



REVIEW ARTICLE

Alternative Medicine in Treatment of Oral Cancer: Insights and Advances

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OPEN ACCESS

PUBLISHED

31 July 2025

CITATION

Baruah, N., Yaji, A., et al., 2025.
Alternative Medicine in Treatment
of Oral Cancer: Insights and
Advances. Medical Research
Archives, [online] 13(7).

<https://doi.org/10.18103/mra.v13i7.6528>

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DOI

<https://doi.org/10.18103/mra.v13i7.6528>

ISSN

2375-1924

ABSTRACT

Oral squamous cell carcinoma continues to pose a major clinical challenge, as even the most advanced treatment options are often associated with significant toxicity and poor long-term outcomes. This study investigates the potential of integrating alternative medicine into existing treatment paradigms, addressing the question of whether alternative therapies can enhance patient outcomes in oral cancer treatment.

A non-systematic review was conducted analysing 21 alternative medicines and their efficacy as mainstay treatment, as well as adjuvant therapy for oral squamous cell carcinoma, focusing on their mechanisms of action, current research status, and future clinical applicability. Significant findings revealed that herbal remedies such as curcumin, celastrol, saffron, and quercetin demonstrate multi-targeted effects, including induction of apoptosis, inhibition of tumor proliferation, modulation of inflammatory and immune pathways, epigenetic regulation, and potentially mitigate the adverse effects of standard treatments.

The results indicate that alternative medicine can significantly enhance the efficacy and safety of conventional therapies, supporting a more holistic approach to patient care. However, large scale clinical trials are necessary to establish standard protocols for their use, assess their safety and efficacy, and determine the optimal integration methods. By fostering interdisciplinary collaboration, this study advocates for a comprehensive framework that includes both alternative and conventional medicine in managing oral cancer, ultimately improving patient outcomes and quality of life.

Keywords: Oral squamous cell carcinoma, Herbal medicine, Chinese medicine, Ayurveda, Phytochemicals, Targeted cancer therapy.

Introduction

As per Globocan 2022, lip and oral cavity cancer is the 16th most common type of cancer in the world with an incidence of 3,89,846 new cases¹. Although there are several approaches being used successfully in the treatment of oral cancer, the complete cure or prevention remains elusive^{2,3}.

Interdisciplinary team approach is a promising measure in the healthcare industry. Nojack Grammar, defined it as the method whereby health care providers from various specialities collaborate to meet common patient needs and provide the most comprehensive treatment planning and implementation of services for patients with different diagnoses⁴.

In theory, a multidisciplinary team makes decisions about oral cancer management following a thorough clinical and radiological review. The mainstay of treatment for OSCC is still surgery. Chemoradiation (CRT) or radiation therapy (RT) is typically used as an adjuvant treatment for individuals who have a high risk of recurrence or also as the primary treatment in cases where surgery is not indicated. But these integral treatments cause numerous side effects leading to a decrease in the patient's quality of life. Hence the need for an alternative or a supplementary treatment is warranted so as to treat the disease and yet maintain a state of well being for the patient⁵.

Although modern medicine incorporates an interdisciplinary team approach in managing oral cancer there is a limited number of literature that teams with alternative medicine specialities in mainstay cancer treatment.

Alternative medicine is a broad term encompassing a variety of medical modalities which range from the ancient Eastern practices of acupuncture and Tai chi to herbal medicine, Reiki, chiropractic manipulation, and more. The term "alternative medicine" is named so as it is regarded as an "alternative" to allopathic medicine or modern medicines⁵.

Many Chinese/ayurvedic herbal medications have gained attention in the last two decades for their ability to both sensitize and defend against radioactive and chemotherapy treatments for cancers, particularly bone cancer and head and neck tumors.⁶ The ancient Indian holistic therapy known as Ayurveda has recently acquired popularity for treating a variety of illnesses, including treatments for oral squamous cell carcinoma and other potentially cancerous conditions. Preparations from Ayurveda have been utilized to boost immunity, alleviate symptoms, and even lessen the side effects of traditional treatments like chemotherapy and radiation⁷.

Also, various herbal medicines have been studied and found to have tumoricidal properties. They are generally considered safe and have few or no adverse effects, especially when compared to synthetic drugs. Hence we can consider them as a promising option in treating oral cancer. Integrating these alternative medicines in an interdisciplinary approach might aid in treating cancer without decreasing the quality of life. However, there seems to be a lack of literature that has evaluated their impact from a research oriented background. Further there is a lack of studies assessing the pharmacologic as well as toxicology profile of the multiple properties of herbal medicines.

The aim of this review is to shed light on the current research status of various herbal alternative medicines which are being studied for their efficacy in treatment of oral cancer, focusing mainly on their mechanism of action and provide information that can help decide their ability to be incorporated in oral cancer treatment.

Methodology:

A non-systematic literature search was conducted in PubMed and Google Scholar for articles published from 2015 to 2025. The search included the following keywords and Boolean operators: ("oral cancer" OR "oral neoplasm") AND ("alternative medicine" OR "complementary

medicine" OR "ayurveda" OR "herbal medicine" OR "chinese medicine"). The search was limited to articles published in English.

The search in PubMed identified 209 results, which were individually reviewed, yielding 185 articles. The search in Google Scholar yielded 854 articles. The search was limited to Research studies, case reports, or clinical trials with full text that used alternative medicine for the targeted treatment of oral cancer. Full texts or abstracts that answered the following questions were included in the study.

- Name/identification of the drug.
- Comprehensive profile of the drug.
- Mechanism of action/ pharmacological rationale behind its selection.
- Specific biomolecular targets modulated by the use of the drug.
- Any adverse effects observed or side effects arising from its use.
- Results/outcomes.

Twenty-seven articles were identified that met the above criteria for inclusion and were finally considered for review after thoroughly examining the quality and content of each one.

We have included the review of 21 herbal or alternative medicines which have been used in treatment of oral cancer. We have specifically focused on their mechanism of action and research studies testing their efficacy exclusively in oral cancer.

1. PURE NEEM LEAF EXTRACT

Neem leaf extract is a natural substance obtained from the foliage of the *Azadirachta indica* tree, which is part of the Meliaceae family. Native to the Indian subcontinent, this botanical agent has been employed in traditional medicine systems, like Ayurveda, for centuries. The extraction process yields a complex mixture of bioactive compounds, including azadirachtin, nimbin, and other limonoids, which are believed to contribute to its therapeutic properties⁸.

Mechanism of action:

Neem leaf extract has garnered interest for its potential to combat cancer through various biological activities.

- Impede the uncontrolled proliferation of malignant cells and trigger programmed cell death (apoptosis) in cancerous cells⁸
- Interfere with tumour angiogenesis.
- Modulation of the body's detoxification enzymes, potentially aiding in the elimination of cancer-causing substances. Neem extract can influence xenobiotic metabolizing enzymes which play a crucial role in the body's detoxification processes, either activating or deactivating potential carcinogens⁹.
- Inhibit Phase I enzymes (which can activate carcinogens) and induce Phase II enzymes (which detoxify them). This dual action could provide a protective effect against cancer development⁹.
- When used in combination with other cancer treatments can potentially enhance the effects of chemotherapy or radiation therapy by promoting cell cycle arrest and reducing radio resistance in OSCC and reduce some of the adverse side effects associated with conventional cancer treatments¹⁰.

Current research status:

-At present, neem leaf extract is being explored as a potential adjunct or complementary therapy rather than a mainstream treatment modality. Study by Morris J et al. (2019) investigates its effects on key signaling pathways (STAT3, AKT, and ERK1/2) involved in cancer growth and spread. It also investigates its ability to modulate the immune system¹⁰.

Future requirements for implementing in clinical practice:

Clinical trials are required to determine its safety and efficacy in humans.

2. TRIPHALA

Triphala (TRP), an Ayurvedic and Thai traditional medicine, is derived from the dried fruits of *Terminalia chebula*, *Terminalia bellirica*, and *Phyllanthus emblica* or *Embolica officinalis*¹¹.

Mechanism of action:

-Inhibit the growth and induce the death of cancer cells effectively.

-A number of active compounds in the formula, especially tannins, induce apoptotic cell death via free radical production in cancer cells.

-High levels of antioxidants in the triphala is capable of protecting normal cells from any free radical-mediated injuries effectively.

-Triphala has high potentials for inhibition and prevention of mutagenesis and metastasis of cancer cells¹².

Current research status:

-Wongnoppavich A assessed anti-tumor effects and underlying genetic mechanisms of herbal medicine Triphala (TRP) in oral squamous cell carcinoma (OSCC) cell lines.(CAL-27 and SCC-9). The functional rescue assay was conducted to investigate the effect of applying the inhibitor and activator of an enriched pathway on the phenotypes of cancer cells. In addition, the zebrafish xenograft tumor model was established to investigate the influence of TRP extracts on tumor growth and metastasis in vivo. The study demonstrated triphala to have a significant inhibitory effects on cell metabolic activity, migration, invasion, and proliferation in OSCC cell lines, accompanied by the induction of apoptosis, which was mediated through the inactivation of the PI3K/Akt pathway¹².

Future requirements for implementing in clinical practice:

-Studies in the mechanism of action of Triphala and the product development as well as safety evaluation of the standard herbal extract are definitely required for future pharmacological applications of Triphala as anticancer agents for cancer therapy.

3.IMPATIENS BALSAMINA L.

Impatiens balsamina L. is used as traditional herbal medicine to treat rheumatism, swelling, beriberi, bruising, and fingernail inflammation¹³.

Mechanism of action:

The crude extracts of I. balsamina L. contain peptides, quinones, and flavonoids which are

known to possess antimicrobial, antipruritic, and anti-dermatitic effects¹³.

Current research status:

Ji-Ae Shin et al assessed Down-regulation of Akt by methanol extracts of Impatiens balsamina L. in oral cancer cell line and demonstrated that MEIB decreased cell viability and induced apoptosis in human OSCC cells. Expression of p-Akt in OSCC tissues showed a negative correlation with survival of OSCC patients. Inhibition of Akt signaling by MEIB was associated with down-regulation of survivin expression and activation of Bax protein during apoptotic event. These findings provide a foundation in cell biology for development of MEIB as a therapeutic drug for human OSCC¹³.

Future research:

Need in vivo- as well as clinical trials for its complete use in clinical application.

4.UROLITHIN A

Urolithin A is the metabolite of natural polyphenol ellagic acid and ellagitannins, generated by gut microbiota. Ellagitannins are considered to be the main precursors of urolithins.

Ellagitannins are polyphenols found in many plant foods, especially in pomegranate fruit, strawberry, walnuts, and tea. Ellagitannins are metabolized in the intestinal tract to ellagic acid. Depending on microbiota composition ellagic acid might be converted to different urolithins – urolithin A, urolithin B, urolithin C, urolithin D, and iso-urolithin A. Among urolithins, the urolithin A is considered highly beneficial as it has anti- inflammatory and anti-cancer properties¹⁴.

Mechanism of action:

- Urolithin A act as an anti-inflammatory agent which in turn causes tumor suppression.

- These anti-inflammatory effects of Urolithin A work by multiple mechanisms that include influencing the NFκB pathway in inflammation and reducing the pro-inflammatory cytokine production¹⁵.

- Urolithin A has also been found to have direct cancer effects by downregulating several oncogenes such as Kirsten-rat sarcoma viral

oncogene homolog (KRAS) and mTOR and also upregulate tumor suppressor genes such as p53 in different cancers¹⁴.

Current research status:

A study by Remadevi et al revealed that urolithin A markedly induced cell death of OSCC in mouse models via the induction of endoplasmic reticulum stress and subsequent inhibition of AKT and mTOR signalling as evidenced by decreased levels of phosphorylated mTOR and 4EBP1¹⁵.

Future requirements for implementing in clinical practice:

Clinical trials are required to determine its safety and efficacy in humans.

5. TERMINALIA CHEBULA

Terminalia chebula, also known as black myrobalan, is a medicinal plant from the Combretaceae family. It is a key ingredient in traditional medicine systems, such as Ayurveda, Unani, and homeopathy. This plant is commonly found across the subtropical and tropical regions of Asia¹⁶. Historically, ripe fruits have been used to manage dental problems such as tooth decay, gum inflammation, and bleeding. Furthermore, it holds importance in Tibetan medicine for addressing cancer¹⁷.

Mechanism of action :

Terminalia chebula exhibits various beneficial attributes, including antioxidant, anti-inflammatory, antibacterial, antifungal, and cytotoxic effects. The ethyl acetate fraction extracted from *T. chebula* fruits can diminish cancer cell survival, trigger programmed cell death (apoptosis), and impede the multiplication and spread of SCC9 cells. The ethyl acetate fraction also boosts the production of reactive oxygen species (ROS), encouraging Caspase-3-dependent apoptosis via the intrinsic apoptosis pathway¹⁷. Specific phenolic compounds such as chebulinic acid, tannic acid, and ellagic acid are the most effective growth-inhibiting components of *T. chebula*¹⁸.

Current research status:

Extracts from *Terminalia chebula* tubers caused apoptosis in an oral cancer cell line at 30 µg/mL after 24 hours, according to an in vitro investigation¹⁶.

Future requirements for implementing in clinical practice:

Further research is needed to comprehend the active ingredients and underlying molecules to explore the potential in combination therapies and effectiveness at different stages of the disease.

6. SOLANUM NIGRUM

Solanum nigrum, commonly known as black nightshade, is an herb belonging to the Solanaceae family. *Solanum nigrum* is composed of various compounds, including alkaloids, steroidal saponins, glycoproteins, antioxidants, and flavonoids, which contribute to its medicinal properties. Traditionally, the leaves of *S. nigrum* have been used to treat mouth ulcers and tuberculosis. It contains approximately 188 phytoconstituents, including steroidal components, steroidal alkaloids, glycoproteins, polysaccharides, and benzoic acids¹⁹.

Mechanism of action:

Solanum nigrum possesses anticancer and antioxidant properties, primarily attributed to the presence of solasodine in its fruits that has the potential to induce apoptosis (cell death) in cancer cells and disrupt their proliferation¹⁹.

- Aqueous extracts of *S. nigrum* (AESN) can increase the production of reactive oxygen species [ROS], which can trigger the mitochondrial apoptotic pathway by promoting caspase-9 and caspase-3 activation¹⁹.

- AESN can hinder glucose uptake in oral squamous cancer cells (SCC), leading to mitochondrial fission.

Current research status:

Current studies on the role of *S. nigrum* in oral cancer therapy have focused on in vitro evaluation of the impact of aqueous extracts of *Solanum nigrum* (AESN) on oral squamous cell carcinoma (OSCC) cells, specifically focusing on cell proliferation, cell cycle, and mitochondrial function²⁰. In addition, mechanistic studies have evaluated how *Solanum nigrum* affects molecular pathways related to apoptosis and cell proliferation and examined the ability of *Solanum nigrum*

extracts to increase reactive oxygen species production in cancer cells^{19,20}. In both studies *Solanum nigrum* has been explored for its potential as an adjuvant chemotherapy agent to enhance the effects of conventional treatments^{19,20}. More research is needed before it can be considered mainstream.

7. TONGLU JIEDU

Tongluo Jiedu is a traditional Chinese medicine (TCM) formulation that emphasizes the principles of "meridian circulation" and "toxin elimination"²¹. According to TCM theory, diseases such as cancer arise from blockages in the meridian system, which disrupt the flow of vital energy or *qi* and blood²².

Its components include bioactive compounds extracted from herbs like *Astragalus* and *Salvia miltiorrhiza*, each reputed to improve immunity and blood flow. The Tongluo Jiedu formula restores this balance by promoting circulation and detoxifying the body. This formula supports microcirculation, enhances immune function, and reduces inflammation, which are critical for managing cancer symptoms and progression²¹.

Mechanism of action:

The key properties of Tongluo Jiedu that make it effective in addressing oral cancer include anti-inflammatory, antioxidant, and immunomodulatory effects.

- The compounds in this formula help combat cancer-related oxidative stress, reduce tumor-promoting inflammation, and strengthen immune defences.
- For instance, ingredients such as *Radix bupleuri* reduce inflammatory responses, whereas *Poria cocos* and *Atractylodes macrocephala* aid in modulating the immune system, creating environments that are less favourable for cancer growth²³.
- The formula also improves circulation, reducing stagnation and promoting toxin elimination, which may alleviate malignancies²³.

Current research status:

Tongluo Jiedu is typically used in combination with conventional treatments, such as chemotherapy or radiotherapy. There is limited evidence to support its efficacy as a standalone treatment for oral cancer.

Studies suggest that it offers a synergistic effect when combined with these therapies, enhancing immune recovery from chemotherapy-induced suppression and reducing treatment-related oxidative stress^{21,22,23}.

Clinical trials are assessing its impact on inflammatory markers, peripheral T-cell subsets, and immune regulation in patients undergoing chemotherapy for oral cancer²². Yin et al. highlighted significant improvements in patients' immune function and oxidative stress levels when Tongluo Jiedu was added to chemotherapy regimens²².

Other investigations have delved into the biological pathways influenced by this formula to uncover the mechanisms behind its anticancer effects^{21,22}.

Future research implications:

Large-scale, multicentre trials have been recommended to validate preliminary findings and assess its broader applicability.

Although its ability to reduce inflammation and improve immunity in advanced cases are studied, more detailed studies are required to determine their exact role in early stage cancers.

8. JUNIPERUS COMMUNIS

Juniperus is a species of evergreen shrubs or small trees that belongs to the family Cupressaceae²⁴. It has been traditionally employed in herbal medicine for its antiseptic, diuretic, and appetite-enhancing properties²⁴. Modern research has revealed its broad pharmacological profile, including antioxidant, anti-inflammatory, antimicrobial, and antidiabetic capabilities. Compounds derived from this plant, including terpenoids, flavonoids, and other bioactive secondary metabolites, have shown promise in combating various illnesses, including cancers^{24,25}.

Mechanism of action:

The anticancer potential of *Juniperus communis* lies in its ability to inhibit tumor growth and induce cancer cell death through specific molecular pathways^{24,25}.

- It demonstrates antioxidant and antiproliferative properties, which target oxidative stress and reduce uncontrolled cancer cell division.

- It can trigger apoptosis (cell death) in oral cancer cells via intrinsic and extrinsic pathways by modulating proteins like Bax, Bcl2, and caspase cascades.
- It can arrest the cell cycle in the G0/G1 phase by regulating tumor suppressors such as p53, p21, and Rb phosphorylation, preventing further cancer progression.
- This selective anticancer effect, which spares normal healthy cells, makes *J. communis* an attractive treatment option.

Current research status:

At present, *Juniperus communis* is best categorized as a complementary option rather than a standalone or mainstream treatment for oral cancer. *Juniperus communis* is focused largely on preclinical studies conducted in laboratory and animal models²⁵.

Current evidence suggests that *J. communis* yields better results when used in combination with other drugs, particularly chemotherapeutic agents such as 5-Fluorouracil (5-FU). Studies reveal a strong synergistic effect between *J. communis* extract and 5-FU, enabling lower drug doses while maintaining effective cancer cell inhibition^{24,25}. This combination reduces toxicity to normal cells and amplifies anticancer benefits.

Studies on other *Juniperus* species like *Juniperus squamata* and *Juniperus indica* have also shown potential in oral cancer treatment²⁶.

Future research implications:

- While the plant extract shows anticancer action independently, its use in clinical settings as a sole therapy has yet to be sufficiently validated for efficacy.
- Large-scale human trials for *J. communis* remain limited, underscoring the need for further clinical research
- Clinical studies need to confirm its exact role in late-stage or metastatic oral cancer.

9. GOJI BERRY

Lycium barbarum, commonly known as goji berry, Chinese wolfberry, or Tibetan goji, is a plant

species belonging to the *Solanaceae* family. It is native to Southeast Europe and parts of Asia²⁷.

This plant has been extensively used in traditional Chinese medicine and as a dietary supplement due to its rich nutritional and therapeutic properties. The berries, which are typically consumed dried, are packed with bioactive compounds, including polysaccharides (known as *Lycium barbarum* polysaccharides, or LBPs), scopoletin, vitamin C analogs, carotenoids (like zeaxanthin and β -carotene), flavonoids, and amino acids, all contributing to its antioxidant and disease-modulating potential²⁷.

Mechanism of action:

The anticancer properties of *Lycium barbarum* mainly arise from its high concentration of bioactive components such as LBPs, flavonoids, and carotenoids. These compounds are known for their antioxidant, anti-inflammatory, and immunomodulatory effects²⁷.

- Inhibit cancer cell proliferation, migration, and adhesion. It achieves this by regulating key cellular signaling pathways, including ERK, AKT, Cyclin D, and others²⁷.
- Enhance immune responses by activating natural killer (NK) cells and inducing the expression of interferon-gamma, which promotes cancer cell death²⁷.
- Bioactive compounds in goji berries also show specific effects, such as causing G1/S cell cycle arrest, which helps control the growth and migration of oral cancer cells²⁸.

Current research status:

Currently, *Lycium barbarum* is viewed as a complementary treatment option rather than a mainstream therapy for oral cancer. By incorporating natural agents like *Lycium barbarum* alongside traditional cancer treatments, researchers aim to reduce the toxic effects of chemotherapy, enhance therapeutic efficacy, and improve patients' overall quality of life. Its use as a complementary therapy is backed by emerging research demonstrating its tumor-sensitizing and immunomodulatory roles²⁷.

Recent studies have explored its effect against oral squamous cell carcinoma (OSCC), focusing on its ability to reduce cell viability, inhibit colony formation, and suppress cancer cell migration²⁷.

Investigations have demonstrated that *Lycium barbarum* extract modulates the expression of proteins such as ERK1/2, AKT1, and Cyclin D, which play critical roles in cancer cell proliferation²⁷.

Future research implications:

Research on *Lycium barbarum*'s role in oral cancer is primarily in the preclinical and in-vitro stages. Clinical and patient-based trials are required to confirm its safety, efficacy, and mechanisms in humans.

10. NARINGENIN

Naringenin is an important phytochemical which belongs to the flavanone group of polyphenols, and is found mainly in citrus fruits like grapefruits and others such as tomatoes and cherries plus medicinal plants derived food. It has anti-inflammatory, antioxidant, neuroprotective, hepatoprotective, and anti-cancer properties²⁹.

Mechanism of action:

A study done in human tongue carcinoma CAL-27 cells showed that naringenin significantly induced apoptosis in CAL-27 cells in a dose-dependent manner. This naringenin-induced apoptosis was mediated through the upregulation of Bid and downregulation of Bcl-xl, which led to increased generation of reactive oxygen species³⁰. Similarly cell apoptosis was noted in OSCC cells in another study by inducing the endoplasmic reticulum (ER) stress signaling through intracellular reactive oxygen species (ROS) production³¹. Another study done on oral cancer cell lines found that naringin treatment significantly reduced cell viability and cell migration compared to the control group. It was also noted that it regulated gene expression of Bcl-2, TGF- β , SMAD2, TNF α , NF κ B, BAD, BAX, and caspase-3, thereby treating oral cancer³².

Current research status:

Naringenin was assessed for anti tumour effects in two murine oral squamous cell carcinoma models

and it was found to increase the mRNA levels of CD169, interleukin (IL)-12, C-X-C motif chemokine ligand 10 (CXCL10) in lymph nodes and cytotoxic T lymphocytes infiltration in tumors. Since CD169+ macrophages are associated with favourable prognosis in numerous malignancies, naringenin can be used in OSCC treatment³³.

Future research implications:

Further clinical trials are required to use naringenin as a means of targeted cancer therapy.

11. QUERCETIN

Quercetin is a naturally occurring flavonoid present in a variety of fruits, vegetables, seeds, and grains³⁴.

It is a potent antioxidant renowned for its therapeutic benefits in combating numerous health issues, including cardiovascular diseases, neurodegenerative disorders, and cancers^{34,35}. Found in foods like onions, apples, berries, and tea, quercetin also exists as a glycoside form in the human diet and is widely available as a dietary supplement³⁵. Studies have linked this bioactive compound with significant anti-inflammatory, antibacterial, and antitumor properties, making it a promising agent in cancer treatment³⁵. In the context of oral cancer, quercetin has drawn attention due to its ability to selectively target cancerous cells while sparing normal ones. Despite its physiological benefits, its poor bioavailability and absorption in humans (as low as 10%) present a key limitation, necessitating further research into improved delivery mechanisms³⁵. Quercetin exhibits potent anti-cancer properties by leveraging its antioxidant, anti-inflammatory, and anti-proliferative capabilities³⁴.

These properties allow quercetin to:

- Neutralize free radicals and reduce oxidative stress, a key factor in cancer development³⁴.
- Inhibit the proliferation of cancer cells and induce apoptosis (programmed cell death) within them³⁴.
- Suppress metastatic pathways, effectively reducing the spread of oral cancer cells to other tissues.
- Regulate pathways involved in angiogenesis which supports the tumor's growth³⁴.

- Additionally, quercetin targets EMT (epithelial-to-mesenchymal transition) markers such as Vimentin, α -SMA, and E-cadherin, halting cellular mechanisms that contribute to invasion and metastasis [citation needed]. It also modulates gene expressions and microRNAs (e.g., miR-16, miR-22, miR-1254), which play vital roles in enhancing apoptosis and reducing tumor invasiveness³⁴.

Mechanism of action:

Oxidative Stress Modulation: In oral cancer cells, quercetin paradoxically increases reactive oxygen species (ROS), creating oxidative stress and triggering cellular death³⁴. At the same time, it protects normal cells from oxidative damage³⁴.

Apoptosis Induction: Quercetin activates apoptotic pathways via mitochondrial and endoplasmic reticulum stress. Key proteins like cytochrome c, apoptosis-inducing factor (AIF), and caspase-8 are upregulated, leading to mitochondrial dysfunction and cell death³⁶.

Cell Cycle Arrest: It induces S-phase or G2/M-phase arrest in cancer cells, preventing cell division and proliferation³⁶.

EMT Regulation: By upregulating E-cadherin (a tumor suppressor protein) and downregulating migratory proteins like Vimentin and α -SMA, quercetin inhibits metastasis³⁴.

miRNA Modulation: It modulates pathways such as miR-22/Wnt1/ β -catenin, leading to reduced tumor growth, cell migration, and invasion [citation needed]. For example, quercetin increases miR-1254 to suppress CD36 expression, which is linked to cancer progression³⁴.

Enzyme Inhibition: It reduces the activity of MMP-2 and MMP-9, enzymes critical for matrix degradation, invasion, and metastasis in oral cancer³⁴.

Current research status:

Quercetin has shown efficacy in early and advanced stages of oral cancer. Preclinical studies, particularly on human oral squamous carcinoma cells, demonstrate that quercetin can reduce tumor viability, inhibit cell migration/invasion, and promote apoptosis across various stages of the disease³⁴.

In the early stages, quercetin can act as a cytotoxic agent to halt tumor progression^{35,36}.

In advanced stages, it helps in managing metastasis and reducing tumor burden. It is also studied for its ability to enhance the efficacy of conventional treatments such as chemotherapy (e.g., combined effects with cisplatin or doxorubicin)³⁵. Its antioxidant potential and ability to scavenge free radicals make it effective in preventing the initiation of oral cancer. By reducing oxidative stress and inflammation, it prevents DNA damage and mutagenesis³⁴. Quercetin has shown promise when used alongside traditional therapies like chemotherapy and radiotherapy. Studies suggest it sensitizes cancer cells to conventional drugs (e.g., cisplatin), reducing the required dose and associated toxicities³⁵.

Key areas of investigation include:

Molecular Pathways: exploring how quercetin impacts apoptosis, cell cycle progression, and gene expression in oral cancer. Studies using cells like SAS, SCC-9, and KON confirm its role in inducing mitochondrial dysfunction and enhancing stress pathways³⁵.

Combination Therapies, investigating quercetin's use alongside chemotherapeutic agents (e.g., cisplatin, doxorubicin) to reduce drug toxicity while improving effectiveness³⁵.

MicroRNA Regulation focusing on quercetin's role in modulating microRNAs such as miR-16, miR-22, and miR-1254, which are critical to reducing cancer cell viability³⁴.

Improving Bioavailability for developing novel delivery methods such as nanoparticles and lipid carriers to overcome the low absorption of quercetin³⁴.

ROS-Induced Death: Studies are examining quercetin's dual role in increasing ROS in cancer cells while reducing oxidative stress in normal cells³⁴.

Future study implications:

Research on quercetin and oral cancer remains largely preclinical, focusing on its biological activity, molecular pathways, and delivery methods. Its specific dosing as a complementary treatment still requires clinical validation³⁴.

12. AMYGDALIN

Amygdalin is a natural compound classified as a cyanogenic glycoside, primarily found in the seeds of certain fruits like apricots, peaches, apples, and bitter almonds³⁷.

Historically, it has been used in traditional medicine and became particularly notable as a complementary therapy for cancer under the name "laetrile" or "vitamin B17," though it is not a true vitamin³⁸. Upon ingestion, amygdalin can break down into glucose, benzaldehyde, and hydrogen cyanide. While hydrogen cyanide is toxic to both healthy and cancerous cells, proponents of amygdalin therapy suggest its selective toxicity toward cancer cells when administered properly³⁷.

Because of its controversial nature, amygdalin use has generated significant debate in the scientific and medical communities, particularly regarding its safety profile and therapeutic efficacy³⁷. Amygdalin's anti-cancer potential is attributed to its ability to release hydrogen cyanide when metabolized within the body.

Mechanism of action:

Amygdalin primarily acts by releasing hydrogen cyanide, which is toxic to cells. The mechanism involves:

A. Metabolism in the Body: Amygdalin is broken down by beta-glucosidase into glucose, benzaldehyde, and hydrogen cyanide. Cancer cells with higher beta-glucosidase activity are particularly vulnerable to the toxic effects of hydrogen cyanide³⁷.

B. Mitochondrial Dysfunction: Hydrogen cyanide inhibits cellular respiration by blocking cytochrome c oxidase activity in the mitochondria. This results in energy depletion and apoptosis, leading to cell death in cancerous tissues³⁸.

C. Induction of Apoptosis: Amygdalin has been shown to trigger apoptosis in various cancer cell types via mitochondrial pathways, characterized by the activation of caspases and disruption of the mitochondrial membrane potential³⁷.

Current research status:

Research on amygdalin's application in oral cancer is mostly preclinical, focusing on its effects in vitro (cancer cell cultures) and in vivo (animal models). In these studies, it has demonstrated the potential to reduce tumor cell proliferation, induce apoptosis, and prevent metastasis, suggesting its potential role in early-stage and advanced-stage oral cancers³⁹.

Amygdalin has also been investigated as an adjunctive therapy to help minimize cancer progression and enhance the effects of conventional treatments like chemotherapy³⁸. Its purported ability to selectively target cancer cells while sparing normal tissues makes it an appealing adjunct for reducing tumor burden. Furthermore, it is believed to enhance the therapeutic effects of primary treatments and potentially alleviate side effects like inflammation or pain associated with oral cancer³⁹. The key areas of investigation include:

A. In Vitro Studies: Studies on oral squamous cell carcinoma (OSCC) cell lines to explore the apoptotic effects and impacts on cell proliferation, migration, and invasion. For example, amygdalin has been observed to trigger apoptosis through mitochondrial pathways and G1/S cell cycle arrest in OSCC cells³⁹.

B. Animal Model Studies: Researchers are evaluating the antitumor effects of amygdalin in animal models, focusing on its ability to reduce tumor volume and limit metastasis³⁸.

C. Combination Therapies: Emerging research aims to assess the potential synergistic effects of combining amygdalin with conventional treatments, such as chemotherapy or photodynamic therapy, to enhance efficacy while reducing toxicity³⁸.

D. Safety and Toxicity: Given the potential risks associated with hydrogen cyanide release, studies are being conducted to optimize the dosage, limit toxicity, and improve drug delivery to cancer tissues while sparing healthy tissues³⁹.

E. Delivery Systems: Efforts are underway to develop advanced delivery systems, such as nanocarriers, to improve the targeted release of

amygdalin and enhance its bioavailability in cancerous tissues³⁹.

Future research implication:

While amygdalin shows promise in limiting tumor growth and reducing cell migration, its effectiveness in human trials remains unproven. However, clinical evidence supporting its efficacy in these areas is sparse and controversial.

Further, the clinical application of amygdalin is limited due to regulatory restrictions in many countries. Most of the available data arises from preclinical evidence, and there is a pressing need for well-designed human clinical trials to validate its safety and efficacy as a treatment for oral cancer^{37,38}.

13. OSBECKIA OCTANDRA

Osbeckia octandra, commonly referred to as "Heen Bovitiya," is a plant belonging to the family *Melastomataceae*⁴⁰. Endemic to Sri Lanka, the plant has long been utilized in traditional medicine for treating conditions such as liver diseases, diabetes, jaundice, hepatitis, and hyperlipidemia⁴⁰. The leaves, roots, and bark are known for their medicinal properties, while the young stems and leaves are also edible. In particular, the *O. octandra* leaf extract has been highlighted for its hepatoprotective, antioxidant, and anticancer properties⁴⁰. It has recently gained attention for its ability to impede the progression of oral squamous cell carcinoma (OSCC), which is one of the most prevalent forms of head and neck cancers. The anticancer effects of *O. octandra* are attributed to the bioactive phytochemicals present in its leaves, including phenols, tannins, flavonoids, alkaloids, and terpenoids⁴¹. These compounds exhibit antioxidant, antiproliferative, and apoptotic properties, making them effective in targeting cancer cells⁴¹.

Mechanism of action:

- Studies have demonstrated that the leaf extract induces DNA fragmentation, G1 cell cycle arrest, and apoptosis in OSCC cells while sparing healthy cells⁴⁰.
- The plant extract influences apoptotic pathways by regulating pro-apoptotic and anti-apoptotic

proteins, such as Bax and Bcl-2, thereby inducing mitochondrial apoptosis⁴¹.

- Another significant mechanism involves the inhibition of reactive oxygen species (ROS) generation, distinguishing *O. octandra*-driven apoptosis from ROS-dependent pathways.

Current research status:

Currently, *Osbeckia octandra* is being explored as an experimental complementary treatment. While it lacks the established status of a mainstream therapy, its low toxicity, antioxidant properties, and ability to target oral cancer cells without affecting healthy tissues make it an appealing adjunct to conventional treatments, such as chemotherapy or radiotherapy⁴⁰.

The plant could help mitigate some of the adverse effects of standard therapies by reducing oxidative stress, which is often heightened during cancer treatment⁴⁰. Further research and clinical trials are needed to fully establish its therapeutic role.

Based on current findings, the anticancer efficacy of *Osbeckia octandra* is highly promising when used alone in early, controlled settings, as it outperformed doxorubicin (a standard chemotherapeutic drug) in reducing OSCC cell viability at a 30 µg/mL concentration⁴⁰.

However, the extract's potential for enhanced cancer control may increase when combined with other drugs or therapies. Although no specific combinatory studies have been conducted yet, *O. octandra's* ability to complement traditional chemotherapeutics by minimizing side effects could make it a valuable adjunct. Its specific mechanisms of action suggest it could synergistically enhance the efficacy of other cancer treatments⁴⁰.

Research on *Osbeckia octandra's* role in combating oral cancer is primarily in the preclinical and in-vitro stages. It is being tested on oral squamous cell carcinoma (OSCC) cell lines, such as YD-38, to study its ability to reduce cell viability, induce DNA damage, and trigger apoptosis⁴⁰. Recent investigations have focused on its role in cell cycle regulation, showing its capability to downregulate cyclin D1 and CDK4/6, leading to

G1 cell cycle arrest⁴¹. Ongoing work also involves the assessment of its mitochondrial apoptosis pathways by observing Bax and Bcl-2 protein expressions.

Future research implications:

- Exploring its effects on epithelial-mesenchymal transition (EMT), further elucidating caspase-mediated apoptosis, and identifying specific bioactive components responsible for its anticancer effects⁴⁰.
- Its role in advanced or metastatic stages of oral cancer remains unclear and requires further investigation.

14. CURCUMIN

The rhizome (root) of the *curcuma longa* is the source of the plant compound curcumin. In addition to being a common perineal plant in south and southeast Asia, it is a member of the ginger family and an active ingredient in turmeric. Dimethoxy-curcumin, bisdemethoxycurcumin, and curcumin (diferuloylmethane) are the three primary constituents. It is used to treat rheumatism, sinusitis, diabetes wounds, biliary disorders, anorexia, coughing, and hepatic problems⁴².

Curcumin is a compound that exhibits a wide range of biological properties, including anti-inflammatory, antibacterial, antifungal, antioxidant, antitumor, and wound healing, in addition to its anticancer properties. It is typically yellow or orange in color. Curcumin has a very low level of bioavailability because it is highly lipophilic, has poor gastrointestinal absorption, and is largely excreted without being absorbed⁴².

According to a study by Lao *et al.* the maximum concentrations of curcumin in the blood when 10 or 12 g of curcumin taken orally, were 50.5 and 57.6 ng/ml, respectively⁴².

Mechanism of action:

Curcumin has been shown to have the ability to alter the following genes, which could have anti-cancer effects on head and neck cancer.

- Curcumin targets a number of different molecules, including interleukin (IL)-1, -2, -6, -8

(interleukins), tumor necrotic factor-alpha (TNF- α), kinase activity epidermal growth factor receptor (EGFR) kinase, mitogen-activated protein kinase protein kinase-A (MAPK PKA), protein kinase-B (PKB), protein kinase-C (PKC), Janus kinase (JAK), transcriptional factor AP-1, b-catenin, cyclic AMP response element-binding protein (CREB), nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), peroxisome proliferator-activated receptor-gamma (PPAR γ), STAT3, p53, c-myc (master regulator of cell cycle entry and proliferative metabolism), and hypoxia-inducible factor-1 (HIF1)⁴⁴.

- Improved levels of interferon-gamma, transforming growth factor-beta, IL-17, immunoglobulin E (Ig) E, proinflammatory cytokine IL-4, and type 1/type 2 helper cells (Th1)/(Th2) ratio in immune system-disturbed circumstances⁴⁵.

Current research status:

Although curcumin controls a number of signaling pathways, the fundamental processes are yet unknown. Curcumin has recently been shown to regulate epigenetics by altering DNA methylation, histone alterations, and miRNA expression in a variety of human malignancies. Curcumin prevented invasion, migration, metastasis, and proliferation. They then altered several signaling pathways in oral cancer cell types, which resulted in apoptosis. However, more clinical research is required to fully assess curcumin's impact on patients with oral cancer⁴⁶.

In vitro cell line studies have demonstrated the role of curcumin in:

- Downregulation of miR-21 expression & inhibits cell growth in oral cancer cells.
- Activation of autophagy and acceleration of apoptotic molecules in oral squamous cell carcinoma.
- Downregulation of NOTCH-1 pathway which in turn leads to downregulation of BCL-2, MMP9, VEGF and cyclin D in oral squamous carcinoma cell lines.
- Downregulation of HPV transcription (NF- κ B and AP-1) in HPV positive oral cancer cell lines.

- Inhibits transcription of E6 oncogene in HPV positive oral cancer cell lines.
- Induces the expression of miR-9 that mediates the inhibition of SSC9 cells proliferation and Wnt/ β catenin signaling pathway in human tongue squamous cell cancer cell lines
- Inhibits NF- κ B that is able to reverse the process of EMT back to MET, reducing Treg-attracting chemokine CCL22, with visible inhibition of Treg migration.
- Decreased the expression of PDL1 and p-STA.
- Reduced cell invasion in hepatocyte growth factor (HGF) induced HSC-4 cell lines. Further it reduced Epithelial mesenchymal transition in both HGF induced HSC-4 and Ca9-22 cell lines by repressing c-Met and ERK activation⁴².

In vivo-studies:

APG-157, a botanical medication that contains several polyphenols, including curcumin, was used in a double-blind, randomized, placebo-controlled, phase 1 clinical research that involved 12 patients with oral cancer and 13 healthy volunteers. For three hours, two transoral doses of either 100 mg or 200 mg were given every hour. The current study's findings indicated that APG-157 might be used as a medication in conjunction with immunotherapy⁴⁶.

Future study implications:

Although the effect of curcumin on diseases is known through in vitro and preclinical studies, clinical studies are hampered due to poor systemic absorption after oral administration. Future studies need to focus on identifying precise mechanisms of curcumin action, methods of increasing the absorption and bioavailability of the drug.

15. ALLYL ISOTHIOCYANATE

Allyl isothiocyanate (AITC) is A common phytochemical found in cruciferous Brassicaceae vegetables, such as cauliflower, broccoli, mustard, wasabi, and cabbage. The strong odor of these veggies is caused by the enzyme AITC. The plant stores sinigrin, a kind of glucosinolate, as a precursor of AITC that is physically separate from myrosin cells that contain myrosinase. When plant

tissues are disrupted, myrosinase is released from its storage position and hydrolyzes the sinigrin to produce AITC and other byproducts⁴⁷.

Mechanism of action

Research studies have demonstrated that AITC can interfere with the cancer cell progression by retarding cell growth, proliferation, migration, and invasion. AITC regulates the DNA methylation process and has been found to decrease DNA methylation in cancer cells. This causes the tumor suppressor gene reactivation which is the gene known to inhibit cancer cell growth and AITC has been found to impede the action of enzymes that regulate the modification of histone named histone deacetylases (HDACs). AITC enhances histone acetylation, modulates the gene expression and prevents cancer cell growth by blocking HDAC activity. As shown by the sub-G1 population the AITC compound was identified to cause the arrest of the cell cycle at the G2/M phase which leads to hindered cell proliferation and apoptosis⁴⁸.

- Downregulates KDM8 and CCNA1 particularly at the G2/M phase, which inhibits cancer cell proliferation causing cell cycle arrest and inhibits in vitro and in vivo oral squamous cell carcinoma growth⁴⁸.

- Interferes with epigenetic markers, such as increase in H3K36me2, which suppresses the oncogenic gene expression which enhances its potential as a therapeutic agent⁴⁸.

- By inhibiting pathways such as JAK-1/STAT-3 in other cancers AITC has shown its anti-invasive and anti-angiogenic properties indicating broader anticancer potential⁴⁹.

Current research status

AITC can prevent lung, breast, gastric, prostate, and bladder cancer based on several preclinical studies but this does not appear in the human pilot trials conducted so far. Using PDTX models the anticancer effects of allyl isothiocyanate (AITC) in oral cancer has been confirmed.

Although AITC is an irritant, poisonous organosulfur compound, both an irritant and toxic, it contains therapeutic characteristics such as

anticancer, antifungal, antibacterial and anti-inflammatory properties

Despite its clinical efficacy the use in practice is difficult due to its low aqueous solubility, instability, and low bioavailability⁴⁷.

16. CELASTROL

Celastrol is a pentacyclic triterpenoid containing various pharmacological properties which is derived from the traditional Chinese medicine *Tripterygium wilfordii* Hook F., which has multiple pharmacological activities. Based on the data, the anticancer activity of celastrol is due to its inhibitory action on tumor cell proliferation, migration and invasion which leads to apoptosis of the cell, autophagy suppression, reduction of angiogenesis and inhibition of tumor metastasis⁵⁰. Celastrol has been found to have therapeutic benefits on vincristine multidrug-resistant oral cancer and to cause the death of chemotherapy-resistant cancer cells. JNK1/2 signalling pathway was The main mechanism of cell apoptosis.

Mechanism of action:

To initiate the cell death in resistant cancer cells celastrol activates the JNK1/2 pathway which stimulates both mitochondrial and Fas-mediated apoptotic pathways, leading to activation caspase and cell death causing arrest of G2/M phase of the cell cycle and ultimately inhibits proliferation⁵¹.

According to a study, Gamboic Acid and celastrol combine together to boost apoptosis in OSCC cells by blocking the NF- κ B pathway. This shows that GA and celastrol may be a good combination for treatment of oral cancer. the mechanism involves GA induced suppression of proliferation and apoptosis In OSCC cells, it also causes the activation of the NF- κ B pathway which enhances the resistance and survival of the cells. Celastrol Blocks GA-induced NF- κ B activation and increase the pro-apoptotic and anti-proliferative properties of GA⁵².

Current research status:

According to recent studies, in the treatment of several cancers such as lung, liver, colorectal, gastric, prostate, renal, breast, bone, brain, cervical,

ovarian cancers and haematological malignancies celastrol demonstrates a wide range of anticancer activities.

Due to its poor water solubility and extensive metabolism Celastrol has low oral bioavailability. The absorption of celastrol is markedly higher in female rats than male. In animal studies formulation techniques such as tablets, nanoliposomes, self-microemulsifying drug delivery systems (SMEDDS), and silk fibroin nanoparticles have been indicated to significantly improve the oral absorption and pharmacokinetic profile of celastrol. These developments imply that better delivery methods can enhance the therapeutic potential of celastrol; still additional pharmacokinetic studies using different animal models are required to explain differences in absorption and direct future drug development⁵⁰.

17. SAFFRON

Saffron is derived from *Crocus sativus* L. flowers and often referred to as "Red Gold" as it is the most expensive spice in the world. The main components are: crocin (derived by crocetin esterification with sugars), crocetin, picrocrocin, and safranal. . These components possess many properties such as antioxidant, antigenotoxic, antimutagenic, and tumoricidal⁵³.

Mechanism of action:

Studies showed that the antitumor activity of saffron is mainly attributed to

- (i) Inhibition of synthesis of DNA and RNA,
- (ii) Inhibition or suppression of cancer cells proliferation,
- (iii) Apoptosis
- (iv) Inhibition of metastasis and angiogenesis, and
- (v) changes in the expression pattern of oncogenes or tumor-suppressive genes⁵⁴.

Current research status:

A study by Sun J et al found that human tongue squamous cell carcinoma cell line, Tca8113 cells, when treated with crocin, decreased cell viability and growth remarkably at 24, 48, 72, and 96 h, in a concentration-dependent manner. It was also seen that 0.4 mM crocin significantly induced both

early and late apoptosis of Tca8113 cells and significantly downregulated the cellular DNA and RNA content⁵⁵.

Crocin and safranal were found to significantly inhibit the growth of (KB cell line) in a study by Jabini et al. But they had less inhibitory effects on the NIH 3T3 cell line. Crocin and safranal was seen to cause apoptotic effects of tumour cells in the KB cell line⁵⁶.

A study analysed effects of Crocin and Cisplatin and their combination on SCC and fibroblast cell lines. It was found that low doses of crocin in combination with cisplatin, had toxic effects on malignant cells and reduced the toxicity of cisplatin in healthy tissue⁵⁷.

Cinnamon–safron, nano cinnamon–safron, and doxorubicin were found to reduce the viability of OSCC cells and increase the percentage of total apoptotic cells and necrotic cell death compared to the untreated group⁵⁸.

Future study implications:

Since saffron has been used with traditional anti-cancer drugs, the future use of saffron looks quite promising. Study of saffron with other chemotherapeutic drugs in clinical trials will go a long way in effective treatment of oral cancer.

18. GINGER

Ginger (*Zingiber officinale* Roscoe) is a common and widely used spice in India and China since ancient times. The health benefits of ginger are mainly attributed to its phenolic compounds, such as gingerols and shogaols⁵⁹.

Mechanism of action:

Gingerol regulates basic processes involved in carcinogenesis which includes influencing cell proliferation, angiogenesis, apoptosis and metastasis. Pro-apoptotic genes are activated which induce apoptosis and the NF- κ B signaling pathway is inhibited which is associated with inflammation, cell survival, and metastasis in many cancers. Gingerol also reduces the levels of pro-inflammatory cytokines such as TNF- α and IL-6, which are often elevated in the tumor

microenvironment and contribute to cancer progression⁶⁰.

Current research status:

6-gingerol was found to have significantly inhibited oral cancer cell growth by inducing apoptosis and cell cycle G2/M phase arrest. It was also seen in the same study that gingerol induced the activation of AMPK and suppressed the AKT/mTOR signaling pathway which represses the growth of cancer cells⁶¹.

A study found that 6-Gingerol showed dose-dependent cytotoxicity in an oral cancer cell line. Also, it showed additive effects when combined with chemotherapeutic drugs like wortmannin and cisplatin⁶². 6-shogaol was seen to suppress proliferation of OSCC cells and also induce apoptosis by regulating the apoptosis-associated factors such as p53, Bax, Bcl-2, and cleaved caspase-3 in an in vitro study. Additionally, 6-shogaol treatment significantly was shown to inhibit the PI3K/AKT signaling pathway⁶³.

Future study implications:

Clinical trials are required to assess efficacy compared to anti cancer drugs.

19. CINNAMON

Cinnamon is a traditional spice that comes from dried bark grown especially in Sri Lanka. They have various biological functions including antioxidant, anti-microbial, anti-inflammation, antidiabetic and anti-tumor activity⁶⁴. Aqueous cinnamon extract has been tested in different studies to evaluate its possible use as an anti-cancer compound⁶⁵.

Mechanism of action:

Anti-tumor effect of cinnamon extracts is by inhibiting the activities NF κ B and AP1 which are seen to be the causes of tumour development and progression in several cancers. Anti-cancer effect of cinnamon extracts can also be attributed to modulation of angiogenesis and effector function of CD8+ T cells⁶⁴.

Current research status

Burmannic acid, an apocarotenoid bioactive compound derived from Indonesian cinnamon, was found to selectively suppress oral cancer cell

proliferation. Notably it showed little cytotoxicity to normal oral cells⁶⁴.

Cinnamomum zeylanicum extract (CZE) and its bioactive compound cinnamaldehyde (CIN) was shown to significantly inhibit the growth and proliferation of oral cancer cells in a dose-dependent manner and further induced apoptosis, cell cycle arrest, and autophagy. A decreased expression of various PI3k-AKT-mTOR pathways related to VEGF, COX-2, Bcl-2, NF- κ B, and proteins post-treatment were also noted in the oral cancer cells⁶⁶.

Future study implications:

Clinical trials are required to assess efficacy compared to anti cancer drugs.

20. RHEIN

Rhein is an anthraquinone compound that can be found in the rhizome of rhubarb, a traditional Chinese medicine herb. It has been shown to have several properties including antibacterial, diuretic, laxative, anti-inflammatory, and antidiabetic properties⁶⁷.

Mechanism of action:

Rhein acts by inducing apoptosis, initiating cell cycle arrest and inhibiting tumour suppressor genes⁶⁸.

Current research status:

Rhein was seen to significantly inhibit oral cancer cell growth by inducing apoptosis and S-phase cell cycle arrest and also tumour cell migration and invasion through the regulation of epithelial-mesenchymal transition-related proteins. Reactive oxygen species (ROS) accumulation was produced by Rhein in oral cancer cells to inhibit the AKT/mTOR signaling pathway⁶⁹.

Emodin, aloe emodin and rhein are active constituents of the herb of *Rheum palmatum* L. The effects of emodin, aloe emodin and rhein on oral cancer cells (SCC-4 cells) were studied together. It was found that they induced DNA damage in SCC-4 cells and the effects of emodin were stronger than that of aloe emodin or rhein. Rhein and other components caused inhibition of DNA repair-associated gene expressions⁷⁰. In another study,

these components were seen to inhibit the protein levels of tumor metastasis related proteins such as matrix metalloproteinase-2 (MMP-2⁷¹). Rhein was seen to induce cell cycle arrest in S-phase through the inhibition of p53, cyclin A and E. It was also seen to produce reactive oxygen species (ROS) and Ca²⁺ release, mitochondrial dysfunction, and caspase-8, -9 and -3 activation in human tongue cancer cell line (SCC-4) which induce endoplasmic reticulum stress and cause apoptosis⁷².

Future study implications:

Rhein, emodin and aloe emodin have been found to bring promising results in invitro studies. Clinical trials are required to establish its use in oral cancer treatment.

21. GINSENG

Ginseng is basically a root with stalks resembling a human body with limbs. It has long been used by ancient Chinese as traditional Chinese medicine. The first documentation of this medicinal herb is dated back to 206 BC⁷³. Botanically termed as *Panax*, this herb derives its Chinese name *Renshen* which means herb resembling human⁷⁴. Ginseng contains various active components including ginsenosides, polysaccharides, flavonoids, volatile oils, amino acids, and vitamins. Of these active components, ginsenosides and ginseng polysaccharides appear to be responsible for the anticancer effect⁷⁵.

Mechanism of action :

Ginseng acts by the following mechanisms:

- Increasing the expression of Bak, Bad, and p53;
- Inducing apoptotic DNA fragmentation, G1, and G2/M phase block;
- Activating Caspase-3;
- Inhibiting MMP-2;
- Decreasing VEGF expression; Src/Raf/ERK pathway;
- Removing ROS;
- Regulating EMT-related proteins;
- Regulating TGF- β pathway-mitochondrial apoptosis⁷⁶.

Current research status:

Ginsenoside Rd was studied in oral squamous carcinoma cells and it was found that it improved Reactive Oxygen Species (ROS) levels and caused mitochondrial membrane potential alterations and DNA damage, which resulted in apoptosis⁷⁷. Noncoding RNA H19 and miR-675-5p, a micro-RNA from H19 promotes cancer cell growth and metastasis of tongue cancer cells. It was seen that Ginsenoside Rd inhibited tongue cancer cell migration and invasion via the H19/miR-675-5p/CDH1 axis⁷⁸. 20(S)-Ginsenoside Rh2 (G-Rh2), one of the main active components of Panax ginseng, was shown to significantly inhibit oral cancer cell growth by inducing apoptosis and cell cycle G0/G1-phase arrest. G-Rh2 was also seen to inhibit oral cancer cell migration and invasion through regulation of epithelial–mesenchymal transition (EMT)-related proteins⁷⁹.

Future study implications:

Human clinical trials are required to establish ginseng as a treatment option.

Discussion

Oral cancer management has traditionally relied on surgery, chemotherapy, and radiotherapy, which, despite their efficacy, are often associated with significant adverse effects and compromised quality of life. Chemotherapy and radiotherapy may cause adverse effects in the mouth because they are unable to distinguish between cancer cells that divide quickly and healthy cells that divide rapidly, including those in the mouth or bone marrow⁸⁰.

The balance between the body, mind, and spirit is the main focus of the traditional Indian medical system known as Ayurveda, which promotes a holistic approach to health. In order to strengthen the body's natural defences and boost the patient's general well-being, the Ayurvedic approach to cancer treatment uses herbal formulations, revitalizing therapies, and supporting activities⁸³. Similar to this, Chinese herbal therapy has emerged as a common adjuvant treatment for cancer and has been demonstrated to improve

patients' immune systems, which in turn improves the prognosis of the disease⁸².

Instead of using targeted treatments to eliminate tumors or malignant cells, herbal medicines utilized in Ayurvedic pharmaceuticals and therapeutic methods try to correct metabolic inefficiency and restore normal tissue functioning. A variety of herbs are used to treat cancer either alone or in combination. It has been noted that these formulations can affect numerous organ systems at once and function on different biochemical pathways. When taken in cancer treatment, these herbs promote complete healing and lessen side effects and complications related to cancer treatment⁷.

This review identified 21 naturally derived compounds that have demonstrated potential anticancer activity against oral squamous cell carcinoma in preclinical settings. Majority of these compounds remain in the early stages of research, with few progressing to clinical trials. The in vitro and in vivo evidence results are promising. Curcumin stands out as the most extensively investigated medication, with ongoing clinical evaluations and established safety profiles.

As mentioned earlier, various chemotherapeutics cause adverse effects like cardiotoxicity, covering almost all classes of traditional chemotherapy drugs such as anthracyclines, platinum compounds and 5-fluorouracil (5-FU)⁸². In order to develop effective strategies to maximize the efficacy and minimize the adverse effects of cancer chemotherapies, Mao et al. reviewed cancer and its treatment-related complications. They proposed using a model to develop drugs or medicines with increased efficacy against cancer and reduced side effects by focusing on their common mechanisms and using appropriate animal models. The authors state that targeting common mechanisms like chronic inflammation, oxidative stress or angiogenesis can help in treating cancer as well as reducing cancer related comorbidities⁸¹. For example, Nuclear factor-kappa B (NF-κB) has been found to be involved in important features of cancer like increased

proliferation, genetic and epigenetic alterations and immune suppression. On the other hand, suppression of NF- κ B can help in chemotherapy - induced cardiac inflammation. Hence a medication acting on NF- κ B pathway can have a dual action⁸⁴. In our review, we found that curcumin, celastrol, ginger and cinnamon works by suppression of NF- κ B and hence can be used to combat cancer as well as to minimize chemotherapy related adverse effects.

Mao et al, also suggested using drug combinations as a means to increase efficacy and reduce adverse effects. Our review has noted that *Juniperus communis*, quercetin, curcumin and saffron have shown to have greater tumoricidal effects with reduced toxicity to healthy tissues when used in combination with traditional chemotherapeutic drugs like 5 - FU, cisplatin, doxorubicin etc. Hence, alternative medicines can be effectively used as an adjunct treatment in oral cancer.

A key drawback noted in alternative medicines is poor bioavailability as noted in studies done with quercetin, curcumin, allyl isothiocyanate and celastrol. Further studies are necessitated to establish effective drug delivery systems which will overall contribute to the success of the medicine against oral cancer.

We can also note that many of these herbs being studied are readily available so they would probably be cost-effective with less adverse effects. However, there is a general lack of evidence regarding the extent of toxicity of these drugs. Further there are not many details available regarding the cost of developing the drug as well as shelf life and mode of administration. There is also insufficient clarity regarding standardization, optimal dosing, pharmacokinetics, route of administration and safety profiles in humans. Addressing these questions through robust clinical trials is critical for regulatory approval and mainstream clinical adoption.

Also, a notable gap in current literature is the absence of interdisciplinary collaboration involving alternative medicine practitioners. Integrating

these experts into research teams could facilitate better case selection, individualized dosing, and understanding of therapeutic windows of the traditional medicines. This integration is essential for transitioning these agents from bench to bedside in a patient-centric, evidence-based manner.

In light of the data presented, this review raises pertinent questions for future exploration:

- Can alternative medicines serve as primary agents in targeted therapy, or are they best suited as adjuncts?
- How can we optimize delivery and absorption while maintaining safety?

Only further studies and clinical trials will be able to answer these questions and integrate alternative medicines as part of conventional therapy for oral cancer.

Conclusion:

Oral squamous cell carcinoma (OSCC) remains a pressing challenge, with conventional therapies often constrained by adverse effects and treatment resistance. This review highlights the emerging role of alternative medicines as potential adjuncts or standalone agents in the targeted management of OSCC.

This review focused on 21 herbal medicines which showed promising results in OSCC cell line studies and animal models. While preclinical data are encouraging, there are no clinical trials of these medications except for curcumin. Also, there is lack of literature on their safety profiles, bioavailability and mode of administration. Despite these limitations, the multi-targeted nature of these compounds offers a compelling advantage over single-pathway chemotherapeutics, especially when used in integrative oncology. To transition from bench to bedside, future research must emphasize clinical validation, interdisciplinary collaboration, and development of advanced drug delivery systems.

Conflict of Interest Statement:

The authors have no conflicts of interest to declare.

Funding Statement:

None.

Acknowledgements:

None.

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