



A systematic review of fisetin in oral premalignant and malignant disorders: Molecular mechanisms and therapeutic potential

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ABSTRACT

Introduction: Oral cavity neoplasms pose a public health concern worldwide. We aimed to systematically review the current molecular mechanisms and preclinical efficacy of fisetin (FIS) in oral premalignant and malignant disorders.

Methods: A systematic review was conducted following the PRISMA guidelines, and keyword searches were performed in electronic databases such as PubMed, Scopus, Cochrane Library, and Web of Science. After screening the publications based on the inclusion and exclusion criteria, the desired data were extracted from the articles and recorded. Also, the risk of bias assessment was conducted using the Quality Assessment Tool for In Vitro Studies (QUIN) and the SYRCLE Risk of Bias tool.

Results: FIS exerts anticancer effects against oral premalignant lesions and oral squamous cell carcinoma (OSCC) via multiple pathways, such as the induction of apoptotic processes, endoplasmic reticulum (ER) stress, and autophagy, accompanied by mitochondrial dysfunction, reactive oxygen species (ROS) generation, DNA breakage, and activation of caspase-dependent signaling. It prohibits tumor cell proliferation due to cell-cycle arrest and suppression of key oncogenic pathways, including RTK/Met-Src, EGFR/Akt/ERK/STAT3, mTOR, and PAK4 signaling. Furthermore, FIS reduces migration, invasion, epithelial-mesenchymal transition (EMT), angiogenesis, and cancer stemness while enhancing antioxidant and detoxification defenses in normal cells.

Conclusion: Preclinical evidence suggests that FIS possesses promising chemopreventive and anticancer properties against premalignant and malignant disorders. However, clinical studies are needed for its clinical application.

Implication for health policy/practice/research/medical education:

Evidence from included studies indicates that fisetin (FIS) can be used as an adjunctive agent for oral premalignant and malignant disorders, due to its potential to modulate multiple pathways implicated in oral carcinogenesis. However, the absence of clinical trials precludes its immediate integration into routine clinical practice. Accordingly, future investigations must focus on rigorously designed clinical trial studies to determine the safety, efficacy, optimal dosage, and pharmacokinetic properties of FIS. Furthermore, elucidation of the molecular mechanisms and translational relevance of naturally occurring compounds such as FIS may inform educational initiatives and the development of evidence-based complementary approaches in oral oncology.

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Introduction

The oral cavity, as the entrance to the digestive system, can be affected by cancers that are a serious problem for the patient. Moreover, this disease has a rising incidence worldwide (1). Approximately 70% of patients are

identified at late stages. This late diagnosis often requires various treatment strategies, which are expensive and typically result in poor prognostic outcomes (2). On the other hand, an initial reduction in quality of life post-treatment was observed, with gradual improvement

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during subsequent follow-up periods. Quality of life in these patients may be affected by cancer stage, anatomical tumor site, human papillomavirus (HPV) status, and the type of therapeutic approach (3). Oral cancers and related precancerous conditions encompass a spectrum of neoplasms involving epithelial and nonepithelial tissues of the oral cavity (4,5). Oral squamous cell carcinoma (OSCC) is the most prevalent malignancy, while other less common malignancies (6,7). In addition, oral potentially malignant disorders (OPMDs), which can be divided into various lesions including leukoplakia, actinic keratosis, erythroplakia, oral submucosal fibrosis, and oral lichen planus, represent important premalignant conditions that are associated with a high risk of transformation to malignancy (8-10).

Treatment of oral cancer should be carried out in collaboration with a multi-treatment strategy, including chemotherapy, radiotherapy, immunotherapy, and finally surgery (9). Complications associated with oral cancer may result from tumor progression or as adverse effects of various treatment modalities. Surgical interventions carry potential risks such as graft failure, delayed wound healing, blood loss, cranial nerve injury, airway disturbances, limited mandibular movement, scarring, and long-term deficits in speech and swallowing, as well as aesthetic deformity, sometimes necessitating extended airway or enteral nutritional support (11,12). Non-surgical treatment strategies, including radiotherapy and chemotherapy, are often associated with both acute and chronic toxicities. These may include oral mucositis, pain, salivary gland hypo-function, xerostomia, hemorrhage, dysgeusia, and dysphagia, all of which can negatively impact nutritional intake and lead to weight loss (4,11). Additionally, immunotherapy may result in immune-mediated toxicities, which represent a major concern associated with this treatment modality (13). The use of natural products and their phytochemicals as therapeutic adjuncts in the management of various diseases has expanded considerably (14-16). Studies show that, in cancer prevention and therapy, phytochemicals exhibit diverse biological activities, including antiproliferative and cytotoxic effects against malignant cells along with other cancer treatments, although their efficacy and safety may vary depending on dosage and context (17-19).

Among dietary flavonoids, fisetin (FIS) has attracted particular interest because of its broad spectrum of biological activities and its ability to target multiple molecular mechanisms associated with cancer development (20). FIS, as a natural phytochemical and dietary flavonoid with the chemical formula C₁₅H₁₀O₆ and a weight of 286.24 g/mol, is found in various plants (21). Figure 1 illustrates the chemical structure of FIS and its quantities that occur in fruits and vegetables that we might consume daily (22,23).

FIS has shown antineoplastic properties by inhibiting specific signaling pathways and preventing the formation

of pro-inflammatory cytokines and free radicals, thus demonstrating its therapeutic potential across various diseases (24).

Because of the increasing global burden of oral cancers, which remains difficult to manage effectively with current therapeutic approaches, and since no comprehensive studies have been conducted to investigate how FIS affects the mechanisms and adjuvant therapies for oral premalignant and malignant disorders, we designed this study to focus on key pathways involved in the initiation and progression of oral tumors.

Materials and Methods

Search strategy

The present systematic review adhered to the 2020 guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A literature search was performed on 10 May 2026 using several online databases, including Medline (PubMed), Scopus, Cochrane Library, and Web of Science. We also employed a systematic review that involved selecting articles published in English, without time restrictions, that included the following terms:

((“Fisetin” OR “3,7,3',4'-tetrahydroxyflavone”) AND (“Cancer of the mouth” OR “Mouth cancer” OR “Oral cancer” OR “Mouth Neoplasm” OR “Oral neoplasms” OR “Oral potentially malignant disorders” OR “Oral neoplasms” OR “Oral cavity neoplasms” OR “Oral dysplasia” OR “Oral melanoma” OR “Oral leukoplakia” OR “Speckled leukoplakia” OR “Oral submucous fibrosis” OR “Oral lichen planus” OR “Proliferative verrucous leukoplakia” OR “Verrucous carcinoma” OR “Erythroplakia” OR “Oral lichenoid lesions” OR “Actinic cheilitis” OR “Lip neoplasms” OR “Oral fibroblasts” OR

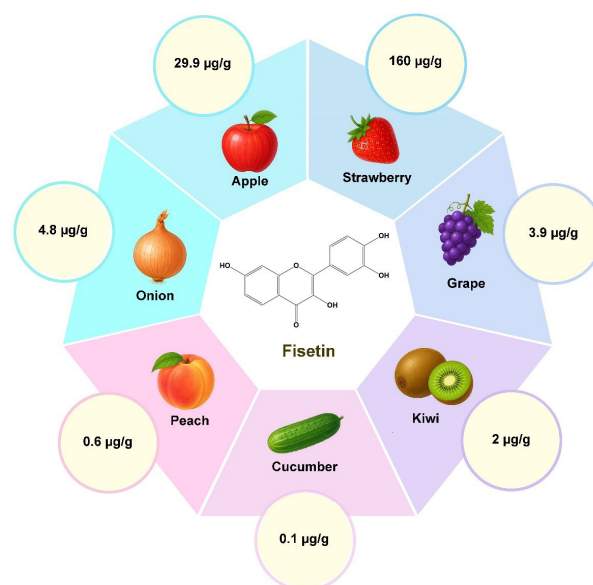


Figure 1. Chemical structure and amounts of fisetin in various vegetables and fruits.

“Fibrotic gingival” OR “Salivary gland neoplasms” OR “Salivary gland malignancies” OR “Mucoepidermoid carcinoma” OR “Gingival neoplasms” OR “Periodontal neoplasms” OR “Tongue neoplasms” OR “Tongue cancer” OR “Gum cancer” OR “Oral squamous cell” OR “human tongue squamous cell” OR “Oral keratinocytes” OR “Human lip epithelial cells” OR “Human head and neck squamous cell carcinoma”)) (Supplementary file 1).

Selection criteria

In this study, we included preclinical and clinical studies that were conducted on the cytotoxic and anticancer effects of FIS in oral premalignant and malignant disorders. Studies that were conducted on oropharyngeal tumors, lacking primary data or not available in full text, were excluded. All types of review papers, letters, case reports, conference proceedings abstracts, grey literature, and publications not written in English were excluded from our review.

Eligible studies aligned with our aim were identified using the PICOS (Population, Intervention, Comparator, Outcome, Study) framework and included if they met the inclusion criteria outlined in Table 1.

Screening process

Study selection was conducted in sequential stages, beginning with a preliminary screening of titles/abstracts and removing duplicates with EndNote software. Records identified as potentially relevant were then subjected to full-text evaluation. Studies were selected based on predefined eligibility criteria, and only those fulfilling all criteria were included. Screening was conducted independently by two reviewers, with discrepancies adjudicated by a third reviewer through discussion. The evaluation of full texts adhered strictly to the established eligibility criteria to maintain methodological consistency and rigor.

Data extraction

Data extraction was performed utilizing a standardized, pre-established form. Variables gathered included the study type, including *in vitro*, *in vivo*, or clinical studies, cancer classification, and the experimental model, such as human, animal, or cell line that the studies used.

Details regarding treatment parameters, including dosage, concentration, and duration, were systematically recorded. Furthermore, the principal molecular mechanisms and outcomes, including effects on apoptosis, cellular proliferation, oxidative stress, inflammation, and signaling pathways, were comprehensively documented.

Risk of bias assessment

The risk of bias and methodological quality of the included publications were appraised using tools appropriate to each study design. *In vivo* preclinical studies were assessed with the SYRCLE Risk of Bias tool, which evaluates potential bias across several domains, and each domain was rated as low, high, or unclear risk of bias, with the latter assigned when insufficient information was provided (25). Furthermore, for evaluating the risk of bias in *in vitro* studies, the Quality Assessment Tool for In Vitro Studies (QUIN) was used. This instrument assigns a score of 2 for parameters that are adequately documented, 1 for those that are inadequately described, and 0 for those with no information reported (26).

Narrative synthesis

The included studies were synthesized using a narrative approach to summarize and integrate the findings, given the anticipated heterogeneity in study design, experimental models, and outcome measures. This synthesis comprised a structured tabulation of study characteristics and a qualitative comparison of key variables.

Results

Literature search findings

As illustrated in Figure 2, 101 studies were retrieved from electronic database searches. After eliminating 24 duplicate records, the remaining records were evaluated for eligibility criteria (inclusion and exclusion criteria). In the screening phase (title and abstract), 24 studies were excluded due to failure to satisfy the inclusion criteria. One of the studies was a letter to the editor and was excluded from our review (27). Moreover, another study was excluded from our review because no oral cancer cells, animal models, or patients were used, and no FIS treatment was administered to any biological system, and it was also conducted entirely *in silico* (28). After final

Table 1. The PICOS (Population, Intervention, Comparator, Outcome, Study) framework of the study

Component	Description
P (Population)	Patients/animals/cells with oral premalignant and malignant conditions, including OPMD, OSCC, salivary gland tumors, and any type of oral cancer.
I (Intervention)	Fisetin (3,7,3',4'-tetrahydroxyflavone) or its derivatives administration on the above population.
C (Comparison)	Untreated with FIS or control groups, or standard therapy.
O (Outcomes)	Antiproliferative, pro-apoptotic, chemopreventive, anticancer effects, molecular signaling pathways, and tumor progression markers.
S (Study type)	<i>In vitro</i> , <i>in vivo</i> , and RCTs.

OPMDs: Oral potentially malignant disorders; OSCC: Oral squamous cell carcinoma; RCTs: randomized controlled trials.

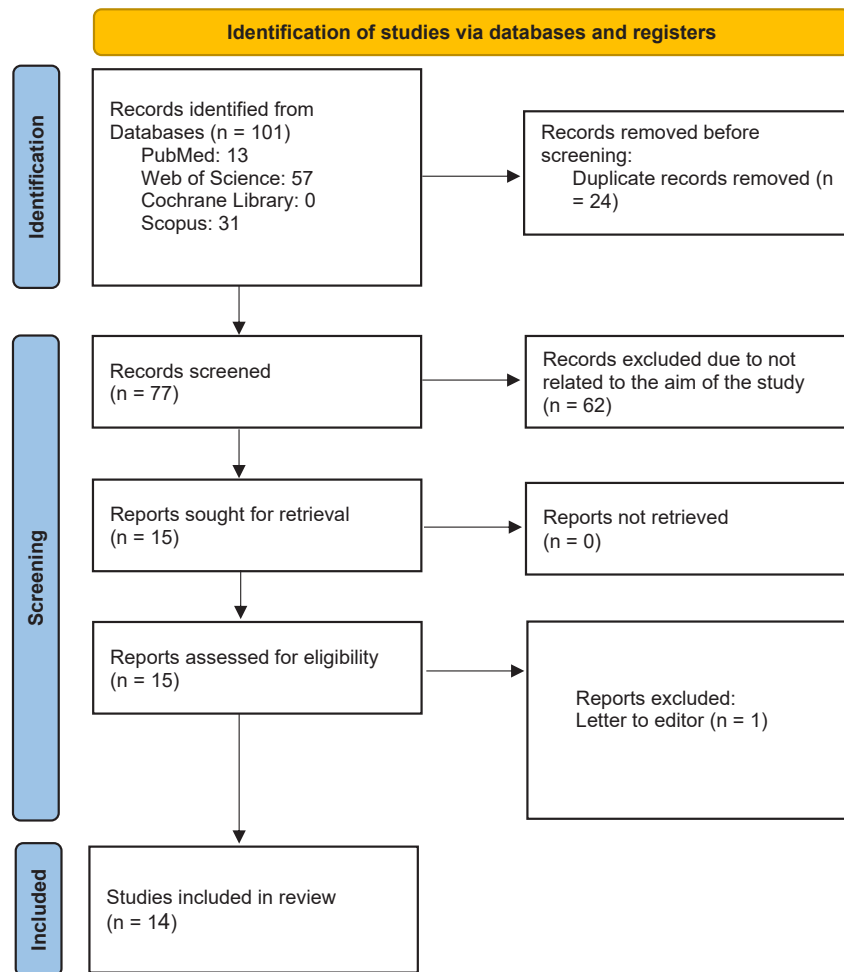


Figure 2. PRISMA flow diagram of studies identification, screening, and inclusion.

screening, 14 studies were included in our review based on our eligibility criteria (29-42).

Overview of included studies

Most of the included publications were conducted *in vitro*, and some studies were also conducted on laboratory animals. Various studies have shown that FIS controls cancer cells through modulation of oxidative stress, disruption of mitochondrial membrane potential, intracellular Ca^{2+} overload, cell cycle arrest, DNA damage, induction of apoptosis, reduced cell survival, modulation of autophagy, histopathologic changes, suppression of metastasis, and tumor progression (Table 2).

Quality assessment

For the assessment of the quality of the included *in vitro* articles, we used the QUIN tool. In this assessment, most publications were classified as moderate risk of bias, and two studies were at high risk. The most common areas rated as not specified were the explanation of the sample size calculation, operator details, randomization, outcome assessor details, and blinding (Figure 3).

The Robvis package was used to create visual summaries of the risk-of-bias assessments. Traffic light plots (Figure 4A) and summary plot (Figure 4B) provided a clear overview of bias in each animal study, covering all assessment areas (43). The methodological quality of the *in vivo* included studies was generally limited due to shortcomings in allocation concealment and blinding procedures (Figure 4A-B). Four studies exhibited a low risk of bias with respect to incomplete outcome data and selective outcome reporting. Overall, three studies, including Sathiyapriya et al (29), Moustafa et al (39), and Yadav et al (40), were categorized as having a higher overall risk of bias (overall 5 scores in low risk of bias), while Li et al also obtained a final score of 4 out of the total 10 dimensions assessed (35). These results indicate that the evidence base may be influenced by performance and detection bias, necessitating cautious interpretation of the reported findings.

Discussion

In this systematic review, we assessed the effects and mechanisms of FIS for oral premalignant and malignant

Table 2. Information, characteristics, and main outcomes of the included studies

Type of study	Cancer types	Studied patients /animals/cells	Treatment details (dosage, duration)	Main molecular mechanisms and outcomes	Reference
<i>In vivo</i>	Oral premalignant lesions and OSCC	Male golden Syrian hamsters	FIS was orally administered at 10 mg/kg bw and applied three times weekly for 14 weeks	↓ Tumor occurrence, tumor size, and overall tumor load, severe hyperplasia, dysplasia, keratosis, and oxidative stress by normalizing lipid peroxidation (TBARS) ↑ Phase II detoxifying enzymes, including GST, GR, and GSH, non-enzymatic antioxidants such as GSH and vitamins C and E, and antioxidant activities (SOD, CAT, GPx)	(29)
<i>In vitro</i>	OSCC	Human OSCC cell lines, including UM-SCC-23 and Tca-8113	Cells were treated with 20-80 μ M FIS for 24 h.	↓ OSCC cell viability ↑ Apoptotic rates ↓ RTK signaling suppresses both the total and Met/Src oncogenic pathways, as well as ADAM9, mTOR, AR, and CDK6.	(30)
<i>In vitro</i>	OSCC	Human oral cancer cell line HSC3	0-100 μ M of FIS were applied to cells for 24 and 48 h.	↓ OSCC cell viability, MCL1, BCL2, BCL-xL, XIAP, and $\Delta\Psi_m$ ↑ Chromatin condensation, DNA damage, selective ROS-mediated apoptosis in tumor cells, Ca^{2+} levels, BID, BAD, BAK, BAX, AIF, EndoG, cytochrome c, APAF1, Fas (CD95), Fas ligand, caspase-8, caspase-9, caspase-3, caspase-6, PARP cleavage, GRP78, ATF-6 β , calpain-1, and caspase-4	(31)
<i>In vitro</i>	OSCC	Human oral cancer SCC-4 cell	FIS was used at a 30-70 μ M concentration for 24-48 h	↓ SCC-4 cell viability, $\Delta\Psi_m$, CDC25C, cyclin A, cyclin B, CDK1, CDK2, Bcl-2, MCL-1, and XIAP ↑ ER stress-dependent apoptosis, caspase-dependent apoptosis, sub-G1 population, chromatin condensation, DNA breakdown, ROS production, intracellular Ca^{2+} release, caspase-3, caspase-4, caspase-8, caspase-9, caspase-12, DR4, DR5, TRAIL, Bax, Bid, cytochrome c, AIF, Endo G, CHK1, CHK2, GRP78, GADD153 (CHOP), ATF-6 α , ATF-6 β , P-PERK, calpain-1, and calpain-2. ↓ G2/M cell cycle	(32)
<i>In vitro</i>	OSCC	CAL-27 and Ca9-22 human OSCC lines	FIS was applied at 10-200 μ M for 24-72 h	↓ Cell viability, $\Delta\Psi_m$, p62/SQSTM1. ↑ Nuclear condensation, nuclei fragmentation, mitochondrial apoptosis, AVOs, LC3B formation, LC3-II, Beclin-1, ATG5/ATG12, Bax, Bak, cleaved caspase-3, and cleaved PARP. ↓ OSCC cell growth and survival, and autophagy	(33)
<i>In vitro</i>	OSCC and head and neck cancer	Human OSCC cell lines: HSC3, Ca9.22 and mucoepidermoid carcinoma cell line: MC3 and head and neck squamous cell carcinoma cell line: HN22	Cells treated with 7.5, 15, and 30 μ M of FIS for 24 h	↓ Cell viability and proliferation, p-mTOR, and Mcl-1 ↑ Apoptosis, PARP cleavage, nuclear condensation and fragmentation, and SESN2	(34)
<i>In vitro and in vivo</i>	OSCC	SCC9, SCC4, Tca8113 (including PAK4-overexpressing cells) and BALB/c athymic nude mice bearing SCC9-PAK4-overexpressing xenografts	<i>In vitro</i> : 2-20 μ M of FIS for 24 h <i>In vivo</i> : oral gavage administration of FIS for 30 days	↓ PAK4, colony formation, cell proliferation, cell migration, wound-healing ability, S-phase cell population, G2/M-phase cell population, and tumor growth in SCC9-PAK4 xenograft mice. ↑ Apoptosis, G0/G1-phase cell population (cell-cycle arrest), caspase-3 cleavage, and PARP cleavage.	(35)

Table 2. Continued

Type of study	Cancer types	Studied patients /animals/cells	Treatment details (dosage, duration)	Main molecular mechanisms and outcomes	Reference
<i>In vitro</i> and <i>in silico</i>	OSCC	Human OSCC datasets (GSE30784, GSE9844, GSE13601, GSE23558, SE37991; 291 tumors, 128 normal tissues), Cal33 and UM-SCC-22B	5-100 μ M of FIS for 48 h (MTT assay) and 25 and 50 μ M for 24 h (RT-PCR)	↓ Cal33 cell viability, UM-SCC-22B cell viability, FST, PLAU, LAMC2, APP, HMGA2, SPP1, PCNA, and EHMT1. ↑ ACACB. ⊥ Tumor progression and survival.	(36)
<i>In vitro</i>	OSCC and salivary gland carcinoma	Human SCC-9, SCC-25, A-253 and Beas-2B normal epithelial cells (control)	FIS was applied at 5-100 μ M for 24, 48, and 72 h	↓ Cell proliferation/viability, $\Delta\Psi_m$, Bcl-2 expression, cell migration/wound healing, apoptotic morphological alterations, including nuclear condensation, nuclear fragmentation, and cytoplasmic vacuolization. ↑ Sub-G1 population, apoptosis (↑Annexin V ⁺ cells), caspase-3 activation, cytochrome c release ⊥ G2/M cell cycle.	(37)
<i>In vitro</i>	Tongue squamous cell carcinoma and salivary gland carcinoma	CAL-27, UCSF-OT-1109, A-253, and normal control, Beas-2B bronchial epithelial cells	Propargyloxy FIS derivative at concentrations 1-40 μ M for 24-48 h	↑ Cytotoxicity against oral cancer cell lines, apoptosis, and cyclin B1 expression ⊥ Proliferation in real-time cell analysis, G2/M cell-cycle arrest. ↓ G0/G1 population.	(38)
<i>In vitro</i> and <i>in vivo</i>	OSCC and tongue and palate tumors	<i>In vitro</i> : SCC-4 oral cancer cells. <i>In vivo</i> : 4-NQO-induced OSCC rat model.	FIS was delivered as fucoidan/hyaluronic acid cross-linked zinc nanoparticles and <i>in vitro</i> exposure for 4-48 h. Moreover, <i>in vivo</i> treatment for 28 days	↑ Cellular uptake, apoptosis, caspase-3, improved histological grade with reduced keratinization, mitoses, nuclear polymorphism, and invasion, and greater antitumor efficacy ↓ Viable cells, cancer stem cell marker ALDH, tumor endothelial cell marker CD284/endothelialin, OSCC serum biomarkers (CEA, SCC-Ag, IAP), CSCs and TECs, angiogenesis, invasion, metastasis, and tumor aggressiveness.	(39)
<i>In vitro</i> and <i>in vivo</i>	Oral/HNSCC, and tongue	<i>In vitro</i> : Human oral squamous cancer Cal33, UM-SCC-22B cell lines <i>In vivo</i> : Athymic female nude mice	<i>In vitro</i> : 25-75 μ M for 24-48 h (effective doses 25-50 μ M). <i>In vivo</i> : 50 mg/kg/day orally in nude mice for 19 days.	↓ Cyclin B1, CDK1, and Cdc25C and modulation of p21 ^{Cip1} , p27 ^{Kip1} , and p53 (G2/M cell-cycle arrest), EGFR/Akt/ERK1/2/STAT3 survival signaling, p62 and Beclin-1 expression, Ki-67 proliferation index, tumor volume, and tumor weight ↑ Cell cytotoxicity, p53/p-p53 expression, DNA damage (comet formation), SAPK/JNK-c-Jun signaling, caspase-8/caspase-3/PARP cleavage, apoptosis, autophagic flux (LC3-II), caspase-mediated degradation of p21 ^{Cip1} and p27 ^{Kip1} , and tumor apoptosis	(40)
<i>In vitro</i>	OSCC	Cal27, Tca8113, HSC2, SCC9, HSC4 cell lines and OSCC patient tissues	NA	↓ MUC1 expression, cell growth, colony formation, migration, and malignant progression ↑ Apoptosis and chemosensitivity to apoptosis	(41)
<i>In vitro</i>	OSCC	Human OSCC cell line SAS co-cultured with oral pathogens	FIS applied at 5-20 μ M and exposure duration 3-6 h	↓ EMT, Migration, TWIST expression, ZEB1 expression, N-cadherin expression, β -catenin expression ⊥ Wnt/ β -catenin signaling induced by heat-killed periodontal pathogens ↑ E-cadherin expression.	(42)

↑: Increase; ↓: Reduce; -: Inhibit

FIS: fisetin; GST: glutathione-S-transferase; GR: glutathione reductase; GSH: glutathione; SOD: superoxide dismutase; CAT: catalase; GPx: glutathione peroxidase; ROS: reactive oxygen species; MCL1: myeloid cell leukemia 1; BCL2: B-cell lymphoma 2; $\Delta\Psi_m$: mitochondrial membrane potential; BID: BH3-interacting domain death agonist; BAD: BCL2-associated agonist of cell death; BAK: BCL2 antagonist/killer; BAX: BCL2-associated X protein; AIF: apoptosis-inducing factor; Ca²⁺: intracellular calcium ions; CDC25C: cell division cycle 25C phosphatase; CDK: cyclin-dependent kinase; ER stress: endoplasmic reticulum stress; ALDH: aldehyde dehydrogenase; NA: not available; EMT: epithelial-mesenchymal transition; OSCC: Oral squamous cell carcinoma; HNSCC: Head and neck squamous cell carcinoma.

Studies	1. Clearly stated aims/objectives	2. Explanation of sample size calculation	3. Explanation of sampling technique	4. Details of comparison group	5. Explanation of methodology	6. Operator details	7. Randomization	8. Method of measurement of outcome	9. Outcome assessor details	10. Blinding	11. Statistical analysis	12. Presentation of results	Overall score	Risk of bias
Li et al. (30)	1	0	1	2	2	0	0	2	0	0	2	2	12 (50.0%)	M
Shih et al. (31)	2	0	1	2	2	0	0	2	0	0	2	2	13 (54.1%)	M
Su et al. (32)	2	0	1	2	2	0	0	2	0	0	2	2	13 (54.1%)	M
Park et al. (33)	2	0	1	2	2	0	0	2	0	0	2	2	13 (54.1%)	M
Won et al. (34)	2	0	1	2	2	0	0	2	0	0	2	2	13 (54.1%)	M
Li, et al. (35)	1	0	0	2	2	0	0	2	0	0	2	2	11 (45.8%)	H
Yadav et al. (36)	2	0	2	2	2	0	0	2	0	0	1	2	13 (54.1%)	M
Kubina et al. (37)	2	0	1	2	2	0	0	2	0	0	2	2	13 (54.1%)	M
Kubina et al. (38)	2	0	1	2	2	0	0	2	0	0	2	2	13 (54.1%)	M
Moustafa et al. (39)	2	0	0	2	2	0	0	2	1	1	2	2	14 (58.3%)	M
Yadav et al. (40)	2	0	1	2	2	0	0	2	0	0	2	2	13 (54.1%)	M
Wang et al. (41)	2	0	1	2	1	0	0	2	0	0	0	2	10 (41.7%)	H
Zhang et al. (42)	2	0	1	2	2	0	0	2	0	0	2	2	13 (54.1%)	M

2

 Adequately specified

1

 Inadequately specified

0

 Not specified

M: Moderate risk of bias (50 to 70%)

H: High risk of bias (<50%)

QUIN tool formula:
 Final score = Total score × (100) / (2 × number of criteria applicable)

Final score: >70% = Low risk of bias; 50 to 70% = Moderate risk of bias; <50% = High risk of bias.

Figure 3. The results of the Quality Assessment Tool for In Vitro Studies (QUIN) for *in vitro* studies.

disorders. The results revealed that FIS, through various pathways, could induce a therapeutic effect on various oral cancer cells. These mechanisms were the pathways that involved oxidative stress, mitochondrial function, cell cycle arrest, DNA damage, intracellular Ca^{2+} , cell migration, cell proliferation, cell viability, apoptosis, autophagy, and cancer cell line cytotoxicity. Consistent with these results, herbal phytochemicals such as flavonoids effectively

modulate and selectively target dysregulated oncogenic signaling pathways in the pathogenesis of various cancers, especially head and neck cancer, target cancer stem cells, and regulate key signaling pathways in head and neck squamous cell carcinomas (HNSCC) (1,11,44-46). Similarly, Zhou et al also reported that FIS via impact on Nrf2/HO-1, reactive oxygen species (ROS) accumulation (H_2O_2 , $\bullet\text{OH}$ and $\text{O}_2\bullet^-$), phosphoinositide 3-kinase/protein

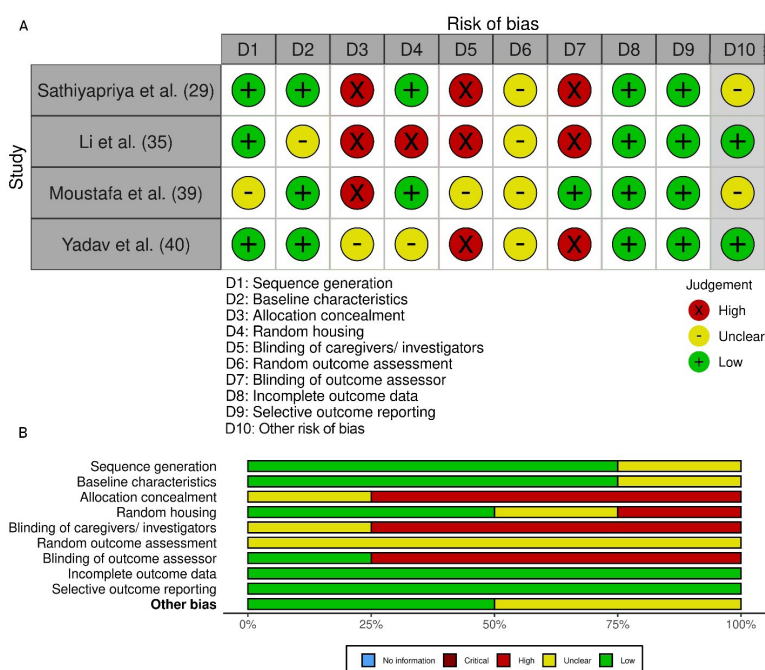


Figure 4. The results of the SYRCLE Risk of Bias tool for *in vivo* studies.

kinase B/mechanistic target of rapamycin (PI3K/Akt/mTOR), vascular endothelial growth factor, and nuclear factor-kappa B (NF- κ B) can induce its chemotherapeutic effects (20). In addition to the mechanisms mentioned, another study showed that FIS can have a synergistic effect on conventional anticancer drugs and have an impact on endoplasmic reticulum (ER) stress responses, cell cycle arrest, impaired mitochondrial function, and apoptosis (22). In this regard, another study conducted by Kubina et al indicated that FIS acts as a chemosensitizer, providing protection against cancer by preventing DNA damage, enhancing DNA repair, exerting antioxidant effects, and inhibiting phase II enzymes in HNSCC (47). A review study also reported that FIS, as an adjuvant anticancer therapy, overcomes the limitations of drug resistance and induces its chemopreventive and therapeutic properties against a spectrum of cancer cell lines. Anticancer effects are primarily mediated through suppression of PI3K/Akt/mTOR, mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), NF- κ B, and Wntless/Integrated- β -catenin (Wnt/ β -catenin) signaling pathways, while activating AMP-activated protein kinase (AMPK) signaling. These effects are related to the induction of caspase-dependent mitochondrial apoptosis, cell-cycle arrest, and the suppression of epithelial-mesenchymal transition (EMT), migration, invasion, and metastasis (48). FIS also modulates tumor necrosis factor-related apoptosis-inducing ligand/death receptor 5 (TRAIL/DR5) signaling, promotes ER stress, and induces receptor-interacting protein kinase 3/mixed lineage kinase domain-like protein (RIP3/MLKL)-mediated necroptosis (48).

These findings should be used with caution, especially given the significant differences in experimental concentrations and treatment methods used across the studies. *In vitro* studies tested a wide range of FIS concentrations, from 2 μ M to 200 μ M, for periods of 24 to 72 hours. While these doses showed consistent anticancer effects in various oral cancer cell models, they may not accurately reflect what can be achieved in humans.

Flavonoids are known to have limited gastrointestinal absorption, and they're often rapidly metabolized and eliminated from the body, which means the levels of flavonoids in the bloodstream are usually low (49,50). As a result, the significant biological effects seen at higher concentrations in lab studies should be viewed more as insight into the mechanisms at play, rather than direct evidence of what could be achieved in a clinical setting. These differences in dosing levels were also apparent in the included animal publications. The variations in dosage, duration, types of animals used, disease models, and drug formulations really underline the difficulties involved in comparing results from different studies. Moreover, translating the doses used in animals to what would be safe and effective for humans isn't straightforward. It requires careful evaluation to determine the appropriate

human equivalent dose, taking into account important factors such as how the drug is absorbed, metabolized, distributed in the body, and available in tissues.

In the following, we will present the most important mechanisms proposed in studies on the anti-cancer effects of FIS in oral premalignant and malignant disorders.

Modulation of oxidative stress, mitochondrial dysfunction, and Ca^{2+} overload

FIS exhibits a dual role in oxidative stress and redox regulation. In 7,12-dimethylbenz(a)anthracene (DMBA) induced hamsters, FIS at 10 mg/kg dosage, indicated chemopreventive effects and inhibited tumor formation by normalizing lipid peroxidation (TBARS) and oxidative stress while restoring antioxidant defenses, through upregulating phase II detoxification enzymes including glutathione S-transferase (GST), glutathione reductase (GR), glutathione (GSH), non-enzymatic antioxidants including vitamin C (ascorbic acid) and vitamin E (α -tocopherol), and recovered enzymatic antioxidant activities, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) (29). On the other hand, FIS can lead to activation of pathways involved in apoptosis by increasing intracellular levels of ROS, Ca^{2+} accumulation, and disrupting mitochondrial membrane potential ($\Delta\Psi$ m), which are mechanistic pathways for anti-cancer effect against human oral cancer cell lines HSC3 and SCC-4 cells (31,32). Elevated selective ROS-mediated apoptosis in tumor cells, such as superoxide anion ($\bullet\text{O}_2^-$), hydroperoxyl radicals ($\text{HO}_2\bullet$), hydroxyl radical ($\bullet\text{OH}$), hydrogen peroxide (H_2O_2), and singlet oxygen ($^1\text{O}_2$), can disrupt calcium homeostasis, resulting in intracellular Ca^{2+} accumulation. Sustained Ca^{2+} overload contributes to mitochondrial dysfunction and activates signaling pathways involved in apoptosis, autophagy, and other forms of programmed cell death, which is a common mechanism exploited by many anticancer agents (45,51).

Cell cycle arrest and DNA damage

Cancer may arise from alterations in proto-oncogenes, which, when mutated, become oncogenes that drive tumor initiation and progression. Furthermore, mismatch repair mechanisms active during DNA replication are essential for preserving genomic stability, as they detect and correct improperly paired bases. Upon detection of such errors, progression through the cell cycle, particularly during interphase, which consists of the G1, S, and G2 phases, may be halted, permitting the repair of damaged nucleotides prior to cell division (52).

FIS inhibits the proliferation of OSCC cells by interfering with cell-cycle progression, thereby restricting cellular viability and division. Su et al demonstrate that FIS (50 μ M), in a time-dependent manner, predominantly induces cell-cycle arrest at the G2/M checkpoint and causes sub-G1 phase apoptosis (32). In another study that was conducted by Li et al, FIS in 10 and 20 μ M dosage (24 h

incubation) inhibited the proliferation of SCC9 and SCC4 cells in G2/M and S-phase (35). FIS at 25-75 μ M for 24- 48 h reduced the viability and proliferation of HNSCC cells and ultimately induced apoptosis in a p53-independent manner by arresting the cell cycle at the G2/M phase and ultimately through the induction of p21^{Cip1} and p27^{Kip1} proteins. Increased expression of these inhibitors further diminishes CDK activity and strengthens cell-cycle arrest (40). FIS decreased the cell population in the G0/G1 phase and induced G2/M cell-cycle arrest at 40 μ M for 24 h, which is linked to the suppression of crucial regulatory proteins required for progression from G2 to mitosis, including cyclin B1, cyclin A, and cyclin-dependent kinase 1 (CDK1). Arrest at these checkpoints impedes cellular progression through essential phases of the cell cycle, thereby suppressing tumor cell proliferation and facilitating the initiation of apoptotic pathways (38).

Moreover, Su et al reported that DNA and nuclear chromatin condensation were observed after FIS was applied at 30, 50, and 70 μ M concentrations in SCC-4 cells. Moreover, 70 μ M of FIS improved internucleosomal fragmentation after 48 h of incubation (32). Another study by Park et al demonstrated that treatment with FIS at concentrations below 100 μ M resulted in pronounced nuclear condensation and fragmentation in CAL-27 and Ca9-22 cell lines, accompanied by a significant increase in the proportion of condensed nuclei (33). Moreover, studies on SCC-9, SCC-25, A-253 HNC cells, and HSC3 cells indicated FIS may impose significant nuclear condensation, fragmentation, cytoplasmic vacuoles, and mitotic deformity (37).

Induction of apoptosis and cell survival

FIS potentially promotes apoptosis in OSCC cells via multiple pathways and mechanisms. FIS treatment of HSC3 OSCC cells resulted in apoptosis via both intrinsic and extrinsic pathways. The intervention increased selective ROS-mediated apoptosis in tumor cells and intracellular Ca²⁺ levels, while reducing $\Delta\Psi$ m. Furthermore, 100 μ M FIS for 24 and 48 h downregulated anti-apoptotic proteins (MCL1, BCL2, BCL-xL, XIAP) and upregulated pro-apoptotic proteins (BID, BAD, BAK, and BAX). Mitochondrial dysfunction led to the release of cytochrome c, apoptosis-inducing factor (AIF), and EndoG, triggering APAF1 and caspase-9 activation. The extrinsic pathway was promoted by increased expression of Fas (CD95), Fas ligand, and caspase-8. Activation of caspase-3, caspase-6, and subsequent PARP cleavage indicated execution of apoptosis. In addition, elevated GRP78, ATF-6 β , calpain-1, and caspase-4 levels implicated ER stress in the apoptotic process (31). In another *in vitro* study that was conducted on SCC-4 human OSCC cells, treatment with a 50 μ M concentration for 24-48 h of FIS was associated with reduced expression of anti-apoptotic proteins (Bcl-2, MCL-1, XIAP) and increased expression of pro-apoptotic proteins (Bax and Bid). Mitochondrial

apoptotic signaling was evidenced by the release of cytochrome c, AIF, and EndoG, leading to activation of caspase-9 and caspase-3. The extrinsic apoptotic pathway was activated by increased expression of DR4, DR5, TRAIL, and caspase-8. Furthermore, enhanced activation of caspase-4 and caspase-12, along with increased GRP78, CHOP, ATF-6 α , ATF-6 β , phosphorylated PERK, calpain-1, and calpain-2 levels, substantiated the involvement of ER stress in FIS-mediated apoptosis (32). Additionally, Park et al administered FIS applied at 10-200 μ M for 24-72 h on CAL-27 and Ca9-22 human OSCC cell lines. FIS induced apoptosis by impacting the mitochondrial pathway and $\Delta\Psi$ m disruption, accompanied by nuclear condensation and nuclear fragmentation. FIS also elevated the expression of the pro-apoptotic proteins Bax and Bak, which promoted mitochondrial dysfunction and activation of the apoptotic cascade. This process resulted in the cleavage of caspase-3 and PARP, indicating execution-phase apoptosis (33).

Other studies also reported that FIS (50 μ M and 80 μ M) increased cell cytotoxicity, inhibiting multiple oncogenic signaling pathways that support OSCC cell lines' growth and survival. The studied targets included receptor tyrosine kinase (RTK) signaling, Met/Src pathways, EGFR/Akt/ERK1/2/STAT3 signaling, mTOR, PAK4, androgen receptor (AR), CDK6, and A Disintegrin and Metalloproteinase 9 (ADAM9). Downregulation of these pathways reduces cell survival and apoptosis (30, 40). Furthermore, FIS induces ER stress by activation of caspases and release of mitochondrial apoptogenic factors, including cytochrome c, AIF, and Endo G, and upregulates GRP78, ATF6 α , PERK, CHOP (GADD153), calpains, and caspase-4/caspase-12, thereby enhancing apoptotic cell death (31, 32).

Modulation of autophagy

Autophagy is a cellular self-digestion function for maintaining cellular homeostasis, which may play an important role in cancer therapy and is context-dependent. Autophagy in the initial phases of neoplasm transformation supports cellular homeostasis by preserving genetic integrity and metabolic balance, which can limit oncogenic events. However, once tumors develop, autophagy frequently serves as an adaptive survival mechanism, promoting cancer cell growth under stress, reducing treatment efficacy, and increasing immune evasion (53). The conflicting reports regarding FIS's effect on autophagy, whether it induces or inhibits this process, may be attributed to the context-dependent nature of autophagy regulation. For instance, Park et al showed that in OSCC Ca9-22 cells, FIS promotes autophagic activation. This was evidenced by a dose-dependent increase in acidic vesicular organelles (AVOs), enhanced conversion of LC3-I to LC3-II, and elevated levels of Beclin-1 and ATG5, along with decreased p62/SQSTM1 levels, indicating an active autophagic flux. Notably, when

autophagy was inhibited using 3-methyladenine or the Beclin-1 inhibitor SP600125, there was an increase in FIS-induced cytotoxicity and apoptosis, suggesting that the autophagy activated by FIS serves as a protective survival mechanism in this model (33). Similarly, research by Yadav et al indicated that FIS fosters autophagy in HNSCC cells, as shown by increased formation of LC3-II and decreased p62 expression, which confirmed functional autophagic flux. However, inhibiting autophagy with chloroquine heightened caspase-3 activation and apoptosis induced by FIS, further supporting the notion of autophagy playing a cytoprotective role (40).

Consequently, these results may stem from autophagy's dual nature; moderate or transient activation might support tumor cell survival by maintaining metabolic balance, while excessive or disrupted autophagic flux could lead to cell death.

Histopathologic changes, suppression of metastasis, and tumor progression

FIS (10 μ M administration for 3–6 h) also inhibits microbe-driven prometastatic metastatic behavior by suppressing EMT in OSCC cell lines. Moreover, it downregulates TWIST, ZEB1, N-cadherin, β -catenin, and Wnt/ β -catenin signaling while increasing E-cadherin expression. These effects reduce cell migration, tumor metastasis, and overall tumor aggressiveness (42). Studies also showed that FIS inhibited colony formation, cell growth and proliferation, cell migration, wound-healing ability, and malignant progression in OSCC and salivary gland carcinoma (35,37,41). Another *in vivo* study conducted by Sathiyapriya et al induced oral premalignant lesions and OSCC and evaluated the chemopreventive efficacy of FIS. Oral administration of FIS at a dose of 10 mg/kg bw was performed three times per week over 14 weeks, with outcomes measured in terms of tumor incidence, volume, and burden, together with histopathological examination of oral tissues (29). Exposure to FIS (5–100 μ M for 48 h) resulted in downregulation of APP, EHMT1, PCNA, PLAU, FST, HMGA2, LAMC2, and SPP1, alongside upregulation of ACACB, which is implicated in growth and tumor progression, and survival inhibition (36). Moustafa et al in their study reported that FIS decreases cancer stem cell (CSC) and tumor endothelial cell (TEC) markers, including ALDH and CD284/endosialin. It also reduces angiogenesis, tumor vascularization, and circulating OSCC biomarkers (CEA, SCC-Ag, and IAP), indicating activity against both tumor cells and the tumor microenvironment in SCC-4 oral cancer cells (39).

FIS's cytotoxicity

FIS has been shown to exert cytotoxic effects against oral cancer cell models via several mechanisms, including inhibition of cell viability and proliferation, induction of apoptosis, mitochondrial dysfunction, oxidative stress, DNA damage, and cell-cycle arrest. Shih et al found that

FIS reduced HSC3 OSCC cell viability in a dose- and time-dependent manner, accompanied by elevated selective ROS-mediated apoptosis in tumor cells, intracellular calcium accumulation, disruption of $\Delta\Psi_m$, chromatin condensation, and DNA damage at a concentration of 40 μ M (31). Su et al observed that FIS decreased SCC-4 cell viability in a concentration- and time-dependent manner, with an IC₅₀ value of 52.8 μ M after 48 hours (32). Park et al reported that FIS reduced the viability of CAL-27 and Ca9-22 OSCC cells in a dose- and time-dependent manner following exposure to concentrations ranging from 0 to 300 μ M for 24 to 72 hours, with Ca9-22 cells displaying lower sensitivity compared to CAL-27 cells (33). Kubina et al showed that FIS increased apoptosis-related responses at sub-IC₅₀ concentrations, as indicated by enhanced caspase-3 activation in SCC-9, SCC-25, and A-253 cells, supporting its pro-apoptotic effect (37).

Zhang et al noted that 10 μ M FIS did not significantly impact OSCC cell viability and was used as a non-toxic concentration for subsequent analyses (42); however, this observation does not define a therapeutic safety margin. However, studies evaluating normal oral epithelial cells or fibroblasts in parallel with cancer cells to establish a selectivity index (IC₅₀ for cancer cells/IC₅₀ for normal cells) remain insufficient.

Limitations of the study

In this study, there was considerable heterogeneity among studies regarding application methods, concentrations, and application protocols, which limited comparisons between studies. In addition, the study included mainly *in vivo* and *in vitro* laboratory studies, and no clinical studies were conducted in this area. The methodological quality of the included studies, which was generally moderate to high, should be considered as a limitation. This could affect the validity and generalizability of the results. Another limitation of our study is that the systematic review protocol was not prospectively registered in PROSPERO.

Conclusion

Based on data from included preclinical studies, FIS exerts potent anticancer effects against oral premalignant lesions and OSCC through multiple mechanisms, including induction of cell viability reduction, inhibition of tumor growth, progression, invasion, and malignant transformation. It also, through the intrinsic and extrinsic apoptosis, ER stress-mediated cell death, G2/M and G0/G1 cell-cycle arrest, ROS-dependent cytotoxicity, activation of DNA damage responses, modulation of autophagy, inhibition of RTK/Met-Src, EGFR/Akt/ERK/STAT3, mTOR and PAK4 signaling pathways, suppression of EMT, migration and metastasis, targeting of cancer stem cells and tumor angiogenesis, and enhancement of antioxidant and detoxification defenses, can inhibit oral carcinogenesis. It is recommended that further clinical

studies be conducted considering different doses of FIS and a wider range of mechanisms and clinical symptoms.

Authors' contribution

Conceptualization: Mehran Taheri Khafri.

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Formal analysis: Mehran Taheri Khafri.

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Methodology: Kosar Farhadi Babadi.

Project administration: Mehran Taheri Khafri.

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Supervision: Mehran Taheri Khafri.

Validation: Zahra Khiali.

Visualization: Zahra Khiali.

Writing-original draft: Zahra Khiali and Mehran Taheri Khafri.

Writing-review & editing: All authors.

Declaration of AI-assisted tools in the writing procedure

Grammarly (Grammarly Inc., USA), an AI-assisted language-editing tool, and ChatGPT were used to enhance the English-language editing process by improving grammar, spelling, and clarity of this paper, and designing some of the parts of the figures.

Conflict of interest

The authors declared no conflict of interest, financial or otherwise.

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Supplementary files

Supplementary file 1. The keywords searched for each database.

References

- Islam MR, Rauf A, Ogaly HA, Ajaj R, Iriti M. Targeting oncogenic signaling pathways in head and neck cancer using nano-phytomedicine: Molecular insights and therapeutic potential. *Phytomedicine*. 2026;157:158283. doi: 10.1016/j.phymed.2026.158283.
- Chatni S, B VM, Pandya K. Economic burden of oral cancer and resource-stratified approach to the management of gingivobuccal cancers. *Oral Maxillofac Surg Clin North Am*. 2026;12:S1042-3699(25)00095-0. doi: 10.1016/j.coms.2025.12.009.
- Yim YB, Han DH, Shin HS. Oral health-related quality of life in oral cancer patients assessed with EORTC instruments: a scoping review. *BMC Oral Health*. 2025;25(1):1854. doi: 10.1186/s12903-025-07280-9.
- Cabral LGS, Martins IM, Paulo EPA, Pomini KT, Poyet JL, Maria DA. Molecular mechanisms in the carcinogenesis of oral squamous cell carcinoma: a literature review. *Biomolecules*. 2025;15(5):621. doi: 10.3390/biom15050621.
- Barroso L, Veiga P, Melo JB, Carreira IM, Ribeiro IP. Molecular and genetic pathogenesis of oral cancer: a basis for customized diagnosis and treatment. *Biology (Basel)*. 2025;14(7):842. doi: 10.3390/biology14070842.
- Zahid E, Bhatti O, Zahid MA, Stubbs M. Overview of common oral lesions. *Malays Fam Physician*. 2022;17(3):9-21. doi: 10.51866/rv.37.
- Muralidharan S, Nikalje M, Subramaniam T, Koshy JA, Koshy AV, Bangera D. A Narrative review on oral squamous cell carcinoma. *J Pharm Bioallied Sci*. 2025;17(Suppl 1):S204-s6. doi: 10.4103/jpbs.jpbs_593_25.
- Kumari P, Debta P, Dixit A. Oral potentially malignant disorders: etiology, pathogenesis, and transformation into oral cancer. *Front Pharmacol*. 2022;13:825266. doi: 10.3389/fphar.2022.825266.
- Kijowska J, Grzegorzczak J, Gliwa K, Jędras A, Sitarz M. Epidemiology, diagnostics, and therapy of oral cancer-update review. *Cancers (Basel)*. 2024;16(18):3156. doi: 10.3390/cancers16183156.
- Jayasinghe RD, Siriwardena B. Clinical aspects of oral cancer and potentially malignant disorders with special relevance to South Asia. *Ann Maxillofac Surg*. 2024;14(2):128-36. doi: 10.4103/ams.ams_184_24.
- Ling J, Zhang L, Wang Y, Chang A, Huang Y, Zhao H, et al. Fisetin, a dietary flavonoid, increases the sensitivity of chemoresistant head and neck carcinoma cells to cisplatin possibly through HSP90AA1/IL-17 pathway. *Phytother Res*. 2023;37(5):1997-2011. doi: 10.1002/ptr.7723.
- Jain DK, Katrolia R, Bhadra R, Ram H, Dwivedi R, Yadav H. Complications associated with surgical management of oral cancer patients: A comprehensive review. *Natl J Maxillofac Surg*. 2025;16(2):203-11. doi: 10.4103/njms.njms_87_23.
- Xue N, Wang Y, Wang Z, Zeng X, Wang J, Zhang X. Trends in immunotherapy for oral squamous cell carcinoma. *Cell Oncol (Dordr)*. 2025;48(5):1159-79. doi: 10.1007/s13402-025-01068-3.
- Darvishi M, Rafsanjani S, Nouri M, Abbaszadeh S, Heidari-Soureshjani S, Kasiri K, et al. Biological mechanisms of polyphenols against *Clostridium difficile*: a systematic review. *Infect Disord Drug Targets*. 2025;25(3):e18715265313944. doi: 10.2174/011871526531394420726115600.
- Rahimian G, Heidari-Soureshjani S, Kasiri K. The biological effects and mechanisms of fisetin on hepatotoxicity, liver injury and liver fibrosis: a systematic review. *Nat Prod J*. 2025;15(8):18. doi: 10.2174/01221031553323240906193500.
- Nikfarjam M, Heidari-Soureshjani S, Rostamian S, Kasiri K. The biochemical effects of resveratrol intake on the neurobehavioral aspects of autism spectrum disorders: a systematic review. *CNS Agents Med Chem*. 2026;26(2):167-82. doi: 10.2174/0118715249387274250521054238.
- Saedi Marghmaleki M, Karimian M, Raeisi E. Chrysin and its nanoformulations in cancer therapy: A systematic review of their radiosensitizing, phototherapy-enhancing potentials. *J Herbmed Pharmacol*. 2026;15(2):175-88. doi: 10.34172/jhp.2026.53576.
- Abdi S, Heidari-Soureshjani S, Rostamian S, Raeisi E. A systematic review of the mechanistic effects of ginsenosides on enhancing radiotherapy and providing radioprotection. *Anticancer Agents Med Chem*. 2026;26(6):583-601. doi: 10.2174/0118715206394677250930145253.
- Santiago LR, Asevedo EA, Park MN, Tallei TE, Maciel

- de Azambuja Ribeiro RI, Shin SW, et al. Phytochemicals as Emerging Antiproliferative Agents in Head and Neck Cancer: Molecular Mechanisms and Therapeutic Strategies. *Pharmacology*. 2026;111(2):74-100. doi: 10.1159/000550172.
20. Zhou C, Huang Y, Nie S, Zhou S, Gao X, Chen G. Biological effects and mechanisms of fisetin in cancer: a promising anti-cancer agent. *Eur J Med Res*. 2023;28(1):297. doi: 10.1186/s40001-023-01271-8.
 21. PubChem [Internet]. PubChem Compound Summary for CID 5281614, Fisetin; [cited 2026 May 21]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004-. Available from: <https://pubchem.ncbi.nlm.nih.gov/compound/Fisetin>.
 22. Fatima R, Soni P, Sharma M, Prasher P, Kaverikana R, Mangalpady SS, et al. Fisetin as a chemoprotective and chemotherapeutic agent: mechanistic insights and future directions in cancer therapy. *Med Oncol*. 2025;42(4):104. doi: 10.1007/s12032-025-02664-x.
 23. Kimira M, Arai Y, Shimoi K, Watanabe S. Japanese intake of flavonoids and isoflavonoids from foods. *J Epidemiol*. 1998;8(3):168-75. doi: 10.2188/jea.8.168.
 24. Chahal SK, Kabra A, Saeedan AS, Ansari MN. Fisetin: a multitarget flavonol bridging oxidative stress, inflammation, aging, and cancer. *Naunyn Schmiedeberg's Arch Pharmacol*. 2026;399(6):7877-99. doi: 10.1007/s00210-025-04912-3.
 25. Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. *BMC Med Res Methodol*. 2014;14:43. doi: 10.1186/1471-2288-14-43.
 26. Sheth VH, Shah NP, Jain R, Bhanushali N, Bhatnagar V. Development and validation of a risk-of-bias tool for assessing in vitro studies conducted in dentistry: The QUIN. *J Prosthet Dent*. 2024;131(6):1038-42. doi: 10.1016/j.prosdent.2022.05.019.
 27. Gunasekaran V, Palanivel S. Treatment of oral cancer cells using natural drug fisetin: an effective phytotherapy. *Nat Prod Res*. 2026;40(4):1106-7. doi: 10.1080/14786419.2024.2405996.
 28. Israr J, Ahamad T, Alam S, Misra S, Gupta D, Ahmad R, et al. Bioactive Compounds from *Achyranthes Aspera* L. Extract: A UHPLC Profile and In Silico Study for Mouth Cancer. *ChemistrySelect*. 2024;9(38):e202402092. doi: 10.1002/slct.202402092.
 29. Sathiyapriya J, Rajeswari K, Annamalai G, Sivakumar K, Suresh K. Chemopreventive and antioxidant efficacy of fisetin in experimental oral carcinogenesis. *Int J Rec Sci Res*. 2013;4:313-9.
 30. Li YS, Qin XJ, Dai W. Fisetin suppresses malignant proliferation in human oral squamous cell carcinoma through inhibition of Met/Src signaling pathways. *Am J Transl Res*. 2017;9(12):5678-83.
 31. Shih YL, Hung FM, Lee CH, Yeh MY, Lee MH, Lu HF, et al. Fisetin Induces Apoptosis of HSC3 Human Oral Cancer Cells Through Endoplasmic Reticulum Stress and Dysfunction of Mitochondria-mediated Signaling Pathways. *In Vivo*. 2017;31(6):1103-14. doi: 10.21873/in vivo.11176.
 32. Su CH, Kuo CL, Lu KW, Yu FS, Ma YS, Yang JL, et al. Fisetin-induced apoptosis of human oral cancer SCC-4 cells through reactive oxygen species production, endoplasmic reticulum stress, caspase-, and mitochondria-dependent signaling pathways. *Environ Toxicol*. 2017;32(6):1725-41. doi: 10.1002/tox.22396.
 33. Park BS, Choi NE, Lee JH, Kang HM, Yu SB, Kim HJ, et al. Crosstalk between Fisetin-induced Apoptosis and Autophagy in Human Oral Squamous Cell Carcinoma. *J Cancer*. 2019;10(1):138-46. doi: 10.7150/jca.28500.
 34. Won DH, Chung SH, Shin JA, Hong KO, Yang IH, Yun JW, et al. Induction of sestrin 2 is associated with fisetin-mediated apoptosis in human head and neck cancer cell lines. *J Clin Biochem Nutr*. 2019;64(2):97-105. doi: 10.3164/jcfn.18-63.
 35. Li Y, Jia S, Dai W. Fisetin Modulates Human Oral Squamous Cell Carcinoma Proliferation by Blocking PAK4 Signaling Pathways. *Drug Des Devel Ther*. 2020;14:773-82. doi: 10.2147/dddt.s229270.
 36. Yadav M, Pradhan D, Singh RP. Integrated analysis and identification of nine-gene signature associated to oral squamous cell carcinoma pathogenesis. *3 Biotech*. 2021;11(5):215. doi: 10.1007/s13205-021-02737-4.
 37. Kubina R, Krzykawski K, Dziedzic A, Kabała-Dzik A. Kaempferol and fisetin-related signaling pathways induce apoptosis in head and neck cancer cells. *Cells*. 2023;12(12):1568. doi: 10.3390/cells12121568.
 38. Kubina R, Krzykawski K, Sokal A, Madej M, Dziedzic A, Kadela-Tomanek M. New Propargyloxy derivatives of galangin, kaempferol and fisetin-synthesis, spectroscopic analysis and in vitro anticancer activity on head and neck cancer cells. *Cells*. 2023;12(18):2288. doi: 10.3390/cells12182288.
 39. Moustafa MA, El-Refaie WM, Elnaggar YSR, El-Mezayen NS, Awaad AK, Abdallah OY. Fucoidan/hyaluronic acid cross-linked zein nanoparticles loaded with fisetin as a novel targeted nanotherapy for oral cancer. *Int J Biol Macromol*. 2023;241:124528. doi: 10.1016/j.ijbiomac.2023.124528.
 40. Yadav M, Kandhari K, Mathan SV, Ali M, Singh RP. Fisetin induces G2/M phase arrest and caspase-mediated cleavage of p21Cip1 and p27Kip1 leading to apoptosis and tumor growth inhibition in HNSCC. *Mol Carcinog*. 2024;63(9):1697-711. doi: <https://doi.org/10.1002/mc.23754>.
 41. Wang Q, Zhang H, Xiang S, Zhang L, Fan J, Xu Z, et al. Targeting MUC1 with fisetin in oral squamous cell carcinoma. *Genes Dis*. 2025;12(3):101357. doi: 10.1016/j.gendis.2024.101357.
 42. Zhang R, Takigawa H, Maruyama H, Nambu T, Mashimo C, Okinaga T. Fisetin inhibits periodontal pathogen-induced EMT in oral squamous cell carcinoma via the Wnt/ β -catenin pathway. *Nutrients*. 2025;17(22):3522. doi: 10.3390/nu17223522.
 43. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. *Res Synth Methods*. 2021;12(1):55-61. doi: 10.1002/jrsm.1411.
 44. Pingping Z, Nan C, Yong T. Phytochemicals and their nanoformulations for overcoming drug resistance in head and neck squamous cell carcinoma. *Pharm Res*. 2025;42(3):429-49. doi: 10.1007/s11095-025-03836-0.
 45. Rahmani AH, Almatroudi A, Allemaleim KS, Khan

- AA, Almatroodi SA. The potential role of fisetin, a flavonoid in cancer prevention and treatment. *Molecules*. 2022;27(24):9009. doi: 10.3390/molecules27249009.
46. Kumar RM, Kumar H, Bhatt T, Jain R, Panchal K, Chaurasiya A, et al. Fisetin in cancer: attributes, developmental aspects, and nanotherapeutics. *Pharmaceuticals (Basel)*. 2023;16(2):196. doi: 10.3390/ph16020196.
 47. Kubina R, Iriti M, Kabała-Dzik A. Anticancer potential of selected flavonols: fisetin, kaempferol, and quercetin on head and neck cancers. *Nutrients*. 2021;13(3):845. doi: 10.3390/nu13030845.
 48. Kubina R, Krzykowski K, Kabała-Dzik A, Wojtyczka RD, Chodurek E, Dziedzic A. Fisetin, a potent anticancer flavonol exhibiting cytotoxic activity against neoplastic malignant cells and cancerous conditions: a scoping, comprehensive review. *Nutrients*. 2022;14(13):2604. doi: 10.3390/nu14132604.
 49. Hu L, Luo Y, Yang J, Cheng C. Botanical Flavonoids: Efficacy, Absorption, Metabolism and Advanced Pharmaceutical Technology for Improving Bioavailability. *Molecules*. 2025;30(5):1184. doi: 10.3390/molecules30051184.
 50. Cattivelli A, Zannini M, De Angeli M, D'Arca D, Minischetti V, Conte A, et al. Bioaccessibility of Flavones, Flavanones, and Flavonols from Vegetable Foods and Beverages. *Biology (Basel)*. 2024;13(12):1081. doi: 10.3390/biology13121081.
 51. Chen YS, Tian HX, Rong DC, Wang L, Chen S, Zeng J, et al. ROS homeostasis in cell fate, pathophysiology, and therapeutic interventions. *Mol Biomed*. 2025;6(1):89. doi: 10.1186/s43556-025-00338-8.
 52. Mercadante AA, Kasi A. Genetics, Cancer Cell Cycle Phases. [Updated 2023 Aug 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK563158/>.
 53. Lu Y, Li A, Liu A, Li M, Wang M. Autophagy in Cancer: Context-Dependent Regulation and Precision Nanomedicine-Enabled Therapeutic Targeting. *Biomedicines*. 2026;14(2):416. doi: 10.3390/biomedicines14020416.

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