

Oral Squamous Cell Carcinoma: A Narrative Review exploring the Anti-Carcinogenic Potential of Traditional Indian Herbal Medicine through Scientific Evidence

(Anticancer Herbs for OSCC: Review)

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ABSTRACT:

Oral Squamous Cell Carcinoma (OSCC) is a malignant neoplasm of the mucosal epithelium in the oral cavity, accounting for over 90% of oral malignancies and approximately 30% of head and neck tumors. Herbal medicines, particularly those used in Ayurveda, offer a complementary approach to conventional cancer treatments, possessing bioactive compounds holds a significant promise in treating OSCC. This narrative review was conducted in accordance with SANRA guidelines. Literature was systematically retrieved from PubMed, SCOPUS, Web of science, AYUSH Research Portal, and Google Scholar employing targeted keywords such as "OSCC," "oral health," "herbal drugs," "oral squamous cell carcinoma," and "Ayurvedic medicine." Pertinent peer-reviewed articles from these indexed databases, supplemented by classical Ayurvedic compendia, were subjected to analysis to elucidate the biological activities of natural compounds derived from herbal interventions in OSCC. After a thorough search in the database, a total of scientifically validated 21 herbal medicines that are mentioned in TIM classics were listed. Herbs like Zingiber officinale, Crocus sativus, Curcuma longa, Boerhavia diffusa, and Triphala exhibit potent antioxidant activities, reducing oxidative stress and DNA damage. Natural compounds in Glycyrrhiza glabra, Cinnamomum zeylanicum, Azadirachta indica, and Nelumbo nucifera show significant anti-inflammatory properties. Many herbal compounds, such as 6-shogaol from Zingiber officinale, curcumin from Curcuma longa, and eugenol from Syzygium aromaticum, induce apoptosis in cancer cells and inhibit their proliferation. Nigella sativa and Glycyrrhiza glabra demonstrate antiviral activity against HPV infections, reducing viral load and preventing malignant transformation. Compounds from Nelumbo nucifera, such as nuciferine and neferine, modulate immune responses and inhibit tumor growth. Tribulus terrestris fruit extracts reduce proliferation, migration, and invasion of cancer cells by inhibiting autophagy. Herbs like Tinospora cordifolia and Calotropis procera enhance the immune response, aiding in the elimination of tumor cells. The ability of herbal medicines to target multiple mechanisms involved in cancer progression highlights their potential as complementary and integrative approaches in managing and treating OSCC. Integrating herbal



medicines into cancer treatment regimens holds promise for more holistic and personalized care, potentially leading to better outcomes and improved patient well-being.

Introduction

Oral Squamous Cell Carcinoma (OSCC) is a malignant neoplasm of mucosal epithelium of Oral cavity and comprises more than 90% of Oral malignancies¹. It is one of the ten leading cancers in the world with high morbidity and mortality and comprises approximately 30 percent of head and neck tumors. Survival rate of OSCC as published by National Cancer Institute is 63 – 85% in early cases and 38% in advanced cases within a period of 5 years². Prevalence is high in South Central Asia and is a leading cause of carcinoma related death among the male population of India; the age standardized incident rate being 12.6 per 100,000 population³. The high risk and prevalence of the disease in India is attributed to the prevalent habits of its population such as smoking, alcohol, chewing tobacco, betel quid and areca nut⁴. Infection with Human Papilloma virus, nutritional insufficiency, immune deficiency and exposure to dust and heavy metals are also found to be associated with the incidence of OSCC⁵. The posterolateral surface and floor of mouth are the most common sites having a natural predilection for OSCC as these are the most common sites for constant accumulation of carcinogens and accounts for about 50% of other less commonly affected sites include the gingivae, palate, retromolar area, buccal mucosa and the labial mucosa⁶.

Herbal drugs play a significant role in cancer care, offering a complementary approach to conventional treatments. Many medicinal plants possess bioactive compounds with anti-cancer properties, including the ability to induce apoptosis, inhibit cell proliferation, and prevent metastasis. These natural agents often have fewer side effects compared to synthetic drugs, making them a valuable option for improving patient quality of life. Additionally, herbal drugs can enhance the efficacy of conventional therapies, reduce chemotherapy-induced toxicity, and boost the immune system.

Ayurveda is the widely practiced Indian system of medicine (TIM) which has a rich, age-old tradition supported by evidence-based literature. Ayurvedic classics have mentioned the use of various herbal drugs for oral care, both as single drugs and in formulations.

Ayurvedic classics highlight several effective formulations for diseases in the oral cavity. Among these, *Arimedadi Thaila*, *Khadiradi Gulika*, *Triphala Kasaya*, and *Lavangadi Vati* are particularly mentioned in classics like *Caraka Samhita* and *Astanga Hridaya*. These formulations are renowned for their therapeutic properties in maintaining oral health and treating various oral conditions.

Clinical features and prognosis

OSCC can manifest asymptotically as erythematous or pale lesion with distinct borders and uneven surface. Erythema, pain and tingling sensation may be seen in some patients. Ulceration, nodularity and tissue attachment can be seen as the disease starts progressing. When traumatized, it can bleed easily and get infected. Large lesions may often affect speech, mastication and swallowing. Disease is more frequently seen in those having Oral premalignant lesions such as oral leukoplakia, oral erythroplakia, oral submucous fibrosis and oral Lichen planus⁷ Regional lymph node metastasis, size and extent of infiltration, site of manifestation and stage of carcinoma determines the prognosis and survival rate. OSCC of posterior part of Oral cavity such as tongue and floor of mouth frequently metastasize to regional lymph nodes and have the worst prognosis. Small primary tumors of anterior aspect of oral cavity with no regional lymph node involvement or distant metastasis has the best prognosis.

Oral Carcinoma is considered under the broader entity of '*Arbuda*' mentioned in Ayurvedic literature. It can manifest in Labial region as *Oshtarbuda*, palatal region as *Talwarbuda*, oropharyngeal area as *Galarbuda* and within the buccal mucosa as *Kapharbuda*/ *Mukharbuda*⁸. The clinical entity *Mukharbuda* manifests as pale or dark brown discoloured lesion within the *Anthakapola* (buccal region) due to vitiation of *Kapha* (one among the bio humors) with a special characteristic feature – aggravates and recurs after rubbing, excising or scraping. All these forms of *Arbuda* are generally considered as incurable entities. Eventhough the disease starts as a result of vitiated *Kaphadosha* (one among the three bio humor) as mentioned in the general etiology of all oral



diseases, vitiation of Vata- Pitta (bio humors) occurs as a result of *Atiyoga* (Excessive use) of *Ruksha* (dry), *Vikashi* (drug attribute which impairs immunity and destruction of tissues), *Kashaya Rasa* (astringent taste) substances such as arecanut and its products, constant irritation and injury to buccal mucosa due to constant use of *Teekshna* (penetrating), *Ksharadravyas* (alkaline substances) such as lime and the alkaloids in tobacco products resulting in a non-healing ulcerated lesion which may develop carcinomatous changes in the later stage.

Ayurveda advocates therapeutic interventions even for incurable diseases considering the fact that the stage of the disease during which treatment was initiated, the immunity and mental strength of the patient, potency and specific properties of medicine such as *Rasayana* (immunomodulatory/ adaptogenic), patient response to the treatment and certain parasurgical procedures such as *Agnikarma* (Therapeutic thermal cautery), *Ksharakarma* (Chemical cautery with medicated alkalies) can have significant impact on healing. Procedures mentioned for treating *Sarvasara Mukharogas* (Diseases manifesting in the buccal cavity) such as *Pratisarana* (local application by rubbing of drug in the form of paste/ concentrate/ powder), *Kabala* (retaining medicine in oral cavity for a prescribed time), can be used as therapeutic interventions for effective drug delivery in OSCC⁹. While selecting the drugs, formulations or drugs having *Rasayana* (immunomodulatory) and *Vranashodhana* (Wound cleansing)- *Vranaropana* (Wound healing) properties should be specifically selected. Clinical studies on conventional therapy with multimodal approaches including Ayurvedic panchakarma, herbal and herbo mineral therapies shows promising results of progression free survival of OSCC patients^{10,11}.

Materials and methods

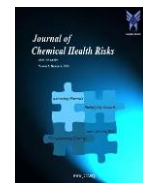
This narrative review was conducted in accordance with SANRA guidelines and registered under OSF Registry to ensure methodological transparency and rigor. Authors conducted an extensive review of Ayurvedic compendia like *Bhavaprakasha*, *Charaka Samhita*, *Ashtanga Hridaya* to find herbal remedies traditionally utilized in oral health. This review examined both contemporary and traditional literature that describes the application of herbal medicines in Ayurvedic medicine, with a focus on those said to provide advantages for dental health. After

these herbal medications were identified, indexed scientific databases were thoroughly searched. The search approach was designed to find research on the effectiveness of these discovered herbal remedies in treating oral squamous cell cancer (OSCC).

Literature was systematically retrieved from PubMed, SCOPUS, Web of science, AYUSH Research Portal, and Google Scholar employing targeted keywords such as “OSCC,” “oral health,” “herbal drugs,” “oral squamous cell carcinoma,” “Ayurvedic medicine,” and the specific names of the identified herbs. Pertinent peer-reviewed articles from these indexed databases, supplemented by classical Ayurvedic compendia, were subjected to thematic analysis to elucidate the biological activities of natural compounds derived from herbal interventions in OSCC. Searches were conducted in the English language, with no limitations placed on the year of publication, and the most recent update to the search was completed in January 2025.

The initial search results were screened for relevance based on titles and abstracts. Studies that explicitly reported on the anti-OSCC activity of the herbal drugs were shortlisted for further review. Inclusion criteria were set to select only those articles that provided empirical data on the efficacy of these herbs against OSCC, including in vitro, in vivo, and clinical studies. From the shortlisted articles, data were extracted on various parameters, including the type of herbal drug, the method of administration, the experimental model used (e.g., cell lines, animal models, human subjects), and the reported outcomes related to OSCC. The findings from the selected studies were synthesized and discussed in the context of their implications for oral health and potential therapeutic applications in OSCC. This discussion highlights the biological mechanisms proposed for the anti-OSCC activity of these herbs.

Figure 1. Narrative Review Flowchart



Narrative Review Process for Herbal Remedies in OSCC

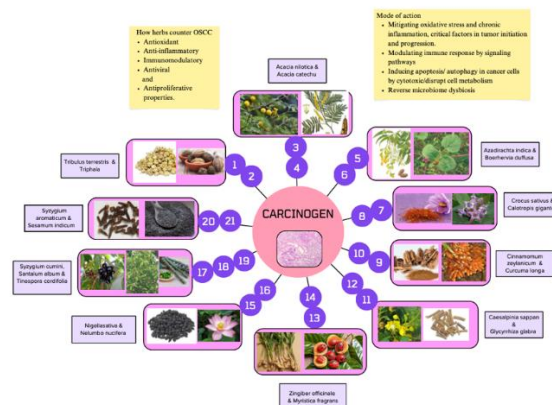
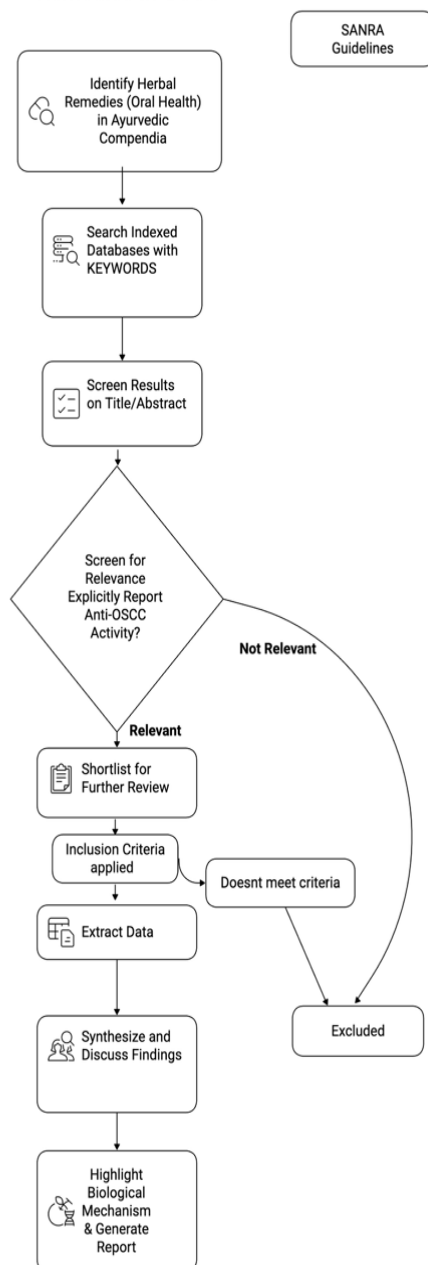


Figure 2. Graphical abstract of drugs of Narrative Review

Boerhavia diffusa Linn

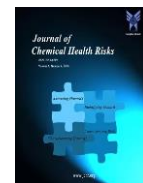
Boerhavia diffusa (BD) Linn. (*Punarnava*) (Nyctaginaceae) is a medicinal plant extensively utilized in the traditional Indian system of medicine. Comprehensive chemical analysis¹² has identified a diverse range of constituents including rotenoids, flavonoids, xanthones, purine nucleosides, lignans, and steroids. Its therapeutic potential can be seen in addressing disorders related to the reproductive, gastrointestinal, respiratory, urinary, hepatic, and cardiovascular systems, as well as in cancer treatment. *B. diffusa* is known for its anti-inflammatory, antiproliferative, anticancer, and immunomodulatory properties. Research has proved the therapeutic efficacy of *B. diffusa* root extracts against oral cancer cell lines. The methanolic extract of *B. diffusa*¹³ demonstrated higher antioxidant activity than the aqueous extract. Significant cytotoxic effects were observed with both methanolic and aqueous extracts on the KB oral cancer cell line, with IC₅₀ values of 36 µg/ml and 30 µg/ml, respectively. The methanolic extract exhibited a higher potential for inducing apoptosis and DNA fragmentation in oral cancer cells compared to the aqueous extract, corroborated by in-silico analysis. The findings indicate that *B. diffusa* root extracts possess significant anti-cancer properties, particularly against oral cancer.

Zingiber officinale Roscoe

Ginger (*Zingiber officinale* Roscoe) (*Shunti*) from the Zingiberaceae family is commonly used as a spice and herbal medicine for ailments like headaches, colds,

Results

After a thorough search in the database, a total of scientifically validated 21 herbal medicines that are mentioned in TIM classics were listed.



nausea, and emesis. Its bioactive compounds, including phenolic compounds such as gingerols, shogaols, and paradols¹⁴ contribute to its diverse biological activities. Ginger exhibits significant antioxidant¹⁵, anti-inflammatory¹⁶, antimicrobial¹⁷, and anticancer properties¹⁸.

An *in vivo* study evaluated the chemo preventive effects of ginger on tongue carcinogenesis induced by 4-nitroquinoline 1-oxide (4-NQ) in male albino rats. The rats were divided into two groups, both receiving 4-NQ in their drinking water, with the second group additionally fed ginger powder. After 32 weeks, the immunohistochemical staining of tongue for Caspase-3 indicated significantly higher apoptosis in the ginger-treated group, while silver nitrate staining assessed cell proliferation. The results showed that the ginger-treated group exhibited no invasion or carcinomas, only hyperplasia with hyperkeratosis and dysplastic lesions, suggesting ginger's potential to prevent tongue cancer through its anti-proliferative and apoptosis-inducing activities¹⁹.

Another study investigated the anticancer effects of 6-shogaol, an active compound derived from ginger, on head and neck squamous cell carcinomas (HNSCCs). Using two HNSCC cell lines, SCC4 and SCC25, researchers treated cells with 6-shogaol and analyzed cell apoptosis and cell cycle progression. Results demonstrated that 6-shogaol significantly induced G2/M phase cell cycle arrest and apoptosis, inhibiting cell survival. These effects were mediated through ERK1/2 and p38 signalling pathways, and 6-shogaol also enhanced the cytotoxicity of cisplatin in HNSCC cells. The findings suggest that 6-shogaol has potential as a novel anti-HNSCC therapeutic agent²⁰.

Nelumbo nucifera Gaertn

Nelumbo nucifera Gaertn, (*Kamala*) a revered herbal plant in ancient medicine, utilizes its leaves, flowers, seeds, and rhizomes for both nutritional and medicinal purposes. Chemical analyses have identified phenols, alkaloids, glycosides, terpenoids, and steroids within the plant, alongside nutritional components such as lipids, proteins, minerals, carbohydrates, and fatty acids. Scientific investigations through *in vivo* and *in vitro* studies confirm the plant's diverse pharmacological activities, including anticancer, hepatoprotective,

antioxidant, antiviral, hypolipidemic, anti-obesity, antipyretic, hypoglycemic, antifungal, anti-inflammatory, and antibacterial effects²¹.

Nuciferine, an alkaloid found in the leaves of *Nelumbo nucifera*, has been shown to influence various biological processes. It inhibits inflammation, regulates the immune system, contributes to the formation of osteoclasts, and suppresses tumor growth. Nuciferine has demonstrated inhibitory effects on various cancers, including oral squamous cell carcinoma. *In vitro* experiments confirmed that nuciferine inhibited the growth, movement, and infiltration of OSCC cells while promoting apoptosis. It significantly suppressed the STAT3 signaling pathway more than other pathways, and activating STAT3 with colivelin reversed nuciferine's effects. *In vivo*, nuciferine's anti-OSCC impact was confirmed using a cell-based xenograft model in mice. However, colivelin reduced nuciferine's tumor-inhibiting effects, suggesting that nuciferine may partially impede OSCC progression by suppressing the STAT3 pathway²².

Neferine's potential in mitigating head and neck cancer was investigated through *in vitro* and *in vivo* studies. *In vitro*, neferine demonstrated efficacy across three different head and neck cancer cell lines (HN6, CAL27, and HN30) by reducing cell viability, inhibiting proliferation, and suppressing migration. It induced apoptosis and autophagy in HN30 and Cal 20 cells, alongside elevated levels of reactive oxygen species (ROS). Neferine activated the apoptosis signal-regulating kinase 1 (ASK1)/JNK pathway, further promoting apoptosis. Moreover, neferine induced autophagy by enhancing autophagosome formation while inhibiting autophagic flux, indicated by increased LC3-II conversion and p62 accumulation. In an *in vivo* study using CAL27 cell-injected nude mice treated with 10 mg/kg neferine, tumor volumes were reduced through enhanced apoptosis marked by elevated cleaved caspase-2 and cleaved PARP levels. Additionally, neferine stimulated autophagy, corroborated by LC3-II conversion and p62 accumulation²³.

Crocus sativus L.

Crocus sativus L., (*Kumkuma*) known as saffron contains many volatiles like terpenes, terpene alcohols, and esters, contributing to its bitter taste, color, and distinctive fragrance due to picrocrocin, crocin, and safranal.



Saffron exhibits diverse medicinal activities, including antihypertensive, anticonvulsant, antioxidant, antidepressant, anti-inflammatory, memory-enhancing and circulation-promoting effects²⁴.

Considering the use of crocin in saffron which is used in the treatment of various malignancies²⁵. The effects of crocin and cisplatin and their combination on SCC and fibroblast cell lines are studied. The study investigated the effects of crocin and cisplatin, individually and in combination, on HN5 squamous cell carcinoma and fibroblast cell lines. Various concentrations of crocin (12.5–50 µg/mL) and cisplatin (2, 4, 8, 16, and 32 µg/mL) were tested, and cell viability was assessed at 24, 48, and 72 hours using the MTT assay. Both crocin and cisplatin showed toxicity against malignant cells, with cisplatin at 8 µg/mL demonstrating significant toxicity to both cancer cells ($P < 0.001$) and fibroblasts. The combination of 12.5 µg/mL crocin with cisplatin had a comparable effect on the HN5 cell line but was less toxic to fibroblasts compared to cisplatin alone ($P = 0.012$). Flow cytometry confirmed apoptosis as the predominant mode of cell death. The study suggests that lower doses of crocin, when combined with cisplatin, may enhance anticancer effects while reducing cisplatin-induced toxicity in healthy tissues.

Another study evaluated the cytotoxic effects of crocin and safranal, active compounds from saffron, on oral squamous cell carcinoma (KB cells) and NIH 3T3 non-malignant cells. Both compounds significantly inhibited the growth of KB cells in a dose-dependent manner, with over 50% growth inhibition observed at all concentrations tested (0.05–4 mM for crocin and 0.2–3.2 mM for safranal) after 72 hours. Conversely, crocin and safranal exhibited less inhibitory effects on NIH 3T3 cell viability, with IC₅₀ values of 2.8 mM and 0.3 mM, respectively, after 72 hours. Flow cytometry analysis revealed that crocin and safranal induced a sub-G1 peak in treated cells, indicating apoptotic cell death, particularly pronounced in KB cells compared to NIH 3T3 cells. However, neither compound affected cell cycle progression. Overall, crocin and safranal demonstrated potent apoptotic effects in the KB cell line while showing relative selectivity against NIH 3T3 cells, highlighting their potential as anticancer agents in OSCC²⁶.

Glycyrrhiza glabra Linn.

Glycyrrhiza glabra Linn., (*Yastimadhu*) a member of the Fabaceae family, has been known for its ethnopharmacological benefits since ancient times. This plant contains a variety of phytochemicals such as glycyrrhizin, 18β-glycyrrhetic acid, glabrin A and B, and isoflavones, which have shown diverse pharmacological effects. Extracts and isolated compounds from *Glycyrrhiza glabra* possess a wide array of biological properties, including antibacterial, anti-inflammatory, antiviral, antioxidant, and antidiabetic activities²⁷.

The insilico study provides insights into *Glycyrrhiza glabra*'s potential therapeutic mechanisms against Oral cancer, as it focuses on exploring *Glycyrrhiza glabra* extract as a potential supplement for oral cancer treatment using network pharmacology. Cytoscape analysis highlighted wortmannin as a key bioactive and identified the androgen receptor as a central gene. Pathway enrichment analysis using DAVID indicated that drug may exert its effect on oral cancer by inducing apoptosis through inhibition of the PI3K-AKT signaling pathway²⁸.

An Invitro study²⁹ study aimed to evaluate the anticancer properties of *Plectranthus amboinicus* (Indian borage, *Karpooravalli*) and *Glycyrrhiza glabra* on the oral cancer (KB) cell line. Ethanolic extracts of *Plectranthus amboinicus* leaves and *Glycyrrhiza glabra* roots were prepared and tested using the MTT assay to assess cell viability. Both extracts demonstrated a dose-dependent decrease in cell viability, with calculated IC₅₀ values of 53.0 µg/ml for *Plectranthus amboinicus* and 43.6 µg/ml for *Glycyrrhiza glabra*. *Glycyrrhiza glabra* exhibited higher cytotoxicity compared to *Plectranthus amboinicus* against KB cells. This study suggests that both medicinal plants possess potent anticancer activity against oral cancer cells, highlighting their potential as alternative therapies.

Syzygium aromaticum L.

Cloves (*Syzygium aromaticum*), (*Lavanga*) have a long history of use in traditional medicine for their anticancer, antibacterial, antifungal, and antiviral properties. The study investigated the anticancer and antioxidant effects of *Syzygium aromaticum* extract on OSCC cell lines



(KB) compared to normal mouse fibroblast cell lines (L292). The ethanolic extract of clove demonstrated dose-dependent antioxidant activity as measured by FRAP, PM, and DPPH assays. MTT, neutral red, DAPI, and double staining assays indicated that the clove extract induced cell death in KB cell lines, with efficacy comparable to standard drugs used in the assays. This suggests that clove extract shows promising anticancer and antioxidant properties against OSCC in vitro, and has potential therapeutic components for treating oral carcinoma³⁰.

Clove oil has a main component, eugenol which has been proven with anticarcinogenic activity in oral squamous cancers³¹. A study showed that eugenol at cytotoxic concentrations reduced ATP levels and increased glycolytic metabolites, and polyamines in both normal oral and oral squamous cell carcinoma cells. This suggests that eugenol induces unprogrammed cell death in these cells³². Several studies on the impact of eugenol in human squamous cancer cells have shown that eugenol exhibits a cytotoxic effect on oral squamous carcinoma cells at doses similar to those that cause cytotoxicity in healthy cells (primary gingival fibroblasts—HGF). Additionally, eugenol alters the metabolic profile of oral squamous cancer cells³³. When incubated with SCC-25, an oral squamous cell carcinoma cell line, eugenol was found to induce apoptosis and cause mitotic arrest at the S-phase.³⁴

Cinnamomum zeylanicum Blume

Cinnamomum zeylanicum (*Twak*) of the family Lauraceae, contains essential oils composed of key components such as linalool, eugenyl acetate, cinnamyl acetate, β -caryophyllene, benzyl benzoate, and predominantly eugenol. Cinnamaldehyde and eugenol are the predominant³⁵ bioactive antioxidant compounds in *C. zeylanicum* due to the presence of active functional groups that they possess in their chemical structures. Cinnamon is known for its antimicrobial and anti-tumor properties, and its bioactive compound cinnamaldehyde (CIN) was studied for its effects on oral cancer cells (SCC-4, SCC-9, SCC-25). In vitro experiments revealed that *Cinnamomum zeylanicum* extract (CZE) and CIN significantly inhibited the growth and proliferation of these cancer cells in a dose-dependent manner, inducing apoptosis, cell cycle arrest, and autophagy. Molecular docking showed that CIN had a high binding affinity to

MAP kinase P38 α and dihydrofolate reductase. Additionally, treatments inhibited invasion and NF- κ B cytoplasmic translocation in the cancer cells. Western blot analysis indicated that CZE and CIN reduced the expression of proteins related to the PI3k-AKT-mTOR pathway, VEGF, COX-2, Bcl-2, and NF- κ B³⁶.

In an in vitro study, aqueous cinnamon extract demonstrated toxicity towards oral squamous carcinoma cells (OSCC), achieving 90% cytotoxicity at 10 mg/mL concentration within 48 hours. Additionally, combining aqueous saffron and cinnamon extracts resulted in a synergistic effect, enhancing cytotoxicity at lower concentrations³⁷.

A study conducted to explore the anticancer potential of essential oil of cinnamon (EOC) against head and neck squamous cell carcinoma (HNSCC) cell lines (FaDu, Detroit-562, and SCC-25) using MTT assay. The Hep-2 cell xenograft model was employed to evaluate the positive bioactivity of EOC. An EGFR-TK inhibitory assay was performed to understand EOC's mechanism of action, and molecular docking experiments with trans-cinnamaldehyde, the major component of EOC identified by GC-MS analysis, were conducted to identify key interactions with the EGFR protein model. EOC demonstrated significant anticancer activity with inhibition rates of 66.12%, 87.32%, and 99.34% for FaDu, Detroit-562, and SCC-25 cell lines, respectively, and reduced tumor burden by 43.5% in the Hep-2 xenograft model while inhibiting 89% of EGFR-TK activity. Docking studies revealed that trans-cinnamaldehyde fit well into the active site of EGFR, forming close contacts with key catalytic residues. The study concluded that EOC exhibits significant anticancer effects against HNSCC cells in vitro, primarily through the suppression of EGFR-TK, and significantly inhibits tumor growth in vivo³⁸.

In another study³⁹, on HSC-3 cells derived from human oral squamous cell carcinoma, cinnamaldehyde at 10 μ g/mL was found to arrest the cell cycle at the G2/M phase and significantly reduce cell viability, inducing DNA damage and apoptotic characteristics, mitochondrial dysfunction, cytochrome c release, and increased cytosolic Ca^{2+} levels. Further studies⁴⁰ demonstrated that cinnamaldehyde exhibited anticancer activity in SCC25 cells by inducing apoptosis and cell cycle arrest at the S-phase, with an IC_{50} of 20.21 μM .



Another study⁴¹ found that cinnamaldehyde, alone and in combination with scorpion venom, showed significant cytotoxic and pro-apoptotic effects on SCC25 cells, with the combination being particularly potent. Additionally, a study⁴² reported that cinnamaldehyde reduced the proliferation of SCC-25, SCC-9, and SCC-4 oral cancer cells in a dose-dependent manner, increasing apoptosis, cytotoxicity, and cell cycle arrest at the G2/M phase, while inhibiting NF- κ B translocation and reducing the expression of COX-2, VEGF, Bcl-2, and NF- κ B. This summarizes recent research on cinnamaldehyde and its related compounds, highlighting their potential as anticancer drug candidate⁴³.

Curcuma longa Linn

Curcuma longa Linn. (*Haridra*), popularly known as turmeric, belongs to the Zingiberaceae family. Curcumin, a longstanding natural remedy, exhibits anticancer properties but faces limitations in bioavailability and tissue penetration when administered in bulk form. Curcumin, derived from turmeric, possesses diverse therapeutic properties, including notable anti-cancer effects. Extensive research indicates that curcumin influences various biological pathways critical in cancer, such as mutagenesis, oncogene expression, cell cycle regulation, apoptosis, tumorigenesis, and metastasis. It has demonstrated anti-proliferative effects across multiple cancer types by inhibiting nuclear factor kappa B (NF- κ B) and its downstream gene products like c-myc, Bcl-2, COX-2, NOS, Cyclin D1, TNF- α , interleukins, and MMP-9⁴⁴.

The study aimed to evaluate the effects of *Curcuma longa* Linn extract on HSC-4 oral squamous carcinoma cells, focusing on cytotoxicity and inhibition of cell migration. Using MTT assays, the extract showed no toxicity across tested concentrations (0.01% to 0.5% w/v), with cell viability maintained above 100% compared to controls. In scratch motility assays, even at the lowest concentration (0.01% w/v), the extract significantly inhibited cell migration (55.26% reduction compared to control, $p < 0.05$). Higher concentrations completely halted cell migration. These findings suggest that *Curcuma longa* Linn extract is non-toxic and effectively suppresses oral cancer cell migration, highlighting its potential as a supplement for dental and oncological therapies⁴⁵.

Another review study aimed to evaluate nano curcumin's potential efficacy as a natural alkaloid against oral squamous cell carcinoma (OSCC). Curcumin is encapsulated into polymeric nanoparticles, thereby enhancing its aqueous solubility and enabling targeted drug delivery to tumor sites, thus minimizing systemic toxicity. Nanoformulations containing curcumin for treating oral squamous cell carcinoma (OSCC) are an area of promising research and hold significant potential as therapeutic agents⁴⁶.

In an experimental study on Sprague Dawley rats, the anti-cancer potential of curcumin on oral squamous cell carcinoma (OSCC) was investigated. Rats were induced with 7,12-dimethylbenz(a)anthracene to induce epithelial dysplasia, a precursor stage of OSCC. Curcumin was administered to the experimental group for 4 weeks, while the control group received no treatment. Histopathological and immunohistochemistry examinations revealed that curcumin significantly reduced the expression of nuclear factor kappa B (NF- κ B) ($p < 0.01$) and cyclooxygenase 2 (COX-2) ($p = 0.03$) compared to the control group. These findings suggest that curcumin effectively suppressed NF- κ B and COX-2 expression in experimental oral squamous cell carcinoma⁴⁷.

Another study investigated the therapeutic potential of curcumin against oral squamous cell carcinoma (OSCC) using a multi-faceted approach. Initially, curcumin targets were identified from several databases, including the Comparative Toxicogenomics Database, Search Tool for Interactions of Chemicals, and Swiss Target Prediction. Differential gene expression analysis using GSE23558 data revealed 927 differentially expressed genes (DEGs), with 308 upregulated and 619 downregulated genes. Weighted gene co-expression network analysis (WGCNA) identified key modules related to OSCC, highlighting 9083 genes. By integrating OSCC-related genes from disease databases, 2591 genes overlapped with those identified from GSE23558. Ultimately, 70 candidate drug-disease interaction genes were identified as potential targets of curcumin in OSCC. Enrichment analysis implicated pathways such as response to oxidative stress and epithelial cell proliferation in curcumin's effect on OSCC. Topological analysis identified VEGFA, AKT1, TNF, HIF1A, EGFR, JUN, STAT3, MMP9, EGF, and MAPK3 as hub



genes. Expression analysis using The Cancer Genome Atlas database showed significant differences in several hub genes between OSCC and normal controls. This provides insights into the potential mechanisms by which curcumin may exert its effects against OSCC⁴⁸.

In an invitro study, the effects of curcumin on various cellular processes related to tumorigenesis were investigated across different cell types and in a xenograft model of oral squamous cell carcinoma (OSCC). Curcumin, at a concentration of 2 μ M, reduced cell proliferation in mesenchymal-like cell lines, while higher concentrations (50 μ M) induced cell death. Treatment with 2 or 5 μ M of curcumin significantly decreased migration speed and directionality in highly migratory cells by 50% and 40%, respectively ($p < 0.05$). Curcumin also dose-dependently reduced cell-cell adhesion in spheroids, particularly those derived from tumor cells. In a xenograft model using patient-derived OSCC cells, curcumin administration inhibited tumor growth and aggressiveness compared to untreated tumors, demonstrating its potential as an anti-tumor agent in oral cancer therapy. These findings suggest that lower doses of curcumin can modulate key processes in tumorigenesis, including migration, highlighting its potential therapeutic utility in cancer treatment⁴⁹.

In another study, the effects of curcumin on miR-9 expression and its impact on oral squamous cell carcinoma (OSCC) were investigated. Clinical OSCC specimens showed significantly lower levels of miR-9 compared to adjacent non-tumor tissues. Curcumin treatment inhibited proliferation of SCC-9 cells by up-regulating miR-9 expression and suppressing the Wnt/ β -catenin signaling pathway. This was evidenced by increased expression of GSK-3 β and phosphorylated GSK-3 β , decreased levels of β -catenin, and reduced cyclin D1 expression. Furthermore, inhibiting miR-9 with anti-miR-9 oligonucleotides attenuated curcumin's growth-suppressive effects on SCC-9 cells and reactivated Wnt/ β -catenin signaling. These findings suggest that curcumin exerts its anticancer effects in OSCC at least partially through modulation of miR-9 and Wnt/ β -catenin signalling pathways, providing new insights for potential therapeutic strategies against OSCC⁵⁰.

A systematic review focuses on evaluating the molecular effects of curcumin on oral cancer cells based on studies

published between 2006 and 2021, sourced from reputed databases. Reviewed studies consistently showed that curcumin reduced cell proliferation and growth in oral cancer cell lines, assessed primarily through MTT assays. Curcumin was also found to induce cell cycle arrest in the S phase and inhibit Tregs migration. Additionally, it reversed epithelial-mesenchymal transition (EMT) to mesenchymal-epithelial transition (MET). Overall, curcumin inhibited proliferation, migration, invasion, and metastasis while inducing apoptosis by modulating various signalling pathways in oral cancer cells⁵¹.

A study aimed to evaluate curcumin's anticancer effects on OSCC and its potential as a complement to cisplatin therapy. Using the Cal27 OSCC cell line, cytotoxicity was assessed via a PrestoBlue™ assay with various concentrations of curcumin, cisplatin, and their combination (5.3 μ M). Curcumin exhibited an IC₅₀ of 27.67 μ g/mL, while cisplatin and combined treatment showed IC₅₀ values of 7.15 μ g/mL and 14.37 μ g/mL, respectively. These findings suggest curcumin holds promise for OSCC treatment and may enhance the efficacy of cisplatin while mitigating its adverse effects⁵².

Myristica fragrans Houtt

Myristica fragrans, (*Jatiphala*) commonly known as nutmeg or mace, belongs to the Myristicaceae family. The essential oil derived from *Myristica fragrans* is known for its antimicrobial, antiseptic, antiparasitic, anti-inflammatory, and antioxidant properties⁵³. An in vitro study⁵⁴ evaluated the cytotoxicity and apoptotic induction potential of *Myristica fragrans* Houtt mace extract on human oral epidermal carcinoma KB cell lines. Using MTT assay, it was found that the mace extract exhibited cytotoxic activity and suppressed cancer cell growth at concentrations ranging from 25 to 125 μ g/mL. The extract also induced apoptosis, as evidenced by reduced Bcl-2 protein and gene expression. These findings suggest that mace extract has potential as a chemo-preventive agent for oral cancer, warranting further in vivo investigations.

Syzygium cumini (L.) Skeels

Syzygium cumini, (*Jambu*) a widely utilized medicinal plant from the Myrtaceae family, is traditionally employed in Indian medicine for treating conditions such



as obesity and diabetes. This plant is abundant in compounds like anthocyanins, glucoside, ellagic acid, isquercitrin, kaempferol, and myricetin⁵⁵.

A study (Ezhilarasan et al., 2019)⁵⁶ to evaluate the cytotoxic potential against oral cancer cells found that *S. cumini* extract induces cytotoxicity, increases intracellular reactive oxygen species (ROS), and promotes apoptosis in human oral squamous cell carcinoma (OSCC) cells, alongside upregulating cadherin-1 protein and gene expression. These findings suggest that *S. cumini* extract could be effective in inhibiting the proliferation of OSCC cells and may be useful for OSCC prevention.

Sesamum indicum L.

Sesamum indicum, (*Tila*) is a plant species belonging to the family Pedaliaceae and the order Lamiales, renowned for its extensive historical application in traditional medicine. Comprehensive analyses have revealed the nutritional composition of sesame seeds, highlighting their significant content of protein (19-35%) and fat (61.7%), along with noteworthy concentrations of essential minerals such as iron (Fe) and calcium (Ca)⁵⁷. Beyond its macronutrient profile, sesame seeds harbor an array of bioactive compounds including sesamin, sesamol, sesaminol, sesamol phenol, and other lignan-like constituents, with sesamin being particularly abundant⁵⁸.

Research has elucidated the multifaceted pharmacological effects of sesamin, encompassing antioxidant, hypocholesterolemic, lipid metabolism modulation, blood pressure regulation, and anti-cancer properties⁵⁹. The anti-cancer potential of sesamin is predominantly attributed to its ability to impede cell proliferation, induce apoptosis, mitigate inflammation, suppress metastasis and angiogenesis, and promote autophagy⁶⁰. While the precise molecular mechanisms underlying sesamin's anti-cancer activity remain incompletely understood, signalling pathways including STAT3, JNK, ERK1/2, p38 MAPK, PI3K/AKT, caspase-3, and p53 have emerged as pivotal mediators^{61,62}.

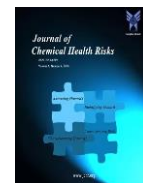
Experimental investigations employing sesamin-treated human oral cancer cell lines FaDu, HSC-3, and Ca9-22 have provided valuable insights into its mechanisms of action. Utilizing methodologies such as wound-healing assays and Western blot analysis, researchers have

delineated the impact of sesamin on cell migration, invasion, and the expression of matrix metalloproteinase (MMP)-2, alongside the modulation of MAPK signalling cascades^{63,64}. Notably, sesamin treatment elicited dose-dependent reductions in cell motility and MMP-2 levels, concomitant with attenuated phosphorylation of p38 MAPK and JNK in FaDu and HSC-3 cells⁶⁵.

Furthermore, sesamol, another prominent lignan constituent of sesame, has garnered attention for its roles as a flavoring agent and quality stabilizer in sesame oil, in addition to its notable antibacterial and antioxidant properties⁶⁶. Evaluation of sesamol's anti-cancer efficacy using in vitro assays on human oral squamous carcinoma (SCC-25) cells has revealed its potent cytotoxic effects, attributed to the generation of intracellular reactive oxygen species (ROS) and the induction of apoptosis, as evidenced by enhanced caspase-9 expression and apoptotic morphology. Moreover, sesamol treatment has been shown to downregulate the expression of Harvey rat sarcoma viral oncogene homolog (HRAS) at both the protein and gene levels, exerting modulatory effects on intrinsic apoptotic marker genes in OSCC cells^{67,68}. Collectively, these findings underscore the therapeutic potential of sesamin and sesamol in combatting oral cancer, implicating diverse molecular pathways in their anti-cancer activities.

Acacia catechu (L.f.) Willd

Acacia catechu (L.f.) (*Khadira*) Willd., commonly known as the Khair or Cutch tree, belongs to the Fabaceae family, and is renowned for its diverse pharmacological properties including hepatoprotective, antipyretic, antidiarrheal, hypoglycemic, anti-inflammatory, immunomodulatory, antinociceptive, antimicrobial, free radical scavenging, and antioxidant activities. The primary phytochemical compounds identified in *A. catechu* include protocathechuic acid, taxifolin, epicatechin, epigallocatechin, catechin, epicatechin gallate, procyanidin, phloroglucin, aldobiuronic acid, gallic acid, D-galactose, afzelchin gum, L-arabinose, D-rhamnose, and quercetin⁶⁹. Recent studies have evaluated the cytotoxic activity of ethanolic extracts of *Acacia catechu* bark⁷⁰ (ACB) and seeds (ACS)⁷¹. against the human squamous cell carcinoma cell line SCC-25. Both studies used the MTT assay to assess cytotoxic effects, with ACB treatments at 25 and 50 µg/mL over 24 hours and ACS treatments ranging



from 0.1 to 1000 $\mu\text{g/mL}$ over the same period. For the ACB extract, the cytotoxicity was confirmed with an IC_{50} of 52.09 $\mu\text{g/mL}$. Apoptosis markers, including caspases-8 and -9, Bcl-2, Bax, and cytochrome c (Cyt-c), were analyzed using RT-PCR. Morphological changes were observed using acridine orange/ethidium bromide (AO/EB) dual staining, while nuclear morphology and DNA fragmentation were assessed using propidium iodide (PI) staining. Cell cycle analysis was performed using flow cytometry. ACB treatment resulted in a significant increase in the expression of apoptotic marker genes, and AO/EB and PI staining revealed membrane blebbing and nuclear membrane distortion, confirming apoptosis induction in SCC-25 cells. These findings suggest that ACB extract may serve as a potential therapeutic agent for oral squamous cell carcinoma. Similarly, the ACS extract demonstrated cytotoxicity with an IC_{50} of 100 $\mu\text{g/mL}$. ACS treatment led to a significant increase in the expression of apoptotic markers, including caspases-8 and -9, cytochrome c, and Bax genes, along with a notable downregulation of Bcl-2 expression, indicating apoptosis induction. AO/EB and PI staining confirmed apoptosis induction by revealing membrane blebbing and nuclear membrane distortion. These results suggest that the ethanolic seed extract of *A. catechu* is cytotoxic at lower concentrations and induces apoptosis in SCC-25 cells. Overall, these studies highlight the potential of both bark and seed extracts of *Acacia catechu* as therapeutic agents in treating oral squamous cell carcinoma by inducing apoptosis in cancer cells.

Triphala

Triphala, a renowned and potent polyherbal Ayurvedic remedy, consists of the fruits of *Embolia officinalis* (*Amalaki*), *Terminalia bellerica* (*Bibhitaki*), and *Terminalia chebula* (*Haritaki*). Research has demonstrated that Triphala is effective for a variety of clinical applications, including appetite stimulation, reduction of hyperacidity, antioxidant, anti-inflammatory, immunomodulatory, antibacterial, antimutagenic, adaptogenic, hypoglycemic, antineoplastic, chemoprotective, and radioprotective effects, as well as the prevention of dental caries⁷².

In studies targeting oral squamous cell carcinoma (OSCC), Triphala (TRP) extracts were investigated for their impact on cell metabolic activity, migration,

invasion, apoptosis, and proliferation in OSCC cell lines CAL-27 and SCC-9. Functional enrichment analysis identified TRP target genes and their involvement in enriched signaling pathways. A protein-protein interaction network highlighted the top ten genes with the highest degree, among which deregulated genes in OSCC tumor samples were identified as hub genes. Notably, five hub genes (JUN, EGFR, ESR1, RELA, and AKT1) were significantly enriched in the PI3K-Akt signaling pathway. TRP extracts significantly reduced cell metabolic activity, migration, invasion, and proliferation while increasing cell death in OSCC cells. The extracts also modulated mRNA and phosphorylated protein levels of key genes, reducing levels of AKT1 and ESR1 and increasing levels of EGFR, JUN, and RELA. Functional rescue assays revealed that co-administration of TRP with the PI3K activator 740Y-P reversed TRP's effects on OSCC cell phenotypes, whereas combining TRP with the PI3K inhibitor LY294002 enhanced TRP's anticancer effects. In vivo studies using a zebrafish xenograft tumor model demonstrated significant reductions in tumor growth and metastasis following TRP treatment. A clinical screening study targeted teenagers from low socioeconomic backgrounds in North India, assessing the reversal of oral lesions using Triphala mouthwash. Screening involved visual inspection with acetic acid, followed by further assessment of positive cases with a pap smear and biopsy for histopathological confirmation. Out of 1095 participants (831 boys and 264 girls), 34 boys were diagnosed with acetowhite-positive lesions. After nine months of Triphala mouthwash use, 85.2% of cases showed no cellular changes, with minor histological alterations observed in a few patients, indicating the mouthwash's efficacy ($P < 0.01$). Additionally, another study evaluated the anticancer properties of Triphala extract on oral cancer cell lines using the MTT assay. The results demonstrated dose-dependent cytotoxicity, confirming the extract's consistent anticancer efficacy⁷³.

Another investigation elucidates the therapeutic potential of the hydroalcoholic extract, particularly its ethyl acetate fraction derived from *Terminalia chebula* fruits as a promising agent against OSCC⁷⁴.

Nigella sativa L.

Nigella sativa (Family Ranunculaceae) (*Upakunjika*) is a well-known therapeutic herb used in various traditional



medical systems, such as Unani and Tibb, Ayurveda, and Siddha. Extensive research has explored its pharmacological properties, revealing a wide range of actions, including antidiabetic, anticancer, immunomodulatory, analgesic, antimicrobial, anti-inflammatory, spasmolytic, bronchodilator, hepatoprotective, renal protective, gastroprotective, and antioxidant effect⁷⁵. Thymoquinone, a major bioactive component of *N. sativa*'s essential oil, plays a significant role in its therapeutic potential⁷⁶.

A study assessed the potential of *Nigella sativa* in treating oral cancer using assays that simulate the conditions of whole seed consumption or seed extract use. A water-based extract of *N. sativa* seeds was prepared to mimic the chewing process. This extract exhibited substantial cytotoxic effects on oral cancer and precancerous leukoplakia cells in vitro at lower concentrations than the estimated oral dose achievable from chewing seeds. The water-based extract contained significant levels of α -hederin and only minor amounts of thymoquinone, suggesting that thymoquinone is not fully released into the aqueous medium during chewing. The cytotoxic effects of the *N. sativa* seed extract differed from those of pure thymoquinone, while α -hederin alone produced similar effects, indicating that α -hederin is the primary component responsible for the inhibitory effect in vitro. Thus, chewing *N. sativa* whole seeds or applying a concentrated extract to oral lesions may offer a cost-effective and widely accessible preventive treatment for individuals at risk of developing oral cancer who lack other preventive options⁷⁷.

Further investigation evaluated the efficacy of *Nigella sativa* extract (NSE) alone and in combination with Cisplatin during the precancerous stage of oral lesions in golden Syrian hamsters. Fifty hamsters were divided into ten groups. Group 1 (control) received only saline, while Group 2 received NSE (30 mg/kg). Groups 3, 5, 7, and 9 were administered the carcinogen 9,10-dimethyl-1,2-benzanthracene (DMBA) in buccal pouches for six weeks, and Groups 4, 6, 8, and 10 for 14 weeks. Groups 5 and 6 received NSE, Groups 7 and 8 received Cisplatin (35.0 μ g/kg), and Groups 9 and 10 received NSE plus Cisplatin (8.0 μ g/kg). Histopathological, immunohistochemical, and histomorphometry analyses, along with kidney and liver function tests and full blood counts, were performed. The severity of dysplasia was

highest in Group 4 (DMBA alone for 14 weeks), while six weeks of DMBA exposure resulted in minor dysplasia. Combining NSE with Cisplatin at a low dose (8.0 μ g/kg) prevented the development of dysplasia with short-term carcinogen exposure and the progression of mild dysplasia to carcinoma with long-term exposure, comparable to a higher dose of Cisplatin (35.0 μ g/kg) alone. Kidney and liver functions improved in the NSE-treated groups. These findings suggest that NSE, when combined with chemotherapeutics like Cisplatin, may provide cancer chemoprevention, enhance the anticancer efficacy of the drug, and reduce adverse effects on normal organs⁷⁸.

Calotropis gigantea (L.) W. T. Aiton

Calotropis gigantea, (*Sweta arka*) is a renowned medicinal herb extensively used in Unani, Ayurvedic, and Siddha medical systems. Its phytochemical constituents include giganteol, α and β calotropeol, β -amyrin, and isogiganteol. The herb is documented for its diverse therapeutic properties, including anti-asthmatic, antioxidant, antibacterial, antiviral, wound healing, anti-inflammatory, antidiarrheal, hepatoprotective, and hypoglycemic effects⁷⁹.

Calotropin, a cardiac glycoside derived from *Calotropis gigantea*, has demonstrated promising anti-tumorigenic properties. Recent research investigated the anti-cancer potential of calotropin against HSC-3 oral squamous carcinoma cells and aimed to elucidate its underlying mechanisms of action. The study used the MTT assay to assess cell viability after treatment with calotropin, revealing significant cytotoxic effects on HSC-3 cells. Flow cytometry analysis indicated that calotropin induces cell cycle arrest and apoptosis in HSC-3 cells. Further, calotropin was shown to inhibit aerobic glycolysis, as evidenced by reduced glucose uptake, lactate production, and lactate dehydrogenase activity. Migration and invasion assays using transwell and Matrigel systems demonstrated calotropin's ability to inhibit HSC-3 cell migration and invasion. Validation of mRNA expression was performed using RT-PCR, confirming that calotropin alters the expression of genes involved in apoptosis and metastasis. Molecular docking studies provided additional support, showing high binding energy between calotropin and key regulatory targets in metastasis-mediated pathways. The findings indicate that increasing doses of calotropin effectively



inhibit the progression of HSC-3 cells, with significant reductions in migration and invasion, suggesting its potential to curb cancer metastasis⁸⁰.

***Azadirachta indica* A.Juss.**

Azadirachta indica, (*Nimba*) a member of the Meliaceae family, is renowned for its health-promoting effects, largely attributed to its high antioxidant content. It is widely utilized in Chinese, Ayurvedic, and Unani medicines, particularly in the Indian subcontinent, to treat and prevent various ailments. Studies have shown that neem and its constituents manage cancer by modulating molecular pathways such as p53, PTEN, NF- κ B, PI3K/Akt, Bcl-2, and VEGF. The leaves of the neem tree have long been used in traditional Ayurvedic medicine to treat oral maladies, thanks to their significant anti-inflammatory properties. NLGP (a glycoprotein isolated from neem leaf) is particularly noted for its potent anti-inflammatory, immunostimulatory, and anti-cancer properties⁸¹.

A recent study explored the epigenetic modifications mediated by NLGP on the OSCC cell line SCC-9, focusing on its role in specific signal transduction pathways. Chromatin immunoprecipitation (ChIP) assays were performed on MNase-digested chromatin from NLGP-treated and untreated SCC-9 cells. ChIP-grade antibodies and isotype-Ig antibodies were used to isolate DNA-protein complexes, which were then analyzed via quantitative PCR (qPCR). This analysis revealed that NLGP treatment led to significant epigenetic changes, which were further confirmed by coimmunoprecipitation assays and immunoblotting of whole cell extracts⁸².

A highly pure supercritical CO₂ neem leaf extract (SCNE) inhibits the onset and development of OSCC by suppressing intra-tumor pro-inflammatory pathways that promote carcinogenesis. Both in vitro and in vivo experiments were conducted to evaluate SCNE's anticancer effects. OSCC cell lines (SCC4, Cal27, and HSC3) treated with SCNE showed significant reductions in proliferation and migration, alongside decreased MMP activity, suggesting its potential to inhibit tumor growth and metastasis. SCNE's preventive effects were also observed in ectopic xenograft and 4NQO-1 (4-Nitroquinoline-1-oxide) carcinogen-induced mouse models of OSCC, with treated mice exhibiting

significantly reduced tumor sizes and tongue dysplasia rates. Further analysis demonstrated that SCNE significantly reduced pro-cancer inflammatory cytokines such as NF- κ B, COX-2, IL-1, IL-6, TNF- α , and IFN- γ in both OSCC animal models. It also inhibited STAT3 and AKT expression and activity in vitro. Notably, the principal active component, nimbolide (NIM), showed strong anticancer efficacy in established OSCC xenografts. Additionally, SCNE treatment promoted the M1 phenotype in tumor-associated macrophages (TAMs) in vivo. These findings collectively support the potential of SCNE as a preventive strategy against OSCC by downregulating pro-cancer inflammatory pathways and highlight nimbolide as a promising novel treatment for existing OSCC⁸³.

***Caesalpinia sappan* L.**

Caesalpinia sappan L., (*Patanga*) commonly known as sappanwood, has a long history of use as a natural dye and medicinal herb in traditional medicine. It is renowned for its anti-inflammatory, antioxidant, and antimicrobial properties⁸⁴.

Recent studies have explored the effects of a chloroform extract of *C. sappan* on cell death in head and neck cancer cell lines. The vitality of HNSCC4 and HNSCC31 cells (head and neck cancer cell lines) was significantly lower in the presence of the chloroform extract compared to HaCaT cells (a control group). Conversely, exposure to n-butanol, methanol, and water extracts of *C. sappan* did not result in significant differences in cell vitality between the cancer cells and HaCaT cells. Notably, the chloroform extract induced an increase in the Sub-G1 phase of the cell cycle and caused nuclear condensation and shrinkage in HNSCC4 cells. Isoliquiritigenin 2'-methyl ether (ILME), a compound isolated from *C. sappan* heartwood, has been studied for its effects on cultured primary and metastatic oral cancer cell lines using MTT assays, fluorescence microscopy, flow cytometry, and western blotting. ILME was found to reduce the proliferation of oral cancer cells in a time- and dose-dependent manner, primarily by inducing apoptosis. This was evidenced by flow cytometry showing sub-G1-phase arrest and annexin V-FITC and propidium iodide staining. ILME activates NF- κ B transcription factors and phosphorylates JNK (c-Jun N-terminal kinase) and ERK. Additionally, ILME administration increased HO-1 expression by activating



the Nrf2 (NF-E2-related factor 2) pathway, leading to the expression of heme oxygenase-1. Tin protoporphyrin, a HO-1 inhibitor, reduced ILME's growth inhibitory effect and inhibited ILME-induced expression of the cell cycle regulators p21 and p53. These findings suggest that ILME may prevent oral cancer by upregulating HO-1 through pathways involving MAP kinases, NF- κ B, and Nrf2, making ILME a promising chemotherapeutic target for anti-oral cancer treatment strategies⁸⁵.

Tinospora cordifolia (Willd.) Hook.f. & Thomson

Tinospora cordifolia, (*Guduchi*) commonly referred to as "Guduchi" or "Giloy," has been extensively utilized in Ayurvedic medicine for centuries to address various health issues. This plant is rich in an array of bioactive compounds, such as alkaloids, diterpenoid lactones, glycosides, steroids, sesquiterpenoids, phenolics, aliphatic compounds, and polysaccharides. These constituents have demonstrated significant therapeutic properties, including anti-inflammatory, anti-diabetic, and anti-cancer activities⁸⁶.

Recent research has explored the effects of *Tinospora cordifolia* (Thunb.) Miers (Giloy) extract (TcE) on oral cancer cell lines. In a study involving the AW13516 oral cancer cell line, cells were treated with an aqueous extract of TcE at concentrations ranging from 5 μ g/mL to 100 μ g/mL for 24 hours, compared to untreated control cells. The induction of apoptosis was assessed through Annexin V flow cytometry and luminometry-based assays measuring Caspase 8, 9, and Caspase 3/7 activity. Additionally, RNA extracted from treated cells was used to evaluate the expression levels of specific metastatic genes (MMP1, MMP10, CXCL8), epithelial-mesenchymal transition (EMT) genes (TWIST1, SNAIL, ZEB1, Oct4), and stemness-related genes (Nanog, Sox2) via quantitative real-time PCR. All experiments were conducted in triplicate to ensure statistical validity. The findings revealed that the aqueous extract of TcE induced apoptosis in AW13516 cells in a concentration-dependent manner, showing efficacy even at the low concentration of 5 μ g/mL. The caspase activity assays confirmed the induction of apoptosis. Moreover, treatment with TcE resulted in a significant dose-dependent reduction in the expression of EMT genes without affecting the expression of metastatic genes. This suggests that TcE induces apoptosis-mediated cell death in the AW13516 oral

cancer cell line while diminishing the cells' epithelial-mesenchymal transition capacity⁸⁷.

Additionally, studies have shown that *Tinospora cordifolia* extracts (TCE) inhibit the proliferation of KB cells, which is associated with cell cycle arrest in the G0/G1 phase. Importantly, TCE's ability to inhibit KB cell growth without affecting the growth of normal peripheral blood mononuclear cells (PBMC) highlights its selective cytotoxicity towards cancer cells. This differential effect underscores *Tinospora cordifolia*'s potential as a promising therapeutic agent in cancer treatment⁸⁸.

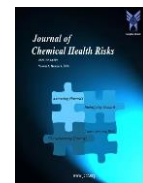
Tribulus terrestris L.

Tribulus terrestris L. (TT), (*Gokshura*) an annual herb from the Zygophyllaceae family, is traditionally employed to enhance sexual performance and manage cardiovascular diseases and diabetes. The fruits and roots of TT have a long history of use in folk medicine across China, India, Sudan, and Pakistan. TT is rich in bioactive phytochemicals such as steroidal saponins, flavonoids, glycosides, phytosterols, tannins, terpenoids, amide derivatives, amino acids, and proteins. Among these, steroidal saponins and flavonoids are considered the most significant metabolites due to their diverse bioactive properties. TT exhibits hepatoprotective, antioxidant, anti-inflammatory, antibacterial, anti-aging, and antitumor effects⁸⁹.

Elevated autophagy is closely associated with the genesis and progression of cancer. Studies have demonstrated that the fruit extracts of *Tribulus terrestris* (TT-fr) and *Xanthium strumarium* inhibit autophagy in SAS and TW2.6 oral cancer cell lines. The extracts exhibited significant inhibitory effects on the proliferation of these oral cancer cells. Moreover, TT-fr extracts notably impeded the migration and invasion of oral cancer cells. The research indicated that TT-fr extracts consistently suppressed autophagic flux, cell proliferation, and the metastatic properties of oral cancer cells, suggesting that TT-fr may contain functional ingredients capable of inhibiting oral cancer cell growth and metastasis⁹⁰.

Acacia nilotica L.

Acacia nilotica (L.), (*Babula*) a valuable medicinal plant indigenous to tropical and subtropical regions, belongs to the Fabaceae family. The primary phytochemicals in this plant include tannins, flavonoids, alkaloids, fatty acids,



and polysaccharides (gums). Extensive pharmacological studies have revealed its significant anti-inflammatory, antioxidant, antidiarrheal, antihypertensive, antispasmodic, antibacterial, anthelmintic, antiplatelet aggregatory, anticancer, and acetyl cholinesterase (AChE) inhibitory properties⁹¹.

A study investigated the combined effects of *Acacia nilotica* (L.) leaf extract (AN) and ethyl gallate (EG), a phenolic compound in AN with protective effects against oral carcinogenesis. This research explored the transition of a tumor cell line to a mouse model, using 4-nitroquinoline 1-oxide (4-NQO) as a carcinogen, simulating the effects of tobacco. After 4-NQO induction, Swiss albino mice developed hyperplasia and dysplasia, progressing to squamous cell carcinoma (SCC). Treatment with AN and EG in mice with dysplasia inhibited SCC development, reducing the tumor burden. The antioxidant capacities of AN and EG were confirmed through biochemical assays. Further biomarker analysis in tongue tissues demonstrated the presence of apoptosis *in vivo*. Additionally, no adverse or toxic effects were observed in rats following oral administration of AN and EG. Therefore, AN and EG show significant potential as therapeutic agents in preventing the progression of oral cancer⁹².

***Santalum album* L.**

Santalum album, (*Sveta Chandana*) an evergreen tree primarily cultivated for its hardwood and essential oil,

boasts a broad spectrum of therapeutic properties, including notable antibacterial and antifungal, antioxidant, anti-inflammatory, anti-spasmodic, diuretic, expectorant and antiseptic activities. These health benefits are largely attributed to its abundant phytochemicals, particularly sesquiterpenes⁹³.

A study examined the biological effects of East Indian sandalwood oil (EISO) and its principal constituents, α - and β -santalol, on various head and neck squamous cell carcinoma (HNSCC) lines. These compounds exhibited cytotoxicity, causing cell cycle arrest at the G2/M phase. Additionally, treatment with EISO and the santalols induced the formation of multipolar mitotic spindles, akin to the effects seen with agents that disrupt microtubule polymerization. Notably, the santalols and EISO inhibited the polymerization of purified tubulin, marking the first demonstration that these compounds can directly bind to tubulin and influence microtubule dynamics. Computational modeling suggested that the santalols bind weakly to the colchicine site on tubulin. Topical application of EISO on an HNSCC xenograft model resulted in reduced tumor growth without noticeable side effects. Therefore, santalols can directly interact with tubulin to inhibit microtubule polymerization, similar to established chemotherapeutic agents, but with significantly lower potency and without the typical toxicity associated with many tubulin-binding drugs^{94,95}.

Table no.1 Herbal Drugs from Traditional Indian Medicine (Ayurveda) Against Oral Squamous Cell Carcinoma (OSCC): Phytocompounds and Mechanisms

Traditional Name	Botanical Name & Family	Phytocompounds	Biological Activity/Mechanism Against OSCC
Punarnava	<i>Boerhavia diffusa</i> Linn. (Nyctaginaceae)	Rotenoids, flavonoids, xanthenes, purine nucleosides, lignans, steroids [Mishra et al., 2014]	Cytotoxic KB cells (IC50: 36 μ g/ml methanolic, 30 μ g/ml aqueous); apoptosis, DNA fragmentation [Gunaseelan et al., 2022]
Shunti (Ginger)	<i>Zingiber officinale</i> Roscoe (Zingiberaceae)	Gingerols, shogaols, paradols [Stoner, 2013]	4-NQO chemo-prevention rats; $\uparrow$ Caspase-3 apoptosis [Khater, 2010]; 6-shogaol G2/M arrest ERK/p38 [Hsu et al., 2023]



Kamala	Nelumbo nucifera Gaertn.	Nuciferine, neferine, phenols, alkaloids, glycosides [Sahu et al., 2024]	Nuciferine ↓growth/migration/invasion ↑apoptosis STAT3 [Xie et al., 2023]; neferine ↑apoptosis/autophagy/ROS ASK1-JNK [Zhu et al., 2021]
Kumkuma (Saffron)	Crocus sativus L.	Crocin, safranal, picrocrocin [Srivastava et al., 2010]	Crocin/safranal apoptosis sub-G1 KB cells [Jabini et al., 2017]; crocin+cisplatin HN5 [Bijani et al., 2021]
Yastimadhu	Glycyrrhiza glabra Linn. (Fabaceae)	Glycyrrhizin, 18β-glycyrrhetic acid, glabrin A/B [Pastorino et al., 2018]	KB cytotoxic IC50 43.6 µg/ml [Caroline et al., 2023]; PI3K-AKT apoptosis [Vaibhav et al., 2022]
Lavanga (Cloves)	Syzygium aromaticum L. (Myrtaceae)	Eugenol	KB cell death MTT/DAPI [Sanikop et al., 20xx]; eugenol ↓ATP S-arrest apoptosis [Raja et al., 2015][Koh et al., 2013][Ulanowska, Olas, 2021]
Twak (Cinnamon)	Cinnamomum zeylanicum Blume (Lauraceae)	Cinnamaldehyde, eugenol, linalool [Weerasekara, 2021]	CZE/CIN ↓proliferation PI3K-AKT-mTOR/NF-κB SCC-4/9/25 [Aggarwal et al., 2022a]; EOC ↓EGFR-TK 89% [Yang et al., 2015]
Haridra (Turmeric)	Curcuma longa Linn. (Zingiberaceae)	Curcumin [Alok et al., 2017]	↓migration/proliferation ↑apoptosis NF-κB/COX-2 [Smith et al., 2021]; miR-9/Wnt [Xiao et al., 2014]; +cisplatin [Pratama et al., 2021]
Jatiphala (Nutmeg)	Myristica fragrans Houtt. (Myristicaceae)	Essential oils [Navneet et al., 2021]	Mace extract cytotoxic 25-125 µg/ml ↓Bcl-2 apoptosis KB [Rengasamy et al., 2018]
Jambu	Syzygium cumini L. Skeels (Myrtaceae)	Anthocyanins, ellagic acid, isoquercitrin [Ayyanar et al., 2012]	↑ROS apoptosis cadherin-1 OSCC cells [Ezhilarasan et al., 2019]
Tila (Sesame)	Sesamum indicum L. (Pedaliaceae)	Sesamin, sesamol, sesamolol [Pathak et al., 2014]	Sesamin ↓MMP-2/migration p38/JNK FaDu/HSC-3 [Zhang et al., 2021]; sesamol ↑ROS/caspase-9 SCC-25 [Ezhilarasan et al., 2021]
Khadira	Acacia catechu L.f. Willd. (Fabaceae)	Catechin, epicatechin, gallic acid, procyanidin [Kumari et al., 2022]	Bark IC50 52 µg/ml seed IC50 100 µg/ml ↑caspases/Bax SCC-25 [Lakshmi et al., 2017a,b]
Triphala	Embolica officinalis, Terminalia bellirica, T. chebula	Polyphenols [Peterson et al., 2017]	↓proliferation/migration PI3K-Akt CAL-27/SCC-9; 85% lesion reversal [Suresh et al., 2019]



	(XXXXXXX)		
Upakunjika	<i>Nigella sativa</i> L. (Ranunculaceae)	α -hederin, thymoquinone [Gholamnezhad et al., 2016]	Water extract cytotoxic α -hederin; +cisplatin prevents DMBA dysplasia [Dagtaz & Griffin, 2021][Attas et al., 2015]
Sweta Arka	<i>Calotropis gigantea</i> L. W. T.Aiton (Asclepiadaceae)	Calotropin, giganteol [Jahan et al., 2016]	↓viability G2/M arrest apoptosis glycolysis migration HSC-3 [Jayaraman et al., 2023]
Nimba	<i>Azadirachta indica</i> A.Juss. (Meliaceae)	Nimbolide, NLGP [Alzohairy et al., 2016]	SCNE ↓proliferation/MMP/NF- κ B/STAT3; NLGP epigenetics SCC-9 [Moris et al., 2019][Chatterjee et al., 2022]
Patanga	<i>Caesalpinia sappan</i> L. (Fabaceae)	Isoliquiritigenin 2'-methyl ether (ILME) [Mekala et al., 2015]	Chloroform ↑sub-G1 apoptosis NF- κ B/JNK/ERK/Nrf2 [Mekala et al., 2015]
Guduchi	<i>Tinospora cordifolia</i> Willd. Hook.f. &Thomson (Menispermaceae)	Alkaloids, diterpenoids, polysaccharides [Saha, Ghosh, 2012]	↑caspases 8/9/3/7 ↓EMT TWIST1/SNAIL AW13516; G0/G1 KB [Patil et al., 2021] [Smith et al., 2021]
Gokshura	<i>Tribulus terrestris</i> L. (Zygophyllaceae)	Steroidal saponins, flavonoids [Zhu et al., 2017]	Fruit extract ↓autophagy/proliferation/migration SAS [Shu et al., 2021]
Babula	<i>Acacia nilotica</i> L. (Fabaceae)	Tannins, flavonoids, gallic acid [Rather, Mohammad, 2015]	Leaf+ethyl gallate prevents 4-NQO dysplasia→SCC ↑apoptosis [Shalini et al., 2017]
Sveta Chandana	<i>Santalum album</i> L. (Santalaceae)	α/β -santalol [Sreevidhya, Chandradhar, 2015]	EISO/santalols cytotoxic G2/M arrest microtubule HNSCC xenograft [Bridgette et al., 2015]

Discussion

Carcinogens present in tobacco, alcohol, betel quid, and areca nut initiates tumor development in the oral cavity, with alcohol further facilitating deeper penetration of these carcinogens. Additionally, chronic inflammation caused by dust and heavy metals, HPV infections, nutritional deficiencies, and oral microbiome dysbiosis contribute to the incidence and progression of oral squamous cell carcinoma.

Herbal agents provide a comprehensive approach to combating OSCC through their antioxidant, anti-inflammatory, immunomodulatory, and antiproliferative properties. These properties are essential in mitigating oxidative stress and chronic inflammation, which are critical factors in tumor initiation and progression.

For instance, Many of these herbal drugs, such as *Zingiber officinale*, *Crocus sativus*, *Curcuma longa*, *Boerhavia diffusa*, and *Triphala* exhibit potent



antioxidant activities that can neutralize reactive oxygen species, thereby reducing oxidative stress and subsequent DNA damage in oral tissues.

Compounds found in *Glycyrrhiza glabra*, *Cinnamomum zeylanicum*, *Azadirachta indica*, and *Nelumbo nucifera* have been shown to possess significant anti-inflammatory properties. These can help mitigate the chronic inflammation induced by carcinogens and heavy metals, thereby reducing the risk of tumor initiation and progression. Many herbal compounds, such as 6-shogaol from *Zingiber officinalis*, curcumin from *Curcuma longa*, and eugenol from *Syzygium aromaticum*, have been shown to induce apoptosis in cancer cells and inhibit their proliferation. Constituents of *Santalum album*, such as α - and β -santalol, disrupt microtubule polymerization and induce cell cycle arrest, exerting cytotoxic effects on cancer cells with minimal toxicity. Phenolic compounds like ethyl gallate in *Acacia nilotica* offer protection against carcinogenesis through antioxidant and apoptotic activities. Eugenol from *Syzygium aromaticum* and cinnamaldehyde from *Cinnamomum zeylanicum* can disrupt cancer cell metabolism, leading to reduced energy production and increased cell death. This metabolic interference can be particularly effective against rapidly proliferating cancer cells.

Nigella sativa and *Glycyrrhiza glabra* have demonstrated antiviral activity, which may be beneficial in controlling HPV infections that are implicated in the pathogenesis of OSCC. By reducing viral load and preventing viral-induced transformations, these herbs can lower the risk of malignant transformation.

Compounds from *Nelumbo nucifera* (lotus), such as nuciferine and neferine, modulate immune responses and inhibit tumor growth via specific signaling pathways. *Tribulus Terrestris* fruit extracts inhibit autophagy in cancer cells, thereby reducing proliferation, migration, and invasion. Herbs like *Tinospora cordifolia* and *Calotropis procera* are known for their immunomodulatory effects, which can enhance the body's immune response to eliminate or control tumor cells more effectively.

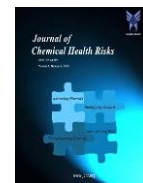
These herbal drugs not only target cancer cells directly but also enhance the efficacy of conventional treatments like cisplatin and boost immune function as shown by 6

shogaol. By addressing various pathways of OSCC pathogenesis, including chronic inflammation, HPV infections, and microbiome dysbiosis, these natural compounds offer a multifaceted therapeutic strategy that may reverse disease progression and improve patient outcomes.

From an Ayurvedic perspective, Oral Squamous Cell Carcinoma (OSCC) manifests as *Mukharbuda*, arising from persistent *Rakta, Mamsa* vitiation, *Tridoṣha* aggravation, impaired *Agni*, *Ama* accumulation, and gradual *Ojas* depletion. The plants examined above demonstrate pharmacological effects that align closely with established principles of *Arbuda* treatment. Herbs like *Haridra*, *Nimba*, *Khadira*, and *Patanga* known for their *Raktaśodhana*, *Viśaghna*, and *Lekhana* qualities correspond mechanistically to the suppression of key inflammatory pathways (NF- κ B, STAT3), angiogenesis, and cancer cell growth. *Rasayana* herbs such as *Guḍuci*, *Triphala*, *Kumkuma*, *Yāṣṭimadhu*, and *Tila* support *Vyadhikṣamatva* and promotes *dhatu*, mirroring their immunomodulatory, apoptosis promoting, and EMT-inhibiting activities. Substances with potent *Agnidipan*, *Amapacana* and *Srotoshodhana* effects, including *Śuṇṭhi*, *Tvak*, *Lavanga*, and *Punarnava*, likely help regulate the tumor microenvironment by addressing metabolic imbalances and *srotorodha*. Additionally, the anti-migratory and anti-invasive properties of *Jambu*, *Tila*, *Kamala*, and *Gokṣura* align with Ayurvedic notions of *Granthi Arbudanasana* and *Mamṣa dhatu prasdana*.

Conclusion

In summary, the diverse therapeutic properties of these herbal drugs—including antioxidant, anti-inflammatory, antiviral, immunomodulatory, and anti-proliferative effects—offer promising avenues for reversing the pathogenesis of OSCC. Their ability to target multiple mechanisms involved in cancer progression highlights their potential as complementary and integrative approaches in managing and treating oral squamous cell carcinoma. The integration of herbal medicines into cancer treatment regimens holds promise for more holistic and personalized care, potentially leading to better outcomes and improved patient well-being. Further clinical research and trials are crucial to recognize herbal medications' potential in countering oral squamous cell carcinoma.



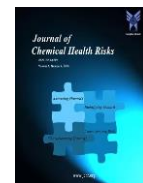
Proposed furtherance

Despite the growing evidence for plant-based interventions, nano-compatible mineral preparations offer untapped potential to address key challenges like low solubility, poor bioavailability, and multidrug resistance (MDR) through integration with nanotechnology-based drug delivery systems (NP-DDS). Bioinspired selenium nanoparticles (SeNPs), for instance, have shown potent apoptosis induction in human OSCC KB-1 cell lines via targeted intracellular delivery, minimizing off-target effects on healthy tissues. Future research extending the current narrative review on herbal remedies for OSCC by conducting a comprehensive systematic review, including herbo-mineral and mineral-based Ayurvedic formulations, such as swarna bhasma, Arogyavardhini, and Kamadudha rasa, which have reported and demonstrated anti-OSCC activities in various case reports, would pave the way for translational trials that bridge traditional herbal, herbo-mineral wisdom with modern technology for evidence-based OSCC management.

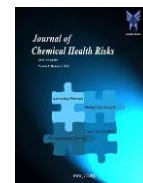
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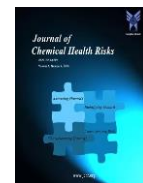
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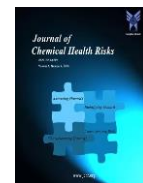
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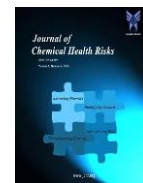
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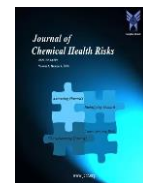
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