time-dependent effects [73].

Additionally, EGCG, with its anti-oxidative, anti-angiogenic, and anti-metastatic properties, effectively prevents the migration and invasion of OSCCs in the tongue and oral floor. It effectively suppressed SCC-4 cell movement and invasion, inhibiting OSCC cell invasion more than migration. It could also be a potential agent to stop OSCC metastasis [74]. Catechins have anti-tumor and anti-HPV properties. However, their short half-lives, poor bioavailability, and stability make them difficult to use in therapeutic settings. To address these limitations, an injectable supramolecular hydrogel called CPBisoG was formed. This hydrogel demonstrated therapeutic efficacy against HPV+ OSCC in vitro and in vivo, with specific suppression against HPV+ OSCC cells. This hydrogel has the potential to treat HPV+ OSCC topically and provide a viable approach for future HPV-related disorders [75]. Tao et al. showed the potential development of EGCG resistance in oral squamous carcinoma cells. The researchers exposed SCC-25 cells to EGCG at varying doses, resulting in an EGCG-resistant phenotype (SCC-25E75R). The resistant cells showed higher resistance to EGCG-induced growth suppression and increased apoptosis. EGCG controlled 42 genes differently across the two cell lines, with resistant cells producing more anti-apoptotic proteins. This could help determine the receptivity of oral cancer to EGCG treatment [76]. EGCG can cause apoptosis and suppress cell proliferation in oral squamous carcinoma cells, with EGCG-generated intracellular ROS being a major factor. It can partially cause mitochondrial malfunction by affecting the electron transport chain and raising ROS levels inside the cell. EGCG administration also decreased intracellular ROS in HGF-1 cells, suggesting specific pro-oxidant effects on oral cancer cells [77]. EGCG has antioxidant effects on normal cells but can cause oxidative stress in oral cancer cells. Sirtuin 3, a crucial mitochondrial redox regulator, is linked to these prooxidative effects. In human OSCC and premalignant leukoplakia cells, EGCG produced ROS, decreased SIRT3 mRNA and protein expression, and altered mRNA transcripts of downstream targets of SIRT3. EGCG can potentially regulate SIRT3 transcription in oral cancer cells [78].

Li et al. investigated the effect of EGCG on inhibiting the biological

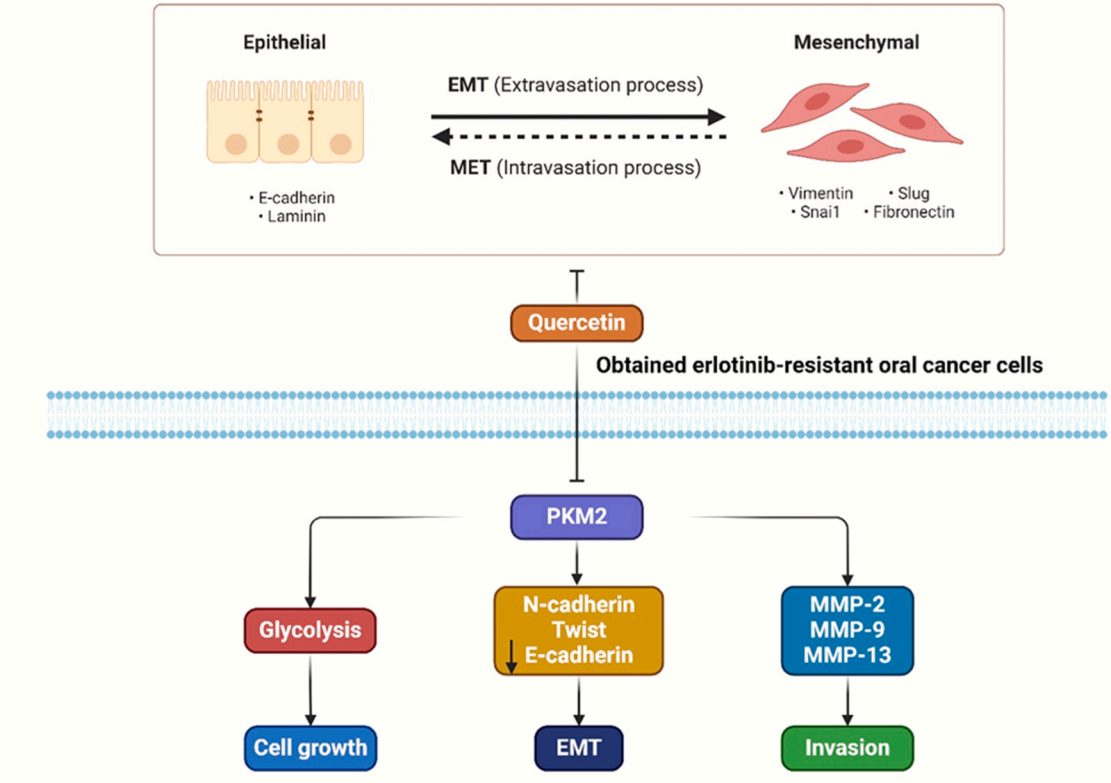

Fig. 4. Therapeutic and preventive role of quercetin in OSCC.

activities of tongue squamous cell carcinoma (TSCC) via the Hippo-tafazzin (TAZ) signaling pathway. EGCG has concentration- and time-dependent effects on CAL27 and SCC15 cells, reducing TAZ, LATS1, MOB1, and JNK protein levels. It influences TSCC migration, invasion, apoptosis, and proliferation via the Hippo-TAZ signaling pathway [79]. Furthermore, Lopez et al. investigated the potential chemotherapeutic effects of diosgenin, zoledronic acid, and EGCG on OSCC. Diosgenin and zoledronic acid significantly reduced cell viability and increased apoptosis, while DG and ZA altered the cell cycle and decreased migration [80]. Yoon et al. involved individuals at a high risk of recurring oral precancerous and carcinomatous lesions who were administered EGCG mouthwash for seven days. It decreases in pEGFR, COX-2, and Ki-67 positive cells following EGCG administration. It is also the first to investigate mouthwash as an oral cancer chemopreventive therapy in patients with oral field cancerization [81]. In addition, Lee et al. showed the influence of EGCG on the expression of B-cell translocation gene 2 (BTG2) in OSCC cells. EGCG inhibits cell proliferation by upregulating BTG2 expression, leading to cell cycle arrest, while BTG2 knockdown inhibits tumor cell development, and overexpression causes downregulated protein expression. It phosphorylates p38, JNK, and ERK pathways. Pretreatments with ERK1/2 inhibitors and SB203580 reduce EGCG activation [82]. Moreover, Koh et al. explored the impact of EGCG on HGF-induced tumor growth and invasion in oral cancer. EGCG reduced HGF-induced Met phosphorylation, invasion, and cell migration in the KB oral cancer cell line, inhibiting c-Met phosphorylation and downstream kinases AKT and ERK. It promotes apoptosis and decreases tumor growth in C3H/HeJ syngeneic mice [83].

3.3. Luteolin

Tjioe et al. aimed to identify and relocate medications harmful to treatment-resistant OSCC. Luteolin, when combined with metixene hydrochloride and nitazoxanide, was found to be a strong cytotoxic agent against oral cancer cells. Its low toxicity and excellent efficacy make it a potential cytotoxic and adjuvant therapy for oral cancer [10]. Luteolin-7-O-glucoside significantly reduced oral cancer cell migration and invasion, inhibiting proliferation and metastasis by inhibiting matrix metalloproteinase-2 expression and p38 activation. It can regulate MMP-2 expression and the extracellular signal-regulated kinase pathway, potentially enhancing oral cancer prognosis [84]. Moreover, Baz et al. explored the efficacy of luteolin and nano-luteolin in preventing OSCC growth through apoptosis. Nano-luteolin significantly outperforms luteolin and 5-fluorouracil in promoting apoptosis in SCC-25 cells. The cytotoxicity and IC50 values decreased dose- and time-dependently when treated with these compounds [85]. Luteolin has potent anti-cancer properties against various human cancer cell lines. This study evaluated luteolin's effectiveness in treating oral cancer. It inhibited cancer cell invasion and migration, increased E-cadherin expression, and suppressed transcription factors, potentially preventing cancer cell invasion and migration [44]. Furthermore, Tu et al. investigated the potential chemotherapeutic impact of luteolin in OCSC. Luteolin is a natural anti-inflammatory agent that effectively inhibits the proliferation, self-renewal, aldehyde dehydrogenase 1 activity, and CD44 positivity of OCSC without causing harm to normal epithelial cells. It also helps OCSC regain radiosensitivity. The study suggests blocking IL-6/STAT3 signaling can reduce OCSCs' carcinogenic potential [86].

3.4. Apigenin

Apigenin (Fig. 3), a flavonoid found in fruits and vegetables, has antiproliferative effects on keratinocytes (HaCaT) and tongue oral cancer-derived SCC-25. The study found a decrease in apigenin-induced cell proliferation, with SCC-25 cells being more susceptible, and apigenin also altered the cell cycle and caused apoptosis. Apigenin has the potential to be a promising chemopreventive drug [45]. Pei et al. investigated the synergistic inhibitory impact of apigenin and platinum-based chemotherapy medication, Oxaliplatin (OXA). OSCCs were divided into three groups: co-treated, apigenin-treated, and control. Results showed that a modest dose of OXA enhanced the migratory, invasive, and angiogenic properties of HSC-3 cells, regulated EMT-associated molecular markers, and increased the inhibitory effect on OSCC growth. LINC00857 significantly reduced the tumor-promoting effects of low-dose OXA. Apigenin can effectively decrease OSCC metastasis [18]. Another study showed that apigenin has anticancer properties against various malignancies. It's the regulation of long noncoding RNAs, particularly LINC00629. Apigenin increases the expression of LINC00629, a transcription factor, and the KLF10-LINC00629-Mcl1 axis, enhancing its growth-suppressive and proapoptotic effects [87].

Additionally, Helton et al. investigated the potential of dietary apigenin and kaempferol as chemopreventive medicines for various malignancies. The researchers applied different concentrations of these flavonoids to FaDu cells, measuring cell proliferation and tumor volumes. Apigenin and kaempferol reduced tumor cell proliferation in vitro, but in vivo, data indicated they exacerbated the tumor burden [88]. Moreover, Silvan et al. found the efficacy of apigenin as a chemopreventive measure in preventing oral carcinogenesis in golden Syrian hamsters. Apigenin treatment effectively prevented oral tumor development after 14 weeks, restoring antioxidant levels, detoxification agents, and lipid peroxidation to normal levels. Apigenin may have prevented oral carcinogenesis by enhancing antioxidant defence mechanisms [89]. Furthermore, Gomez-Garcia et al. investigated oral carcinogenesis in hamsters by applying DMBA topically, with three batches treated with varying concentrations of DMBA and apigenin. Results showed that carnosic acid and potassium apigenin had chemoprotective properties against DMBA-induced carcinogenesis, with carnosic acid showing the smallest volume of malignancy [90]. Oral leukoplakia, a rare condition causing white lesions in the oral cavity, can be treated conservatively with a 3D bioprinter. Apigenin forms a mucoadhesive oral film. The film was tested on a rat model, showing a significant chemopreventive effect. The apigenin-loaded film could help prevent carcinogenesis and could be used to create customized films for patients with oral leukoplakia [91].

3.5. Hesperidin

Hesperidin, a drug that inhibits the expression of Programmed Death-L1 in oral cancer cells, significantly decreases cell migration and proliferation. This is obtained by phosphorylating STAT1 and STAT3, which lowers PD-L1 protein expression. Hesperidin has the potential to be utilized as an adjuvant treatment for oral cancer, potentially enhancing cancer cell survival and avoiding anti-tumor immunity [19]. Wahed et al. showed the anticarcinogenic properties of Hesperidin against the HEp-2 laryngeal carcinoma cell line, compared to Doxorubicin (DOX) found that hesperidin exhibited anti-proliferative effects that increased over time. Hesperidin, a drug that increases the expression of the tumor suppressor gene P53 and decreases the anti-apoptotic Bcl-2 gene, has the potential as a co-adjuvant or pro-drug in oral cancer management [92]. Another study on hesperidin's anticancer properties demonstrated that it effectively inhibited pro-inflammatory and apoptotic signaling pathways in human oral cancer cells. The study utilized MTT assay, real-time RT-PCR analysis, and in silico docking to assess the inhibitory effect on cancer cell development. Hesperidin, a cytotoxic agent, showed a dose-dependent effect on cell proliferation, reducing the expression of inflammatory mediators like TNF-α, IL-1-β, IL-6, NF-κB, and B-cell lymphoma 2 mRNA. Hesperidin also increased the expression of BAX mRNA, suggesting cell death enhancement. It is a promising treatment option for oral cancer due to its anti-inflammatory properties and cytotoxic effects [46]. Hesperidin has anti-inflammatory, antioxidant, and anti-carcinogenic properties. Hesperidin-G has been studied for its potential use in treating oral stomatitis. Hesperidin-G

showed scavenging ability against superoxide anion and hydroxyl radicals, reduced thiobarbituric acid reactive compounds, and did not affect the anti-tumor activity of human OSCC [93]. In addition, Tanaka et al. showed the impact of diosmin and hesperidin on oral carcinogenesis in male F344 rats. At six weeks of age, the animals were divided into experimental and control groups and were fed either diosmin or hesperidin. 4-nitroquinoline 1-oxide caused mouth cancer in animals after 7 weeks, but after 8 weeks, animals were given test compounds, transitioned to a basal diet, and switched to a diet. The animals were euthanized after the trial. The study found that incorporating flavonoids hesperidin and diosmin can effectively prevent the growth of oral neoplasms caused by 4-nitrophenol O, potentially by reducing cell proliferation in the oral mucosa [94].

3.6. Naringenin and naringin

Myiricetin (MYR) and naringenin (NAR) have anticancer properties on OSCC and HaCaT cells. Flavonoids reduced SCC-25 cell growth, but NAR effectively targeted cancer cells while maintaining HaCaT growth unaffected. The suppression of cell proliferation was not associated with apoptosis but with cell cycle disturbance. Both flavonoids impeded cell migration, making them potential chemopreventive drugs for oral cancer [95]. OSCC is a prevalent oral cancer due to betel nut consumption. Over half of patients relapse after treatments, and their prognosis worsens when distant metastases develop. NAR has antitumor effects on various cancers, but its effects on OSCC remain unclear. NAR induces ROS production, apoptosis, and ER stress in OSCC cells, causing apoptotic signaling and triggering caspase-mediated apoptosis. NAR has effects on OSCC cells [96]. Kawaguchi et al. investigated the role of CD169 + macrophages in OSCC and the anti-tumor effects of NAR, which activates these cells. Results show that higher CD169 + macrophage levels in local lymph nodes and higher CD8 + cell counts within tumor sites are associated with better prognosis and higher CD8 + cell counts. NAR administration also inhibits tumor growth and increases mRNA levels of CD169, IL-12, and CXCL10 [20]. Oral cancer is a malignant tumor with a poor prognosis. NAR has anti-inflammatory and antioxidant properties. This research aims to understand the relationship between NAR and tongue cancer and identify a potential therapeutic target. NAR promotes apoptosis in CAL-27 cells, mediated by overexpression of Bid and downregulation of Bcl-xl [47]. Additionally, a study compared the effectiveness of free NAR against DMBA-induced oral carcinogenesis to NAR-loaded nanoparticles (NARNPs). The nanoparticles have a limited size distribution and an encapsulation efficiency of around 88 %. NARNPs significantly reduced histological lesions and prevented tumor formation in DMBA-treated animals. NARNPs also showed stronger antioxidant, anti-lipid peroxidative, and anti-proliferative effects than free NAR. NARNPs may be a helpful drug carrier for cancer chemoprevention [97].

Another study compared the effectiveness of free NAR in oral carcinogenesis with the biomolecular changes in the chemopreventive response of prepared NARNPs using Fourier Transform Raman spectroscopy. OSCC developed in golden Syrian hamsters after DMBA exposure. Raman spectra showed tumors had higher nucleic acid, phenylalanine, and tryptophan contents. NARNPs had a more substantial anticancer impact [98]. Oral cancer is the most aggressive and persistent primary malignant sarcoma globally, and chemotherapy has not advanced in years to overcome its harmful side effects. The study utilized the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) technique to analyze the pro-apoptotic effects of naringin on oral cancer cell lines. The study found that naringin treatment significantly reduced the viability of oral cancer cells, with an inhibitory concentration of 125.3 μM/mL. Naringin increases caspase-3, Bcl-2-associated protein X, Bcl-2-associated agonist of cell death, TGF-β, SMAD2, TNFα, and NFκB expression while downregulating B-cell leukemia/lymphoma 2 expression. Naringin therapy also decreased cell migration, demonstrating its potential as a treatment for oral cancer [99, 100].

3.7. Chrysin

Chrysin, an apigenin analog, has shown the potential to enhance chemotherapy efficacy by modulating apoptotic signaling pathways. In OSCC, combined with Cisplatin, it promotes cell death through DNA damage. Chrysin significantly increased Cisplatin's cytotoxic action, elevated γ-H2AX expression, reduced antioxidant enzyme expression, and increased ROS levels. The combination therapy may improve patients' OSCC clinical results, supporting Chrysin's chemo-sensitizer action in OSCC cells [48]. Propolis has anticancer properties due to its polyphenols. Ethanolic extracts contain polyphenolic components like chrysin, caffeic acid, p-coumaric acid, and ferulic acid, which have been found to induce apoptosis in human tongue squamous cell carcinoma cells. This suggests that propolis polyphenols can inhibit proline consumption for collagen production [101].

3.8. Kaempferol

Kaempferol, a plant-based polyphenol, has been suggested as a potential cancer treatment due to its anti-metastatic properties, as demonstrated in a study. This was due to reduced MMP-2 and TIMP-2 expressions, suppressed c-Jun activity, and inhibited ERK1/2 phosphorylation. The findings could help prevent oral cancer metastasis [49]. Kang et al. showed that EGb 761 induces caspase-3-dependent apoptosis in oral cavity cancer cells. Kaempferol and quercetin effectively inhibit oral cavity cancer cell proliferation at a 40 μM dose. These components, when combined with caspase-3, induce apoptosis in a caspase-3-dependent manner, suggesting they could be potential anti-oral cavity cancer therapies [102].

3.9. Silibinin

Silibinin has potential anticancer effects on oral cancer, and it was found that it effectively inhibited the growth of oral cancer cells. The study utilized various techniques to analyze oral cancer cells, including trans well assays, flow cytometry, immunoblotting, and a Ca9–22 xenograft mouse model. Silibinin inhibited cell proliferation, colony formation, apoptosis, ROS production, and cell cycle arrest during the G0/G1 phase. The substance also inhibited the migration and invasion of these cells by regulating the expression of proteins involved in the epithelial-mesenchymal transition. In naked mice, silibinin reduced the growth of xenograft tumors without overt harm [51]. A study uses tissue microarray technology to evaluate the clinical impact of Jumonji-C domain-containing protein 5 (JMJD5) on OSCC patients. High JMJD5 expression was found to be correlated with tumor size, cervical node metastases, clinical stage, and lower survival rate. JMJD5 expression could help identify patients with an adverse prognosis and potentially prevent cancer growth in PDTX models and in vitro. JMJD5 has the potential to serve as a crucial prognostic marker and therapeutic target for OSCC [103]. Autofluorescence spectroscopy is a highly sensitive technique used to identify early metabolic reactions following cancer treatment. The study utilized autofluorescence spectroscopy to analyze metabolic changes in redox state during DMBA-induced hamster buccal pouch carcinogenesis and compare the effectiveness of silibinin-loaded nanoparticles. Results showed that DMBA-induced tumor tissues had a lower optical redox ratio, indicating more metabolic activity. Nanoparticulate silibinin treatment was more effective than free silibinin in reducing squamous cell carcinoma formation and restoring fluorophore emission. The study suggests that combining autofluorescence spectroscopy with PC-LDA can accurately identify metabolic alterations and modifications in response to anti-cancer medication therapies [104]. Raman spectroscopy investigated the biochemical changes induced by free silibinin and its nanoparticulate form against DMBA-induced oral carcinogenesis. Nanoparticulate SIL demonstrated a more potent

anticancer effect than free SIL in preventing tumor formation and restoring multiple Raman bands to their normal range. The study demonstrated the effectiveness of Raman spectroscopy and PC-LDA diagnostic algorithms in identifying molecular changes in response to anticancer medications [105]. Furthermore, another study on milk thistle seed extracts found that silibinin interacts with cancer-related cell signaling pathways, exhibiting anticancer effects in vitro and in vivo. Silibinin treatment for 24 h caused cytotoxicity in SCC-25 cells, promoting apoptosis through mitochondrial cytochrome c and caspases 3 and 9, making it a potential treatment option for OSCC [21,106].

3.10. Fisetin

Fisetin, a flavonoid with anti-inflammatory, anticancer, and antioxidant properties, has increased apoptotic cell death in OSCC cells, suggesting potential for autophagy suppression in cancer treatment. Combining fisetin with a powerful autophagy inhibitor could be a beneficial adjuvant for oral cancer [107,108]. Fisetin has anti-proliferative properties in OSCC cells. Treatment suppressed PAK4 expression, sped up apoptosis, decreased proliferation, and inhibited tumor growth [15]. In human OSCC, fisetin suppresses tumor cell proliferation and promotes apoptosis. It inhibits Met/Src signaling pathways, reducing the production of disintegrin and metalloproteinase 9 protein [52]. Shih et al. investigated fisetin's cytotoxic effects on HSC3 human oral cancer cells, revealing that it decreased mitochondrial membrane potential, increased caspase-8, −9, and −3 activities, and induced apoptotic cell death. Fisetin increases pro-apoptotic proteins and cleaves caspase-3, −8, −9, cytochrome c, apoptosis-inducing factor, and endonuclease G, triggering apoptotic cell death through mitochondria and endoplasmic reticulum stress [109]. Su et al. found that fisetin reduced ΔΨm, increased caspase-3, −8, and −9 activities, and promoted apoptosis in human oral cancer SCC-4 cells in vitro. It increased proapoptotic proteins and reduced antiapoptotic proteins. It also causes cell death through caspase, mitochondria, and ER stress mechanisms [110]. Fisetin, an anticancer medication, is restricted due to its instability and hydrophobicity. Researchers have developed nanosystems using zein, hyaluronic acid, and fucoidan for cancer treatment. The FS-loaded cross-linked Zn nanoparticles (ZFH) showed the best particle size, surface net charge, and entrapment efficiency. ZFH showed significant anticancer activity in vitro and in vivo, reducing serum biomarkers, caspase-3 levels, and tumor grade. These refined ZFH nanoparticles hold promise as targeted nanotherapy for oral cancer treatment [111]. Sathiapriya et al. used golden Syrian hamsters as models to investigate fisetin's chemopreventive and antioxidant effects on DMBA-induced oral carcinogenesis. Fisetin significantly inhibited tumor development and restored the hamster buccal pouch's antioxidant and lipid peroxidation levels, indicating its anti-lipid peroxidative and chemopreventive action [112].

3.11. Baicalein

Oral cancer is primarily caused by OSCC, accounting for over 90 % of cases. Baicalein has been found to modify p65 and the NF-κB pathway, causing lethal effects on tumor cells. A study using CCK-8 tests and flow cytometric analysis found that baicalein inhibits OSCC cell proliferation, inducing apoptosis and inhibiting NF-κB activity. Baicalein's effects were amplified by Sp1 silencing [53,113]. Tang et al. explored the potential anticancer properties of baicalein against OSCC through a network pharmacology analysis. The study analyzed gene co-expression networks, gene-protein interaction networks, and molecular docking between HIFA and baicalein. The study identified the top 10 genes with high centrality measurements, with HIF1A expression positively correlated with CD4 + T cell infiltration levels but negatively correlated with B cell infiltration. Baicalein may be a viable treatment option for OSCC [114]. Moreover, Li et al. investigated baicalein's molecular targets and anticancer efficacy in OSCC in vitro. It significantly triggered apoptosis in Cal27 OSCC cells, demonstrating its cytoprotective function. It also caused Cal27 cells to produce ROS, which enhanced autophagy. The findings suggest further research on inhibiting ROS-dependent autophagy to increase baicalein activity in OSCC treatment [115]. Additionally, Wang et al. investigated the relationship between baicalein's anti-proliferation action and OSCC growth and invasiveness. The researchers treated different groups with BAI, MEK inhibitor, or BAI alone. The study found that cells treated with BAI exhibited higher levels of E-cadherin and Vimentin but lower survival rates. Baicalein also suppressed the growth and invasiveness of OSCC, possibly through the ERK-FAK signal pathway. It can suppress OSCC growth and invasiveness [54]. Baicalein was studied in oral cancer cells HSC-3. It boosts AhR activity and suppresses cell growth, downregulating the expression of CDK4, cyclin D1, and phosphorylated retinoblastoma (pRb). The reduction of pRb is linked to baicalein activation of AhR but not cyclin D1 or CDK. Pre-treating cells with LiCl prevented the decline in cyclin D1 and restored the reduction in pRb [116]. Furthermore, a study showed the therapeutic efficacy of baicalin in treating OSCC cells and the role of the ferroptosis-related gene FTH1 in OSCC. A predictive model was created using bioinformatic analysis, with FTH1 being the most up-regulated FRG. FTH1 expression was significantly up-regulated in OSCC samples and correlated with survival, immune cell infiltration, and treatment sensitivity. Baicalin targeted FTH1 to reduce its expression, promoting ferroptosis and inhibiting proliferation and EMT [117,118]. Vijay et al. evaluated baicalein's anticancer activity in human oral cancer KB-cells using an MTT assay and DCFH-DA test. Baicalein completely inhibited cancer cells at 80 μM, and at 40 μM, it considerably inhibited cells. It has an anticancer effect due to its ability to raise ROS levels [119].

3.12. Genistein

Genistein has anti-cancer effects, a potent natural anti-angiogenic drug, on tumor growth, angiogenesis, and in vitro invasion in an OSCC model. Results showed down-regulation of VEGF mRNA expression, reduced gelatinolytic activity, and decreased in vitro invasion. The study found no significant differences in tumor development and metastatic behavior between the experimental and control groups. Genistein application may not be sufficient for OSCC treatment [120]. Park et al. evaluated the effectiveness of EGFR pathway inhibition in OSCC using cetuximab and genistein. The researchers applied cetuximab to two OSCC cell lines, HSC3 and KB, and assessed their downstream protein expression. The expression of p-EGFR and p-Akt in HSC3 cells was reduced in vitro when treated with dual anti-EGFR drugs. In vivo, both cell lines showed a significant decrease in proliferation and growth delay when combined. The study suggests that targeting different molecular pathways is necessary for a good therapeutic response, as not all types of OSCC cells respond equally [121]. Approximately 7 million individuals worldwide suffer from cancer, which accounts for 12.5 % of all fatalities. It has been demonstrated that the anticancer medication genistein has pleiotropic effects on cancer, metabolism, and inflammation. A flow cytometry analysis (FMA) study investigated the onco-suppressive effects of genistein in hamsters during DMBA-induced oral carcinogenesis. DMBA significantly altered the aneuploid DNA patterns, increased the activity of DNA proliferation in 47.22 % of the hamsters, and raised the values of S-phase fragments. Nevertheless, after receiving genistein medication, these alterations lessened. Genistein may be utilized as an onco-suppressive medication to stop cancer from spreading, and FMA [122]. OSCC has high morbidity and death rates due to late-stage diagnosis. Despite advancements in therapy, oral cancer still has a 50 % five-year survival rate. Chemopreventive measures could complement or substitute existing treatments. Isoflavones, such as genistein, biochanin A, and daidzein, have been shown to have antitumor effects in various malignancies, including oral cancer. Different isoflavones in OSCC cell lines regulate signaling pathways differently, suggesting the need for further study using tumor progression models [55]. Dev et al.

have synthesized genistein nanoformulations (GLNPs) to induce apoptosis in OSCC selectively. The nanoparticles were tested in two cell lines, JHU011 and L929. GLNPs caused apoptosis in OSCC cells only, resulting in increased reactive oxygen species production, Bax mitochondrial translocation, and caspase 3 activation. They also downregulated polycomb group proteins Bmi 1 and EZH2, promoting the withdrawal of epigenetic transcription repression. GLNPs control EZH2 expression through 3PK inhibition and proteasomal-mediated degradation [123].

Additionally, Hussein et al. observed the effects of genistein and oxaliplatin on OSCC in newborn Syrian hamsters. The researchers used the CD44 antibody as a marker to study their role in cancer development. Genistein and oxaliplatin significantly reduced the carcinogenesis process in DMBA-induced OSCC, cancer stem cell activity, and proliferation. Oxaliplatin had a chemotherapeutic effect during carcinogenesis, while genistein played a role in chemoprevention. The combined effect was superior to each agent acting alone [124]. Genistein contains high concentrations of isoflavonoids that inhibit in vitro angiogenesis and cell proliferation. This study assessed genistein's anti-cancer potential for OSCC angiogenesis and basement membrane invasion. Genistein therapy effectively reduced cellular invasion through the artificial basement membrane and significantly reduced MMP-2 activity, indicating its potential as an anti-cancer drug [125]. Yang et al. investigated the potential chemopreventive effects of genistein on angiogenesis and oral carcinogenesis in hamster cheek pouches. Male Syrian golden hamsters were given DMBA solution for six weeks and then gavaged with genistein for 12 weeks. The study found no significant difference in the incidence of visible oral tumors between the genistein and control groups. However, three animals in the genistein-treated group developed fibrosarcomas, indicating that genistein and DMBA encourage oral submucosa stroma tumor growth [126]. Furthermore, genistein inhibits tumor cell growth and prevents carcinogenesis. In a study using an oral carcinogenesis model of a hamster buccal pouch, genistein treatment led to a delay in carcinogenesis, with a lower VEGF protein expression. Genistein's anti-angiogenic activity may contribute to its chemopreventive effect on oral carcinogenesis, while potentially playing a role in cancer development [127].

3.13. Anthocyanins

Anthocyanins decreased cell viability and prevented migration and invasion. Increased NLRP3, caspase-1, and IL-1β expression were linked to pyroptosis activation. Anthocyanin-activated pyroptosis was inhibited, and cell survival, migration, and invasion rates increased with caspase-1 inhibitors [56]. OSCC is the most prevalent form of the disease. Anthocyanins can suppress carcinogenesis. It has antiproliferative and apoptotic effects on OSCC and antimetastatic action. It could be a promising class of natural chemicals for OSCC treatment and prevention [128]. Chinese medicine traditionally uses colored rice variants, including white rice lines. Anthocyanins act as chemopreventive agents against cancer, inhibiting the migration and invasion of CAL 27 cancer cells in vitro. They also repressed matrix metalloproteinases-2 activity and suppressed NF-κB p65 expression. Anthocyanins from purple glutinous indica rice can inhibit these pathways [129]. A study aims to isolate anthocyanin, purify, fractionate, and assess its anti-metastatic ability against OSCC using *Bridelia retusa* cell suspension culture. The 2, 4-D, and kinetin significantly accelerate callus formation from leaf explants. Growth hormones, light, carbon supply, and pH affect anthocyanin production. The study investigated the cytotoxicity of *B. retusa* anthocyanin extracts on human OSCC cells using cell adhesion and survival assays [130]. Madanakumar et al. showed the anti-metastatic efficacy of anthocyanin, a compound found in *Bridelia retusa* cell suspension culture, against OSCC. Results show that 2, 4-D enhances callus production, with light-containing medium yielding the best results [130].

4. Bioavailability

The research on the biological activity of phytochemicals in humans requires a thorough understanding of their pharmacokinetics and bioavailability. Oral bioavailability refers to the percentage of dietary bioactive components that enter the bloodstream and are transported to specific tissues and organs for biological activities. The human body recognizes flavonoids as xenobiotics. Therefore, the absorption and digestion of substances are crucial for their transport to the intended tissues and organs for positive effects after consumption [131,132]. Flavonoids' effective concentrations in vitro are significantly higher than those in human plasma, despite their proven biological activities in numerous preclinical models [133]. Flavonoids, when consumed, must navigate through the intricate structures of the gastrointestinal tract to reach their effective concentrations at their sites of action [134]. Dietary flavonoids' bioavailability is influenced by their physicochemical properties, active efflux by proteins, and extensive biotransformation by enzymes like gut microbiota and hepatic metabolism [131]. Flavonoid glycosides, which are dietary forms of flavonoids, are inactive and require enteric hydrolysis to convert into their active aglycones. Bacterial and epithelial β-glucosidases hydrolyze quercetin and genistein glucosides to their aglycones in the human oral cavity, specifically in saliva and epithelial cells. Remarkably, only glucose conjugates were hydrolyzed; other glycosides either degraded very slowly or were not susceptible to salivary hydrolysis. As a result, there was a notable variation in the rate of hydrolysis between individuals. Aglycones in the oral cavity may have anticancer properties, as shown by the cytotoxicity of quercetin and genistein on oral cancer cells in vitro [135]. Recent research highlights the significant inter-individual variability in intraoral bioactivation of anthocyanins through microbial, salivary, and epithelial β-glucosidases. Scientists discovered that hydrolytic, phase II, and efflux transporting enzymes are functional in the human oral mucosa, similar to the small intestine. Saliva contains glutaronidated phase II anthocyanin conjugates [136].

5. Clinical studies

HPV infections, alcohol misuse, and tobacco use are linked to tongue SCC. Despite improved clinical results, 50 % of patients die within five years. Flavonoids, secondary plant metabolites with anti-inflammatory, anti-cancer, and antioxidant properties, are attractive therapeutic agents [137]. Clinical trials currently focus on flavonoids found in tea catechins, as they are the only flavonoids being studied for oral cancer. A phase II clinical trial involving 59 patients with oral mucosa leukoplakia randomized to either a mixed tea product or a placebo plus topical glycerine. The first clinical trial utilized green tea for treating an oral premalignant lesion. Applying tea extract directly to lesions can increase the local concentrations of active ingredients. Mixed tea is a dried blend of water-soluble green tea extract, green tea polyphenols, and tea pigments like theaflavins and the rubigins. The size of oral lesions dropped in 37.9 % and grew in 3.4 % of the 29 patients who received tea after six months of treatment, while it declined in 10.0 % and increased in 6.7 % of the 30 participants who received a placebo [138]. For four weeks, smokers who received a green tea extract (2000–2500 mg/day) saw less DNA damage in their oral keratinocytes. Additionally, the percentage of cells in the S phase decreased, accumulating in the G1 phase, with DNA content becoming more diploid, elevated apoptotic markers, and suppressed cell development [139]. Another phase II, randomized, placebo-controlled study assessed green tea extract's ability to prevent oral cancer. The study investigated the effects of administering green tea capsules containing 13.2 % EGCG (26.9 % of catechins) to 41 individuals with high-risk oral premalignant lesions. For 12 weeks, patients were randomly assigned to receive green tea extract three times a day at a dose of 1.0 g/m2 ($n = 10$), 0.75 g/m2 ($n = 9$), 0.5 g/m2 ($n = 11$), or a placebo. A complete response refers to all lesions disappearing, while a partial response involves a 50 % or greater reduction

in the total diameters of all assessed lesions. Even though the rates did not approach statistical significance, the investigators discovered that the two high-dose arms (0.75 and 1.0 g/m2) had greater clinical response rates (58.8 %) than either 0.5 g/m2 (36.4 %) or a placebo (18.2 %), indicating a dose-response impact of green tea extract. The extract was generally consumed, except diarrhea, oral/neck pain, and insomnia, possibly due to its caffeine content at higher dosages. There was no difference in oral cancer-free survival between the green tea extract and placebo groups at a median follow-up of 27.5 months [140]. EGCG mouthwash reduced oral carcinogenesis indicators in high-risk individuals with oral field cancerization, but not statistically significant. EGCG was found in saliva but not plasma, suggesting it is locally bioavailable in oral mucosa without significant systemic absorption [81]. Kooshyar et al. found quercetin can help patients with blood cancers avoid and alleviate chemotherapy-induced oral mucositis. The study involved 20 adults with high doses of chemotherapy. The intervention group received 250 mg quercetin capsules twice a day for four weeks. Nine of the 20 patients developed oral mucositis, with the intervention group experiencing a higher mean severity. Quercetin was less common but more severe in the intervention group [141].

6. Conclusion and future perspective

Flavonoids, which possess numerous molecular signaling pathways, have shown potential in preventing and treating OSCC. These substances modify vital mechanisms, such as cell cycle control, apoptosis induction, inflammation reduction, and oxidative stress attenuation, impacting the development of OSCC. Flavonoids such as EGCG, quercetin, and curcumin interact with NF-κB, MAPK, and p53, limiting tumor growth and increasing sensitivity to standard therapy. Clinical evidence supports the therapeutic potential of flavonoids, but outcomes vary due to patient groups, doses, and study methodologies. Despite some trials indicating positive outcomes, more research is needed to integrate positive trials into routine clinical practice. Future studies should improve flavonoid therapy by investigating synergistic effects with current medications, customizing treatment based on individual biomarkers, and optimizing dosage and delivery techniques. Flavonoids offer potential benefits to existing OSCC treatments. The study on flavonoids in OSCC has found their potential as effective preventive and therapeutic agents for this aggressive cancer. Flavonoids effectively target various signaling pathways crucial in the pathophysiology of OSCC to provide their therapeutic benefits. These processes involve reducing inflammation, promoting apoptosis, reducing oxidative stress, and regulating the cell cycle progression. Flavonoids like quercetin, curcumin, and EGCG disrupt NF-κB, MAPK, and p53 pathways, inhibiting tumor growth and increasing treatment susceptibility. Additionally, flavonoids are beneficial adjuncts in OSCC treatment, with specific trials demonstrating tumor shrinkage benefits and improved patient outcomes. The variability in clinical outcomes underscores the challenge of integrating these findings into consistent treatment strategies. The therapeutic potential of flavonoids requires careful consideration of factors such as dose, bioavailability, and patient-specific reactions. Future research should focus on determining optimal flavonoid dosages and delivery strategies to maximize therapeutic benefits and minimize potential adverse effects. Advances in drug delivery technologies, such as nanotechnology and liposomal formulations, enhance flavonoid bioavailability and targeted delivery to tumor sites. Customizing flavonoid therapy treatment plans to each patient's unique profile may improve outcomes. Biomarker research could identify patients most from flavonoid-based therapy, enabling more targeted and effective treatment plans. The study highlights the need to investigate the potential synergistic effects of flavonoids when combined with conventional medicines like immunotherapy, radiation, and chemotherapy. This strategy may reduce resistance development and enhance the overall effectiveness of OSCC treatment. Further research is needed to understand the precise mechanisms by which flavonoids function. This is a part of understanding their connections with crucial biological targets and their impact on tumor microenvironmental variables. Flavonoid-based treatments need long-term, large-scale clinical trials to confirm their effectiveness and determine their place in typical OSCC treatment plans. The primary objectives of these trials should be to assess the long-term outcomes, potential adverse effects, and overall survival benefits. Research on various flavonoids and their derivatives could lead to the discovery of new treatments with enhanced anti-cancer properties. The discovery of new flavonoids and their distinct mechanisms of action could lead to the development of advanced therapeutic options. In conclusion, flavonoids have significant potential for treating OSCC, but further research and clinical validation are needed before they can be effectively integrated into successful treatment plans. The application and utilization of these tools will be crucial in enhancing the outcomes for OSCC patients. Flavonoids like quercetin, EGCG, fisetin, and baicalein effectively combat OSCC by altering signaling pathways, reducing angiogenesis, increasing apoptosis, and inhibiting tumor proliferation. However, clinical translation is hindered by limited targeted administration and poor oral bioavailability. Future research should focus on personalized delivery systems and combinatorial regimens. Developing predictive biomarkers could accelerate the transition from molecular knowledge to evidence-based therapeutic application.

CRediT authorship contribution statement

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Clinical trial number

Not applicable.

Human ethics and consent to participate declarations

Not applicable.

Institutional review board statement

Not applicable.

Informed consent statement

Not applicable.

Funding

This research received no external funding.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgements

All the authors are thankful to their own institutions and to the Deanship of Research and Graduate Studies, King Khalid University, Abha, Saudi Arabia, for financially supporting this work through the Large Research Group Project under Grant no. R.G.P.2/480/46.

Data availability

All data supporting the findings of this study are available in the paper.

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