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Review Article

Healing with Herbs: Clinical Implications of Botanicals in Oral Cancer: A Comprehensive Systematic Review

Saranya Ramsridhar[1,2,*], Chandini Rajkumar[2], Vishnu Priya Veeraraghavan[1], Arul Prakash Francis[1], Khadijah Mohideen[3], Murali Balasubramaniam[2], Ilanchezhian Jothi Prakaash[4]

[1]Department of Biochemistry, Saveetha Dental College and Hospital, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, INDIA.
[2]Department of Oral Pathology, Sathyabama Dental College and Hospital, Sathyabama Institute of Science and Technology, Chennai, Tamil Nadu, INDIA.
[3]Department of Oral and Maxillofacial Surgery and Diagnostic Sciences, Faculty of Dentistry, Najran University, Najran, KINGDOM OF SAUDI ARABIA.
[4]Department of Orthodontics, Madha Dental College and Hospital, Chennai, Tamil Nadu, INDIA.

ABSTRACT

Background: Oral Squamous Cell Carcinoma (OSCC) poses a significant global health burden, with conventional treatments often limited by severe side effects and suboptimal efficacy. Botanical drugs have emerged as promising complementary therapies due to their multitargeted mechanisms, low systemic toxicity, and ability to enhance treatment outcomes. This review explores their anticancer potential, mechanisms, and therapeutic applications in OSCC. **Aim:** To evaluate the therapeutic potential, mechanisms of action, and clinical relevance of botanical drugs in OSCC treatment and prevention, including their role in managing Oral Mucositis (OM). **Materials and Methods:** A systematic review was conducted following PRISMA guidelines using databases like PubMed, Scopus, Web of Science, and Cochrane. Eligible studies included *in vitro* experiments on OSCC cell lines, animal models, and Randomized Controlled Trials (RCT's) evaluating botanical drugs for OSCC treatment or chemo-radiotherapy-induced OM, while studies on non-standardized medicinal plant extracts were excluded. The ROBINS-I tool evaluated the risk of bias. **Results:** Nine studies met inclusion criteria, covering botanical agents such as genistein, curcumin, resveratrol, and Antitumor B (ATB). These compounds exhibited anticancer effects through apoptosis induction, angiogenesis inhibition, anti-inflammatory properties, and oxidative stress modulation. APG-157 and nanomicelle curcumin capsules effectively alleviated OM, improving patient quality of life. Challenges included low bioavailability and lack of standardization. Risk of bias was low in four studies and moderate in four. **Conclusion:** Botanical drugs demonstrate strong potential for OSCC treatment, offering anti-inflammatory, antioxidant, and anticancer benefits with low systemic toxicity. They may serve as standalone or adjunct therapies, enhancing conventional treatments. However, further large-scale clinical trials and improved formulations are essential for clinical integration.

Keywords: Anticancer, Botanical drugs, Chemo-radiotherapy, Complementary therapy, Oral squamous cell carcinoma, Oral mucositis.

Correspondence:
Saranya Ramsridhar
Department of Biochemistry, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai-600077, Tamil Nadu, INDIA.
Email: saranyaramsridhar@gmail.com

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INTRODUCTION

Oral cancer, predominantly OSCC, represents a significant global health challenge with high mortality and morbidity rates. Conventional treatments such as surgery, radiotherapy, and chemotherapy often come with severe side effects, limited efficacy in advanced stages, and a 5-year survival rate below 50% in many regions. This has prompted the search for alternative therapies, including the use of botanical drugs, which offer promising advantages due to their bioactive phytochemicals with anticancer, anti-inflammatory, and antioxidant properties.[1]

Botanical drugs are standardized, clinically validated pharmaceutical products derived from medicinal plant materials and approved for therapeutic use. They undergo rigorous evaluation for safety, efficacy, and quality, with regulatory oversight from agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA).[2,3] In contrast, plant extracts are raw or semi-processed preparations obtained from plant parts (e.g., leaves, roots, flowers) through methods like solvent extraction or distillation. These extracts contain complex mixtures of phytochemicals that are not standardized for pharmaceutical use and are primarily utilized

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in dietary supplements, cosmetics, or traditional medicine.[4] Recognizing this distinction is essential to ensure that only standardized, evidence-based botanical drugs are considered for therapeutic applications in oral cancer. Botanical drugs play a significant role in the prevention and treatment of oral cancer. They offer multiple therapeutic advantages due to their diverse bioactive compounds, low systemic toxicity, and ability to target key pathways in carcinogenesis.[5]

These natural compounds offer a complementary or alternative approach to conventional therapies due to their multitargeted mechanisms, low systemic toxicity, and affordability. They play a key role in inducing apoptosis by targeting apoptosis pathways, promoting programmed cell death in cancer cells while sparing healthy tissues.[6] For instance, berberine (*Berberis aristata*) and baicalein (*Scutellaria baicalensis*) induce mitochondrial dysfunction in OSCC cells, activating caspase cascades and suppressing tumor growth.[7] Many botanical compounds, such as curcumin (*Curcuma longa*) and resveratrol (*Vitis vinifera*), activate apoptotic pathways in oral cancer cells by modulating key regulators like p53, caspases, and Bcl-2 proteins which prevents uncontrolled cancer cell proliferation.[8,9] Curcumin induces apoptosis, inhibits angiogenesis, and modulates inflammatory pathways. It also possesses strong anti-angiogenetic properties; compounds like Epigallocatechin Gallate (EGCG) from green tea inhibit angiogenesis by suppressing Vascular Endothelial Growth Factor (VEGF) expression, reducing tumor blood supply and promotes apoptosis.

Inflammation is a key driver in cancer development, progression, and metastasis of oral cancer. It contributes to carcinogenesis by creating a tumor-promoting microenvironment through persistent immune activation, oxidative stress, and release of pro-inflammatory mediators. Chronic exposure to carcinogens leads to epithelial damage and activation of immune cells such as macrophages, neutrophils, and dendritic cells, initiating the inflammatory cascade.[10] Botanical drugs like baicalein have anti-inflammatory effects which reduce the expression of inflammatory mediators such as COX-2, NF-κB, and IL-6, curbing tumor progression. It also significantly reduces inflammation and inhibits the process of metastasis by inhibiting Cyclooxygenase (COX) and Lipoxygenase (LOX) pathways, the enzymes that are responsible for producing inflammatory mediators like prostaglandins and leukotrienes. Drugs like gingerol (*Zingiber officinale*) and baicalein act as natural COX and LOX inhibitors.[11,12] Some plant-derived compounds modulate gene expression related to inflammation through epigenetic mechanisms, including DNA methylation and histone acetylation.

Antioxidant properties have a strong significance in preventing and managing oral cancer due to their ability to counteract oxidative stress, a key contributor to carcinogenesis. Antioxidants neutralize Reactive Oxygen Species (ROS), preventing DNA damage, mutations, and cellular transformations that can initiate and promote oral cancer. Carcinogens like tobacco and alcohol generate free radicals that can damage cellular components, including DNA, proteins, and lipids. Antioxidants protect these biomolecules, reducing the mutagenic and carcinogenic effects.[13] Hence, Phytochemicals present in botanical drugs that are rich in antioxidants neutralize ROS, protects against DNA damage and tumor initiation. For instance, lycopene from tomatoes and anthocyanins from berries exhibit strong antioxidant activity.[14,15] Botanical drugs have shown effectiveness in the early stages of oral cancer development by preventing malignant transformation of precancerous lesions. Curcumin, for example, has demonstrated the ability to reverse oral leukoplakia and prevent progression to OSCC.[16]

Botanical compounds like resveratrol enhance the efficacy of chemotherapy and radiotherapy by sensitizing cancer cells and reducing resistance. It suppresses tumor growth by modulating cell cycle regulators and enhancing oxidative stress in cancer cells.[17] Plant-derived antioxidants mitigate the toxicity of conventional treatments, improving patient quality of life. Cancer Stem Cells (CSCs) are a major cause of recurrence and metastasis in oral cancer. Botanical drugs, such as wogonin from *Scutellaria baicalensis*, have shown promise in targeting CSCs by inhibiting their survival pathways.[18]

Carcinogens like tobacco and alcohol generate free radicals damages cellular components, including DNA, proteins, and lipids. Antioxidants protect these biomolecules, reducing the mutagenic and carcinogenic effects.[19] Compounds such as curcumin, resveratrol and baicalein have demonstrated efficacy in modulating molecular mechanisms like apoptosis, cell cycle arrest, and inhibition of angiogenesis.[20] Furthermore, recent literatures suggest that diets rich in plant-based antioxidants reduce oral cancer risk by neutralizing ROS and enhancing immune responses.[21,22]

This systematic review aims to explore the anticancer potential of botanical drugs for oral cancer, by synthesizing evidence from RCTs, animal models, and *in vitro* studies. It further examines their mechanism of action, dosage, clinical outcomes, and adverse effects to assess their potential as complementary or alternative therapies for managing OSCC and chemo-radiotherapy-induced OM.

MATERIALS AND METHODS

Study protocol

The Systematic review adhered to the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for the selection of studies, synthesis of data, and eventual dissemination of results.[23]

Information sources and literature search strategies

Literature search was conducted on PubMed, Scopus, Web of science, Embase, Cochrane and CINAHL to find research papers published from inception till November 2024 that assessed botanical drugs for their prevention and treatment of oral cancer. The MeSH combinations includes "Botanical drugs OR Plant drugs OR Botanical medicine" AND "oral cancer OR anticancer property OR oral cancer treatment OR oral cancer prevention" AND "complementary therapy OR alternative therapy". These keywords were categorized into three groups, and a comprehensive exploration of all conceivable combinations among the terms in these three groups was conducted. The identified articles were then imported into Mendeley Desktop 1.13.3 software (Mendeley Ltd., London, England) to identify and eliminate duplicates.

Study selection

The study selection was based on the following inclusion and exclusion criteria

Eligibility criteria

Inclusion criteria

1. Studies should include botanical drugs used for oral cancer treatment.
2. Studies should include botanical drugs used for the OM treatment induced by oncological therapies.
3. Animal studies and randomized controlled trial.
4. Studies published only in English language.

Exclusion criteria

1. Case reports and case series.
2. Review articles are excluded.
3. Studies about medicinal plant extracts.

All relevant text, tables, and figures were assessed during data extraction, and discrepancies between the two authors were resolved by discussion or consensus. The third reviewer resolved any disagreements occurred between the two reviewers.

Data Extraction

Data including study title, first author, journal, year of publication, place of study, study design, potential components (botanical name), sample size, intervention (dosage), measurement components, method of analysis and outcome assessments were extracted for the process of data synthesis.

Risk of bias analysis

To assess the risk of bias of included studies, A revised tool to assess risk of bias in randomized trials was used. [24] Risk of bias was assessed by two independent reviewers for all the studies included and discrepancies were resolved by discussion with a third reviewer. The domains for risk of bias assessment were based on bias arising from the randomisation process, bias due to deviations from the intended intervention, due to missing outcome data, measurement of the outcome and bias in the selection of the reported result.

RESULTS

Study Selection

The initial search resulted in 109 studies, out of which 29 full-texts articles were selected for the review process. The final synthesis yielded 9 studies after excluding articles which were narrative reviews, case reports and systematic reviews which were included in the current review (Figure 1).

Study characteristics

All the included studies were based on the botanical drugs used for oral cancer treatment and those used for the treatment of the OM occurring due to chemotherapy/radiotherapy. The studies included in the review are *in vitro*, animal studies and RCTs. The characteristics such as botanical drugs, potential components (botanical name), sample size, intervention (dosage), measurement components and method of analysis were included. A total of 9 botanical drugs were included in the data synthesis, which includes three RCTs, two animal studies, two *in vitro*, a combination of animal study and a RCT and a combination of animal and *in vitro* study (Tables 1 and 2).[25-33]

Outcome assessment

Genistein was effective in downregulating VEGF expression, reducing angiogenesis and invasion *in vitro*, though tumor growth and metastasis remained unaffected. ZengShengPing demonstrated promising chemopreventive effects by significantly reducing oral cancer incidence in animals and lesion size in humans. SAMITAL showed notable efficacy in reducing OM, pain and improving the quality of life in patients undergoing chemo/radiotherapy. APG-157 and nanomicelle curcumin capsules demonstrated anti-inflammatory effects by reducing pro-inflammatory cytokines like IL-1β and IL-6 and improving OM outcomes in clinical settings. Resveratrol and quercetin synergistically inhibited cancer cell growth and induced apoptosis in SCC-15 cells, with higher efficacy in combination. PAC (*Curcumin analog*) combined with cisplatin enhanced cancer cell death by inducing apoptosis, autophagy, and oxidative stress, while inhibiting mitochondrial potential. ATB demonstrated low bioavailability, emphasizing the need for advanced delivery systems to enhance its therapeutic efficacy. These findings underscore the multitargeted mechanisms of botanical drugs, including anti-inflammatory, apoptotic, and angiogenesis inhibition effects, while highlighting challenges like bioavailability and the need for further clinical validation. The

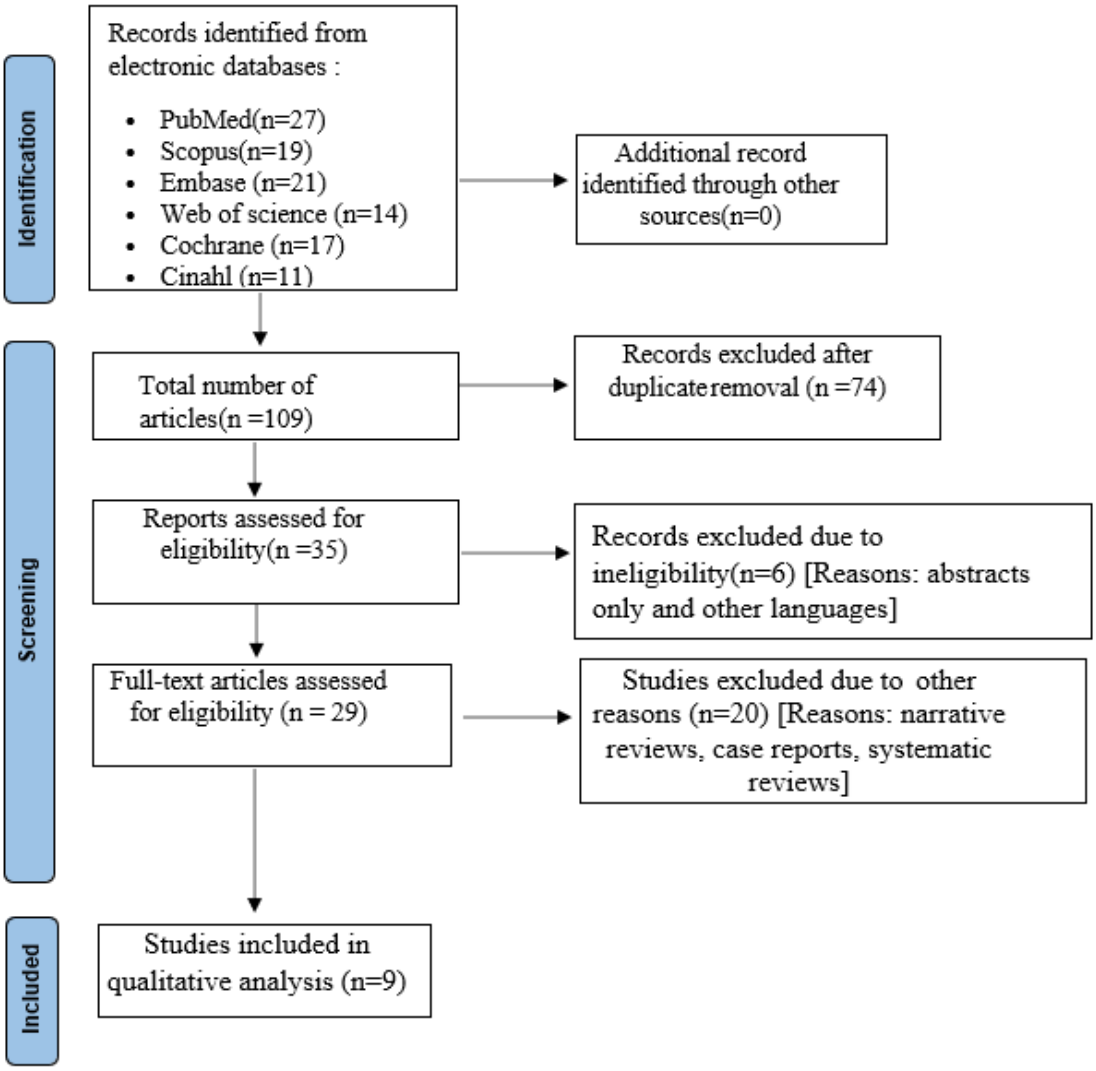

Figure 1: PRISMA flowchart displaying the process of selection of studies.

included studies exhibited methodological heterogeneity in terms of study design (*in vitro*, animal models, and RCTs), interventions, and outcome measures, which precluded quantitative synthesis and necessitated a narrative approach to data interpretation.

Risk of bias and applicability

Figures 2a and 2b shows the risk of bias assessment of all the studies according to the ROBINS-I tool.[24] Nine studies were used for the bias assessment out of which four showed a moderate risk of bias and one showed a low risk of bias across all the domains, implying strong methodological outcomes and reporting.

DISCUSSION

Therapeutic mechanisms of botanical drugs

Botanical drugs offer a multi-targeted approach to oral cancer treatment, combining chemopreventive and therapeutic effects. Their advantages lie in their multitargeted actions, low systemic toxicity, and ability to work synergistically with conventional therapies. This systematic review encompasses various studies investigating the efficacy of botanical drugs in managing oral cancer, emphasizing their mechanisms, outcomes, and potential for integration into clinical practice. The evidence demonstrates that botanical drugs offer significant therapeutic benefits, often targeting critical oncogenic pathways while reducing the adverse effects associated with conventional therapies. Figure 3 summarizes the key mechanisms by which botanical drugs exert their therapeutic effects in OSCC.

Evidence from Key Agents

Genistein

Genistein, derived from *Glycine max* (soybean), demonstrated anti-angiogenic properties in oral cancer cells by down-regulating VEGF mRNA expression and reducing gelatinolytic activity. A study demonstrated that genistein reduced the invasive potential of OSCC cells *in vitro*.[25] This was evidenced by its ability to suppress the activity of enzymes such as MMPs, particularly

Table 1: Characteristics of the included studies.

Author, Year	Country	Study design	Botanical drug	Potential components (botanical name)	Sample size	Intervention (dosage)
Myoung H *et al.*, 2003[25]	Korea	*In vitro*/Animal study	Genistein	Soybean (*Glycine max*).	NA	Cell culture: "Matrigel" matrix-coated 9-mm cell culture was used where HSC-3 cells were seeded and cultured with serum-free DMEM. Control group: No Genistein Experimental Group: Genistein 0.5 mg/kg.
Sun Z *et al.*, 2010[26]	China	Animal study/ RCT	Zeng Sheng Ping (ZSP)	*Sophora tonkinensis* Gagnep., *Bistorta officinalis* Delarbre., *Sonchus arvensis* L., *Prunella vulgaris* L., *Dioscorea bulbifera* L., *and Dictamnus dasycarpus* Turcz.,	Animals: 10 each in 3 groups Humans: 60 each in placebo and study group.	Animal models:6 g/kg BW/day for 10 weeks Human subjects:4 tablets, 3 times per day for 8–12 months.
Pawar D *et al.*, 2013[27]	Italy	RCT	SAMITAL	*Vaccinium myrtillus, Macleaya cordata* and *Echinacea angustifolia.*	Placebo group: 10 Experimental Group: 20.	Placebo group: Coloured sachet without the drug Experimental Group: Received SAMITAL 4 times/day for 50 days along with chemo/ Radiotherapy.
Siddappa G *et al.*, 2017[28]	USA	Animal study	Curcumin and Metformin.	Curcumin (*Curcuma longa*) and Metformin.	115	Control group: Plain drinking water Experimental Group: 50 µg/mL [33] 4-Nitroquinoline-1-oxide (4NQO).
Basak SK *et al.*, 2020[29]	USA	RCT	APG-157	Curcumin *(Curcuma longa).*	32	3 × 100 mg and 3 × 200 mg.
Singh V *et al.*, 2020[30]	India	In vitro	Phytochemicals-Resveratrol and quercetin.	Resveratrol (*Vitis vinifera*), and quercetin (*quercetum*).	NA	Trypan Blue Dye Exclusion Assay: Resveratrol (10, 20, 25, and 50 mM) and quercetin (10, 25, and 50 mM).

Author, Year	Country	Study design	Botanical drug	Potential components (botanical name)	Sample size	Intervention (dosage)
Semlali A *et al.*, 2023[31]	Saudi Arabia	In vitro	PAC/cisplatin	Curcumin (*Curcuma longa*) analog.	NA	Different concentrations of cisplatin (ranging from 0.1 _M to 1 _M), either alone or in conjunction with PAC (2.5 and 5 _M.
Bui D *et al.*, 2021[32]	USA	Animal study	Antitumor B (ATB)	KAC:matrine, dictamine, fraxinellone, and maackiain.	5	i.v. (500 mg/kg ATB), i.p (500 mg/kg ATB), and oral administration (100, 500, 4000 mg/kg ATB and 5 mg/kg individual KACs).
Kia SJ *et al.*, 2021 [33]	Iran	RCT	Nanomicelle Curcumin capsules	Curcumin (*Curcuma longa*).	Placebo group:25 Experimental Group: 25.	Placebo group: capsules made of sugar Experimental Group: 80 mg nanomicelle Curcumin capsules Both the groups consumed the capsules twice a day after food along with chemo/radiotherapy.

DMEM: Dulbecco's Modified Eagle Medium; KAC: key active components.

MMP-2, which are involved in extracellular matrix degradation and cancer cell invasion. Immunohistochemical analysis revealed lower CD31 immunoreactivity in genistein-treated OSCC cells, indicating reduced endothelial cell presence and angiogenic activity in the tumor microenvironment. Despite these molecular effects, no statistically significant difference in tumor growth and metastasis was observed between the experimental and control groups as the results were not significant. This suggests that while genistein may inhibit specific molecular pathways, its standalone application may not be sufficient, necessitating future studies on combination therapies to enhance efficacy are required to statistically evaluate these findings.

Zeng Sheng Ping (ZSP)

ZSP, a multi-herb formulation containing components like *Sophora tonkinensis* and *Prunella vulgaris*, showed significant chemopreventive effects in both animal models and human subjects. In animal studies, the incidence of oral cancer was reduced from 55.2% to 22.2%, and in humans, lesion size decreased in 67.8% of the study group compared to 17% in the placebo group. The results from the combined animal study and RCT shows the multi-targeted action of ZSP, which reduces cellular proliferation and promotes regression of precancerous lesions, making it a promising preventive strategy.[26] Furthermore, in a DMBA-induced hamster model, ZSP-2 significantly reduced tumor development by inhibiting inflammation, angiogenesis (reduced CD31, VEGF, and COX-2), and promoting apoptosis (increased caspase-9 and p53, upregulated PTEN) highlighting its potential for improved efficacy and reduced toxicity in chemoprevention.[34]

SAMITAL

SAMITAL, formulated with *Vaccinium myrtillus, Macleayacordata*, and *Echinacea angustifolia*, demonstrated significant efficacy in reducing OM severity in patients undergoing chemo/radiotherapy. The experimental group showed notable reductions in OM and pain from day 4, along with improved quality of life. This indicates the potential of SAMITAL as an adjunct therapy to mitigate treatment-related toxicities, improving patient compliance and outcomes.[27] SAMITAL granules when administered through oral suspension of 20 mL, four-times daily has been proven to be reducing the chemo-radiotherapy induced OM and improved the quality of life of patients with head and neck carcinomas.[35]

Curcumin-Based Therapies

Botanical drugs like curcumin (*Curcuma longa*) and resveratrol (*Vitis vinifera*) suppress inflammatory pathways by downregulating

NF-κB, COX-2, and pro-inflammatory cytokines. This is crucial in inflammation-driven cancers such as OSCC. The combination of curcumin and metformin exhibited superior efficacy in reducing tumor volume compared to individual treatments. Tumor volume in the combination group was significantly smaller compared to curcumin and metformin individually. This highlights the synergistic potential of combining botanical drugs with existing pharmacological agents to target cancer stem cells and inhibit tumor progression.[36]

APG-157, a curcumin-based drug, achieved significant reductions in pro-inflammatory cytokines (IL-1β, IL-6, and IL-8) in the salivary supernatant of cancer patients. Liquid chromatography/mass spectrometry revealed therapeutic levels of curcumin analogs, peaking at 3 hr post-administration. These findings demonstrate the anti-inflammatory and immunomodulatory effects of APG-157, making it a promising systemic and local therapy for oral cancer management.[28,29]

Similar to these findings, another *in vitro* study evaluated PAC in combination with cisplatin, significantly enhanced oral cancer cell death through apoptosis, autophagy, and mitochondrial stress. The study highlights the importance of botanical analogs in potentiating the effects of conventional chemotherapeutic agents, reducing the required dosage of cisplatin and minimizing associated toxicities.[31] Nanomicelle curcumin capsules significantly reduced the severity of OM and pain in patients undergoing chemo/radiotherapy. The enhanced bioavailability and sustained release of curcumin highlight the potential of nanotechnology in improving the therapeutic efficacy of botanical drugs. The study group exhibited significantly better outcomes compared to the placebo group in all measured parameters. Additionally, NRS (Numerical Rating Scale) incremental gradient

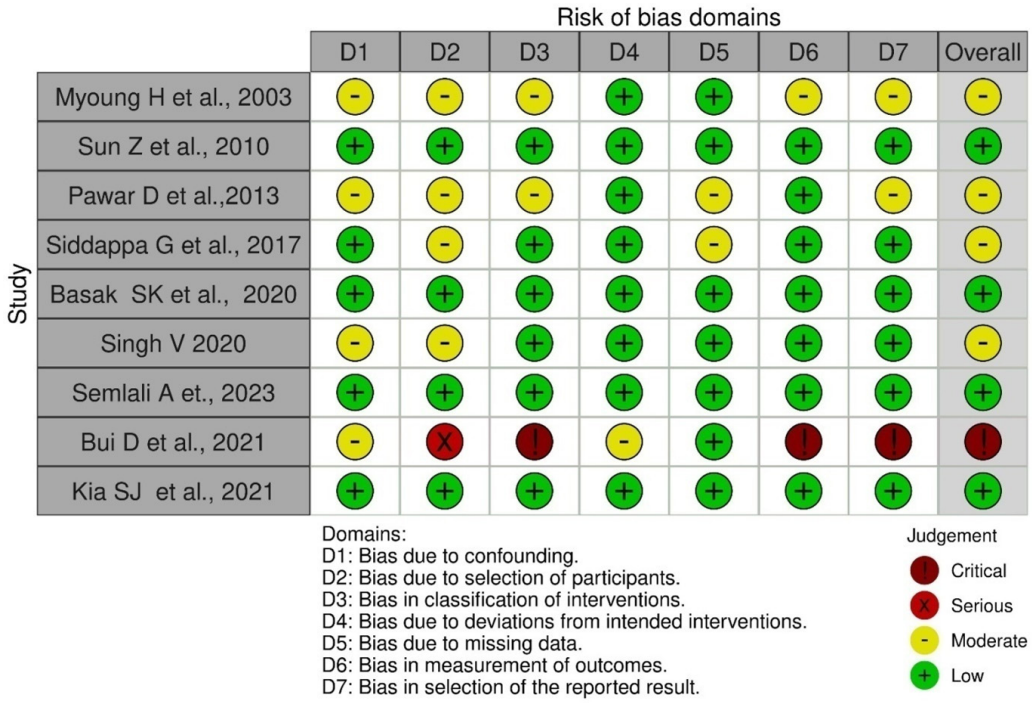

Figure 2a: ROBINS-I tool for the RoB evaluation of the included studies.

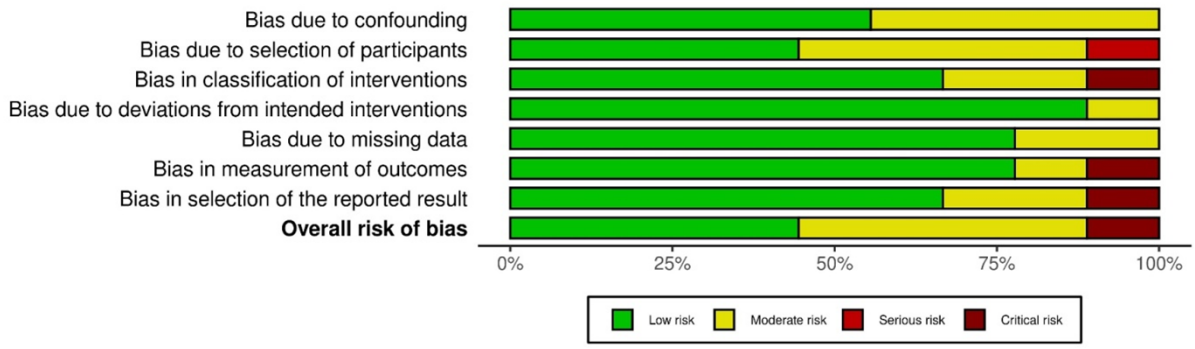

Figure 2b: Summary plot of the RoB evaluation of the included studies with ROBINS-I.

in control group was more than study group. OM severity in patients who underwent only chemotherapy in the control group were significantly more than the study group in all weeks. In patients who were under chemotherapy and head and neck radiotherapy, OM in control group was significantly more intense than the study group only in the fourth and seventh weeks.[33]

Resveratrol and Multi-Phytochemical Strategies

The combination of resveratrol (*Vitis vinifera*) and quercetin (*Quercetum*) showed enhanced efficacy in inducing apoptosis and reducing cell proliferation in SCC-15 oral cancer cells. These effects are attributed to its capacity to modulate various signaling pathways involved in cell growth and survival.[37] In the included *in vitro* study, each resveratrol compound individually inhibited growth by 40-50%, their combination led to 50% inhibition at lower concentrations, underscoring their synergistic effects. This demonstrates the potential of multi-phytochemical approaches to maximize therapeutic outcomes.[30] Similarly, resveratrol has been shown to inhibit glioblastoma cell growth and acts as chemo-preventive agent against cancers such as breast, oral, pancreatic, brain, prostate, and lung.[38]

ATB

ATB is composed of six Chinese herbs containing Key Active Components (KACs) like matrine and dictamine, demonstrated low oral bioavailability, ranging from 0.2% to 9%. Pharmacokinetic study in mice revealed that these components have low oral bioavailability, primarily due to first-pass metabolism in the liver and intestines. Notably, matrine exhibited higher concentrations in saliva compared to plasma, suggesting its preferential distribution to the oral cavity, which may enhance its therapeutic effects against oral cancer. Despite its limited bioavailability, pharmacokinetic studies suggest the need for improved delivery systems to harness its anticancer potential effectively. [32]

In a study involving 4-NQO-induced oral cancer model in mice, ATB administration resulted in a significant reduction in oral tumor multiplicity. Specifically, treatment with ATB led to a 65% decrease in tumor formation, indicating its potential as a chemopreventive agent against oral cancer.[39] Furthermore, a clinical study involving healthy volunteers examined the secretion of matrine, one of ATB's active compounds, into human saliva. Participants received a single oral dose of ATB tablets (2400 mg), and the study monitored matrine levels in plasma and saliva. No adverse effects were reported during this study, indicating that ATB was well-tolerated in a clinical setting.[40]

While these studies suggest that ATB has a favorable safety profile, it is important to note that comprehensive data on potential adverse effects especially with long-term use are limited. As with any therapeutic agent, individual responses can vary and the possibility of adverse effects cannot be entirely ruled out. Therefore, further clinical studies are warranted to fully assess the safety and efficacy of ATB in the prevention and treatment of Oral cancer.

Adverse Effects of Botanical Drugs

While botanical drugs demonstrate promising therapeutic potential, their safety profiles must be considered. Curcumin (*Curcuma longa*) has been associated with mild gastrointestinal disturbances, including nausea and diarrhea, particularly at higher doses.[36] Resveratrol (*Vitis vinifera*) may cause abdominal discomfort, diarrhea, and nausea at doses of 2–5 g/day.[41] ZSP

Table 2: Outcome of the reported studies based on the botanical drug, measurement and analysis.

Author, Year	Botanical drug	Measurement components	Method of analysis	Outcome assessment
Myoung H *et al.*, 2003[25]	Genistein	Genistein at different concentrations (0.5–95.0 μg/mL) for 24 hr.	*In vitro*: Cell proliferation assay, northern blot analysis for VEGF, bFGF and MMP-2, *in vitro* invasion assay and gelatin zymography.	Down-regulation in VEGF mRNA expression, but not in bFGF and MMP-2 mRNA expression, reduced gelatinolytic activity, a significantly lower CD31 immunoreactivity were observed. Tumor growth and metastatic behavior in the experimental group and the control group were similar with no significant difference.

Author, Year	Botanical drug	Measurement components	Method of analysis	Outcome assessment
Sun Z *et al.*, 2010[26]	ZengShengPing	ZSP	AgNOR and PCNA-labeling index.	Animals: Incidence of oral cancer (tongue) reduced from 55.2% to 22.2% in the study group ($p < 0.05$). Humans: Size of the oral lesion reduced in 67.8% of the subjects in the study group compared to 17% in the placebo group ($p < 0.01$).
Pawar D *et al.*, 2013[27]	SAMITAL	Anthocyanosides, alkaloids and alkylamides.	Investigator-modified WHO scale for OM adapted from International Mucositis Scale and the WHO Mucositis Scale.	SAMITAL group showed a significant ($p < 0.05$) reduction in OM, pain reduction from day 4 till the end of the course and improvement in the quality of life.
Siddappa G *et al.*, 2017 [28]	Nitroquinoline-1-oxide (4NQO)	CSC-specific markers (*CD44* and *CD133*).	FACS Assay; Cell Migration Assay; Clonogenic Survival Assay.	Tumor volume was reduced in the combination arm (0.69±0.03 mm^3; *p= 0.0431*), when compared to the individual treatment arms (curcumin: 2.54 mm^3; metformin: 1.44±0.33 mm^3) and the Control Arm II (6.66±2.37 mm^3).
Basak SK *et al.*, 2020 [29]	APG-157	curcumin, DMC, Bisdemethoxycurcumin (BDMC), Tetrahydrocurcumin (THC), Glucuronidated Curcumin (CG), DMC-glucuronide (DMCG), and BDMC-glucuronide (BDMCG) concentrations with hexadeuterated curcumin.	liquid chromatography/mass spectrometry.	Treatment with APG-157 resulted in circulating concentrations of curcumin and analogs peaking at 3 hours with reduced IL-1β, IL-6, and IL-8 concentrations in the salivary supernatant fluid of patients with cancer.

Author, Year	Botanical drug	Measurement components	Method of analysis	Outcome assessment
Singh V *et al.*, 2020 [30]	Phytochemicals-Resveratrol and quercetin	Combination of Resveratrol and quercetin on Cal-33 and SCC-15 OCCs and noncancerous HEK-293 cells.	MTT assay; Trypan Blue Dye Exclusion Assay; Cell Cycle Analysis;Quantitative Reverse Transcription/ Polymerase Chain Reaction; Western Blot Analysis; Comet Assay or Single-Cell Gel Electrophoresis.	Trypan Blue dye exclusion assay: Individually, Resveratrol at 10 μM and 25 μM concentration in SCC-15 cells showed a 40% and 50% inhibition respectively; however, 25 μM concentration exhibited a significant increase in the percentage of cell death (p-value < 0.001) and Quercetin at 10 μM and 50 μM concentration showed a 50% inhibition of cell growth in SCC-15 cells (p-value < 0.05 and p-value 0.03). In combination, 25 μM of quercetin with 20 μM of resveratrol concentration in SCC-15 cells showed 50% inhibition of cell growth in SCC-15 cells. On the contrary, 50% inhibition of cell growth in Cal-33 cells was observed with 10 μM of quercetin and resveratrol concentration each.
SemlaliA et., 2023 [31]	PAC/cisplatin	PAC (1, 2.5, 5, and 10 _M) with and without cisplatin (0.01, 0.1, 0.5, 0.8, and 1 nM).	Cell growth was measured using the MTT assay, while cell cytotoxicity was evaluated using an LDH assay.	Enhanced oral cancer cell death by inducing apoptosis, autophagy, and oxidative stress. Inhibits the mitochondrial membrane potential.
Bui D *et al.*, 2021 [32]	Antitumor B (ATB)	Oral bioavailability	Pharmacokinetic parameter analysis.	KACs at 500 mg/ Kg ATB dose oral bioavailability values were 9.0 ± 3.3%, 4.6 ± 2.8%, 3.9 ± 1.9%, and 0.2 ± 0.1% which are low.

Author, Year	Botanical drug	Measurement components	Method of analysis	Outcome assessment
Kia SJ *et al.*, 2021[33]	SinaCurcumin	Curcumin	WHO Mucositis Scale for measuring OM; NRS for pain score.	Severity of OM were significantly high in the placebo group in the first ($p = 0.010$), fourth ($p = 0.022$) and seventh ($p < 0.001$) weeks compared to the study group. Pain grade was lower in the study group in the seventh week ($p = 0.001$).

AgNOR: Silver Stained Nucleolar Organizer Region; CSC: Cancer Stem Cell; HEK: Human Embryonic Kidney; bFGF: Basic Fibroblast Growth Factor; MMP 2: Matrix Metalloproteinase-2; NRS: Numerical Rating Scale; OCC: Oral Cancer Cells; OM: Oral Mucositis; PCNA: Proliferating Cell Nuclear Antigen; SCC: Squamous Cell Carcinoma; VEGF: Vascular Endothelial Growth Factor; ZSP: Zeng Sheng Ping.

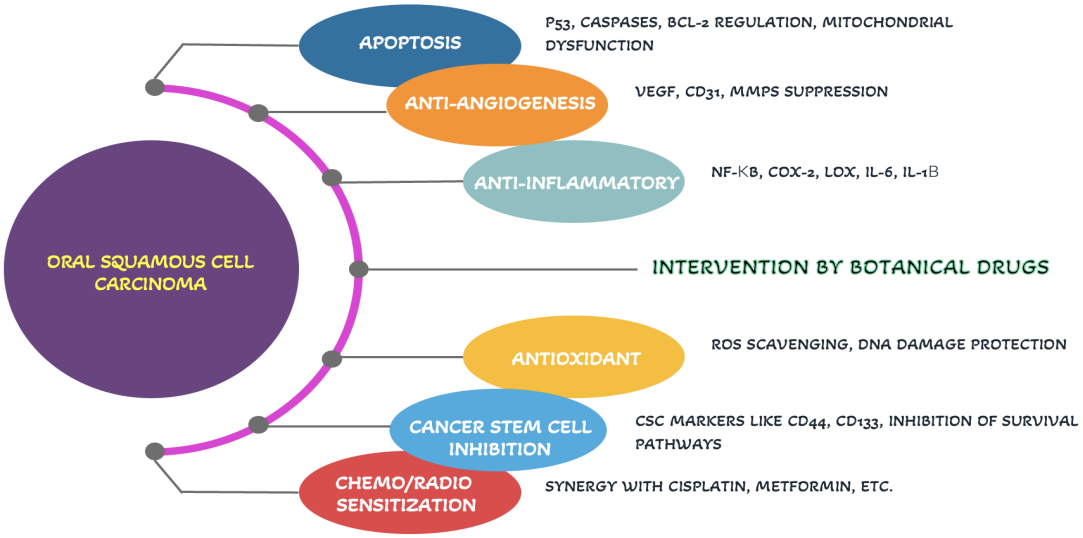

Figure 3: Schematic representation of the major molecular pathways targeted by botanical drugs in OSCC.

has been linked to elevated Alkaline Phosphatase (ALP) levels in animal studies, indicating potential hepatotoxicity.[34] Though ATB was well-tolerated in early human trials, long-term safety data are lacking.[40] These findings highlight the importance of dose optimization, long-term toxicity assessment, and formulation refinement to ensure patient safety.

Strengths and Limitations

This review has several strengths, including adherence to PRISMA guidelines, a comprehensive search of six major databases, and inclusion of evidence from *in vitro*, animal, and clinical studies. It also critically appraises the therapeutic potential of standardized botanical drugs specifically for OSCC and chemo-radiotherapy-induced OM, providing a translational perspective. However, limitations exist. The exclusion of non-English studies may have introduced language bias. The included studies exhibit methodological heterogeneity in design, interventions, and outcomes, limiting direct comparisons and precluding meta-analysis. Additionally, the small number of high-quality clinical trials reduces the generalizability of the findings.

Future Research Directions

Future studies should focus on standardizing botanical formulations with defined active components, conducting well-designed RCTs (including combinatorial therapies), and developing bioavailability-enhancing strategies such as nanocarriers. Long-term safety, herb–drug interactions, and molecular profiling for personalized therapy also warrant investigation to support clinical integration.

CONCLUSION

This review highlights the multifaceted mechanisms and therapeutic potential of botanical drugs as complementary or alternative therapies for oral cancer and chemo-radiotherapy-induced OM. Their anti-inflammatory and antioxidant properties make them promising candidates for tumour suppression, symptom relief, and improved quality of life. Integrating these agents with conventional treatments may offer a holistic approach to oral cancer management. However, challenges such as low bioavailability and lack of standardization necessitate advanced formulation techniques and rigorous large-scale clinical trials. Addressing these gaps could facilitate the safe and effective incorporation of botanical drugs into mainstream cancer care.

ABBREVIATIONS

OSCC: Oral Squamous Cell Carcinoma; **PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **ROBINS-I:** Risk of Bias in Non-randomized Studies–of Interventions; **ATB:** Antitumor B; **EGCG:** Epigallocatechin gallate; **VEGF:** Vascular endothelial growth factor; **COX:** Cyclooxygenase; **LOX:** Lipoxygenase; **ROS:** Reactive Oxygen Species; **CSs:** Cancer stem cells; **OM:** Oral Mucositis; **RCT:** Randomized Controlled Trial; **IL:** Interleukin; **MMP:** Matrix Metalloproteinase; **ALP:** Alkaline phosphatase; **NF-κB:** Nuclear Factor-kappa B; **COX:** Cyclooxygenase; **DMEM:** Dulbecco's Modified Eagle Medium; **KAC:** Key active components; **AgNOR:** Silver stained nucleolar organizer region; **HEK:** Human embryonic kidney; **bFGF:** Basic fibroblast growth factor; **NRS:** Numerical Rating Scale; **OCC:** Oral cancer cells; **PCNA:** Proliferating cell nuclear antigen; **ZSP:** Zeng Sheng Ping.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

This systematic review explores the therapeutic potential of botanical drugs in the treatment of OSCC and chemo-radiotherapy-induced OM. OSCC remains a significant global health burden, with conventional treatments often limited by toxicity and suboptimal long-term outcomes. Botanical drugs, derived from well-characterized medicinal plants and subjected to regulatory scrutiny, offer a promising adjunct or alternative due to their multi-targeted mechanisms, low toxicity, and affordability.

A comprehensive search was conducted across six major databases (PubMed, Scopus, Web of Science, Embase, Cochrane, and CINAHL) up to November 2024, in adherence with PRISMA guidelines. After screening 109 records, 9 studies (including RCTs, animal studies, and *in vitro* experiments) met the inclusion criteria and were subjected to critical appraisal using ROB 2.0 and ROBINS-I tools.

The findings indicate that botanical drugs exhibit significant anti-cancer effects in OSCC through pathways involving apoptosis induction, angiogenesis inhibition, anti-inflammatory activity, and antioxidant mechanisms. Key compounds such as curcumin, resveratrol, baicalein, genistein, and quercetin showed efficacy in modulating cancer-related pathways and improving OM symptoms. Notably, agents like SAMITAL and nanomicelle curcumin improved patient-reported outcomes in clinical settings.

While botanical drugs offer notable promise, challenges such as low bioavailability, limited clinical trials, and lack of standardization persist. This review underscores the need for further pharmacokinetic optimization and robust clinical validation to support the integration of botanical drugs into mainstream oral cancer management.

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