Frontiers in Bioscience Scholar

Front. Biosci. (Schol Ed) **2022**; 14(3): 24
https://doi.org/10.31083/j.fbs1403024

Review

Naturally-Occurring Bioactives in Oral Cancer: Preclinical and Clinical Studies, Bottlenecks and Future Directions

Monica Butnariu[1], Cristina Quispe[2], Javad Sharifi-Rad[3,*], Eduardo Pons-Fuster[4], Pia Lopez-Jornet[4], Wissam Zam[5], Tuyelee Das[6], Abhijit Dey[6,*], Manoj Kumar[7], Marius Pentea[1], Ali H. Eid[8,9], Almagul Umbetova[10], Jen-Tsung Chen[11,*]

[1]Banat's University of Agricultural Sciences and Veterinary Medicine "King Michael I of Romania" from Timisoara, 300645 Timis, Romania
[2]Facultad de Ciencias de la Salud, Universidad Arturo Prat, Avda. 1110887 Iquique, Chile
[3]Phytochemistry Research Center, Shahid Beheshti University of Medical Sciences, 19858-58962 Tehran, Iran
[4]Instituto Murciano de Investigación Biosanitaria (IMIB-Arrixaca-UMU), Clínica Odontológica Universitaria Hospital Morales Meseguer Adv. Marques de los velez s/n, 30008 Murcia, Spain
[5]Department of Analytical and Food Chemistry, Faculty of Pharmacy, Al-Andalus University for Medical Sciences, 35XQ+C2F Tartous, Syria
[6]Department of Life Sciences, Presidency University, 1212 Kolkata, India
[7]Chemical and Biochemical Processing Division, ICAR – Central Institute for Research on Cotton Technology, 400019 Mumbai, India
[8]Department of Basic Medical Sciences, College of Medicine, QU Health, Qatar University, 2713 Doha, Qatar
[9]Biomedical and Pharmaceutical Research Unit, QU Health, Qatar University, 2713 Doha, Qatar
[10]Faculty of Chemistry and Chemical Technology, Al-Farabi Kazakh National University, 050040 Almaty, Kazakhstan
[11]Department of Life Sciences, National University of Kaohsiung, 811 Kaohsiung, Taiwan
*Correspondence: javad.sharifirad@gmail.com (Javad Sharifi-Rad); abhijit.dbs@presiuniv.ac.in (Abhijit Dey); jentsung@nuk.edu.tw (Jen-Tsung Chen)
Academic Editor: Luca Testarelli
Submitted: 18 March 2022 Revised: 16 July 2022 Accepted: 1 August 2022 Published: 19 August 2022

Abstract

Oral cancer (OC) is the eighth most common cancer, particularly prevalent in developing countries. Current treatment includes a multidisciplinary approach, involving chemo, radio, and immunotherapy and surgery, which depends on cancer stage and location. As a result of the side effects of currently available drugs, there has been an increasing interest in the search for naturally-occurring bioactives for treating all types of cancer, including OC. Thus, this comprehensive review aims to give a holistic view on OC incidence and impact, while highlights the preclinical and clinical studies related to the use of medicinal plants for OC prevention and the recent developments in bioactive synthetic analogs towards OC management. Chemoprophylactic therapies connect the use of natural and/or synthetic molecules to suppress, inhibit or revert the transformation of oral epithelial dysplasia (DOK) into oral squamous cell carcinoma (OSCC). Novel searches have underlined the promising role of plant extracts and phytochemical compounds, such as curcumin, green tea extract, resveratrol, isothiocyanates, lycopene or genistein against this malignancy. However, poor bioavailability and lack of *in vivo* and clinical studies and complex pharmacokinetic profiles limit their huge potential of application. However, recent nanotechnological and related advances have shown to be promising in improving the bioavailability, absorption and efficacy of such compounds.

Keywords: oral cancer; head and neck squamous cell carcinoma; phytotherapy; curcumin; green tea extract; bioavailability; nanotechnology

1. Introduction

Cancer is one of the most common causes of morbimortality worldwide [1], and representing nearly 10 million deaths in 2020 [2]. Furthermore, more than 50% of all cancer cases occur in developing countries [3].

Oral cancer (OC) is the 8th commonest type of cancer worldwide, being most common in developing countries [3]. OC and oropharyngeal cancer together represent the 6th most frequent neoplasm worldwide, with about 400,000 new cases diagnosed each year, despite vary greatly depending on the geographical setting. In effect, the incidence can be 20 times greater in some regions compared to others (e.g., Malaysia or Sri Lanka) [4]. Likewise, differences in both incidence and mortality have been observed by comparing the epidemiological data of industrialized countries with that of developing countries [4]. Such variations in incidence have been mainly related to environmental factors, like smoking and alcohol consumption, and diet [5]. Although both smoking and alcohol have been largely searched in relation to OC risk, data related to dietetic factors are more limited [6].

By definition, OC is a type of head and neck cancer, arising on the lip or oral cavity, with 90% being classified as squamous cell carcinoma [7]. It includes all malignant tumors, including salivary glands, metastatic tumors of other epithelial organs and nerve-related malignant tumors arising from submucosal regions (Fig. 1) [7]. Pain, sticky saliva, xerostomia (dryness of mouth), feeding and speaking difficulties are the most common physical complains shown by OC patients [8]. The treatment depends upon the

cancer stage and location. Ideally, it comprises a multidisciplinary approach involving chemotherapy, radiotherapy, immunotherapy and surgical removal of the tumor or their combination, often accompanied by severe side effects [9].

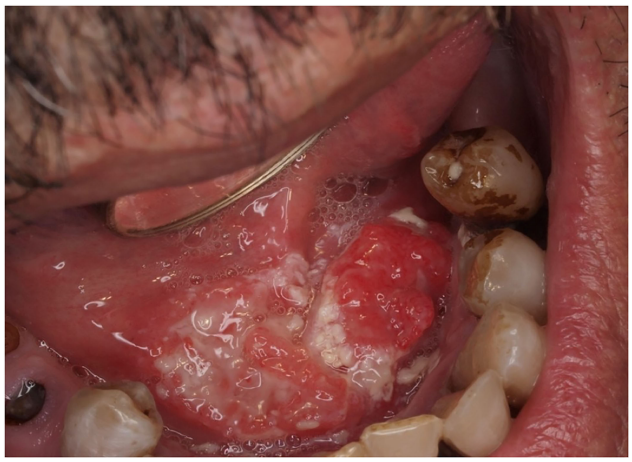

Fig. 1. Oral cancer on the floor of the mouth in a smoking patient (There is written informed consent signed by the patient to use this image).

This type of cancer is mainly diagnosed at advanced stages, causing high morbimortality rates. However, it is known to be preventable, since most exogenous risk factors are avoidable (e.g., tobacco smoking, heavy alcohol consumption) [10,11]. Additionally, ultraviolet (UV) exposure, poor oral hygiene, herpes virus infections are other relevant risk factors [12]. Therefore, the WHO Global Oral Health Programmed recently co-sponsored international meetings with a focus on OC prevention. The main preventative approaches are the treatment of potential human papillomavirus (HPV) infections, avoidance of alcohol, and abstinence or withdrawal from tobacco use and the intake of antioxidants-rich diets [13].

On the other side, medicinal plants are characterized by a secular use for the prevention and treatment of multiple diseases [14]. Recently, plant-food-derived natural compounds have attracted researchers given their remarkable anticancer abilities [15]. The National Cancer Institute has identified about 35 plant foods that can prevent several oral diseases, such as garlic, onion, ginger, umbelliferous vegetables, turmeric, cruciferous vegetables, whole wheat, oats and various plants (e.g., thyme and mint) [16–18]. In addition, the use of such bioactive molecules in combination with cytotoxic drugs appears to increase their efficacy while exert no toxic effects to normal cells [19]. Therefore, chemoprevention is a valuable and promising strategy to block the incidence of OC [20], through the strategic combination of phytochemicals with chemo-preventive agents for effective clinical applications, as provides an indispensable source of pharmacological agents with distinctive mechanisms for modern drug development [21]. However, there are several other herbal plants which can cause OC if consumed excessively. Betel nut (Areca nut) chewing and betel quid consumption is one such example which is one of the main causal agents of OC throughout the Asia-Pacific region [22].

A number of reviews which focused on oral health and cancer are published recently [23,24]. These reviews are more focused on the effect of the plant extracts on oral cancer or health but limited aspects of pre-clinical and clinical studies are covered. In this sense, this review is intended to give a holistic view towards the incidence and impact of OC. It also highlights the pre-clinical and clinical studies related to the use of medicinal plants for OC prevention. Recent developments in bioactive synthetic analogs towards the management of oral cancer are also discussed.

2. Methodology

We collected and retrieved relevant information from several online sources/servers and databases, including PubMed (https://pubmed.ncbi.nlm.nih.gov/), Science Direct (https://www.sciencedirect.com), Web of Science (https://www.webofscience.com), Google Scholar (https://scholar.google.com/), ResearchGate (https://www.researchgate.net/), and Scopus (https://www.scopus.com) using the keywords “Incidence and impacts”, “ethnopharmacology,” “head and neck squamous cell carcinoma,” “phytotherapy”, “natural products,” “nanocarriers,” “clinical trials” etc., combined with oral cancer and head and neck squamous cell carcinoma to cover scientific investigations. Chemical structures were retrieved from ChemSpider (http://www.chemspider.com). The scientific names of plants were validated using the Plants of the World Online | Kew Science website (https://powo.science.kew.org/).

3. Incidence and Impacts of Oral Cancer

In 2018, the WHO estimated that cancer burden increased to 18.1 million new cases and 9.6 million deaths per year. Also, it has been reported that 1 in 5 men and 1 in 6 women are diagnosed with cancer over lifetime, with 1 in of 8 men and 1 in 11 women dying from this disease [25].

As previously referred, OC is the 6th commonest cancer worldwide, and occurs in oral cavity environment. It can include squamous cell carcinoma (SCC), salivary gland and odontogenic neoplasms, although most cases (~90%) are SCC [26]. WHO estimates that tobacco and excessive alcohol consumption play a leading role in around 90% of OC cases [27]. In the past few decades, despite the improvement of therapeutic methods, the survival rate of OC has not changed significantly (5-year survival rate slightly >50%) [28]. Annually, more than 400,000 new cases are anticipated worldwide. In the EU, there are projected 66,650 new cases each year [29] and the American Cancer Society estimates 53,000 new cases and 10,860 deaths in 2019 [30].

Interestingly, OC incidence in higher in developing countries, namely in South-Eastern countries and parts of Eastern Asia, Central and Eastern Europe, and parts of North and South America. In South-Central Asia, OC is the 3rd commonest cancer, and in India, the age-standardized rate of incidence of OC is 12.6/100,000 individuals. Based on the WHO report, Asian countries account for 73.3% of the global deaths from the lip and oral cavity cancers and have the leading rate of mortality compared to other continents. Europe and Africa have the 2nd and 3rd highest-mortality rate, respectively. Lately, there was stated an increased rate of OC in developed countries, including Denmark, France, Germany, Scotland, and to a lesser extent, in Australia, Japan, New Zealand, and the USA, which is thought to be a result of the aging of population and of the raise in the prevalence of risk factors [27]. In most countries, OC is more frequent in men than women, with the ratio of males to females being of 1.5:1, while to oropharynx cancer is of 2.8:1 [5].

As indicated, the risk of OC increases with age, being more common in people older than 50 years [5]; however, evidence shows that the incidence of OC has clearly changed. The disease has increased in individuals younger than 45 years in the past 4 decades, and studies show a decrease in the rate of classical OC (older patients) in the last years worldwide, being related to a decrease in smoking and alcohol intake [31]. On the other hand, many young OC patients have never drunk alcohol or smoked. In fact, new evidence suggests strong connections between HPV infection, hereditary factors, immunodeficiency and OC [31,32].

4. Phytotherapy and Ethnopharmacology as Upcoming Strategies for Oral Cancer

OC treatment is multimodal and involves radio, chemo and immunotherapy, and surgery. Despite the existing clinical interventional strategies (surgery and drug administration), the mortality rate of head and neck squamous cell carcinoma (HNSCC) remains high. In this sense, new and more effective treatments with fewer adverse effects are needed [33].

Natural plant products have been used for centuries, and their bioactive components offer promising perspectives for the development of new chemotherapies or adjuvant treatments capable of avoiding the conventional therapies-associated cytotoxic effects [34–36]. Briefly, chemoprophylactic therapies involve the use of natural and/or synthetic compounds to repress, inhibit or revert the transformation of DOK into oral squamous cell carcinoma (OSCC). For instance, it has been suggested that diet can prevent from OC, particularly through a high consumption of fruits and vegetables (rich in micronutrients, such as β-carotene, vitamin C, vitamin D, and flavonoids) [37,38]. Recently, the beneficial role of vitamin D in preventing the OC was reviewed. The experimental evidences suggest a relationship between serum calcidiol concentration in the optimal level of $\sim$32 ng/mL and prevention of cancer [39]. Utilization of natural products as drug in treatment of various ailments is also reviewed recently [40].

New investigations have progressively revealed the anticancer effects of multiple phytochemical compounds, being often classified according to their function and chemical structure [41–43]. However, to afford benefits following ingestion, these substances need to be absorbed and metabolized before being transported to both tissues and organs, and many challenges need to be surpassed (e.g., toxicity at the required doses, low bioavailability or triggering resistance mechanisms), and in such perspective the use of nanoparticles and other agents have been viewed as a key to resolve part of these issues [44,45].

In the case of oral lesions, in particular, the success of intraoral administration of natural products is conditioned by the effectiveness of the administration vehicles used, i.e., the capacity to effectively deliver the agent and to maximize patient adherence to therapy. In this regard, many polymeric vehicles, such as mucoadhesive gels, patches, tablets, oral rinses and aerosols have been searched for potential use in local intraoral administration. Although many of these administration strategies have been used in OC, to date, most chemoprophylactic trials have been unable to optimize drugs' administration based on the evaluation of local pharmacokinetic parameters (e.g., determination of oral intraepithelial concentration of the agent, metabolites formation, stability and/or release kinetics). Moreover, the inclusion criteria used (e.g., patients with benign hyperkeratotic lesions and a lack of smoking cessation) complicate the comparative chemoprophylactic efficacy analyses between trials [36,46]. The number of clinical trials, registered and ongoing, on international databases, trial registers can be seen in Table 1. Major bioactives involved in the prevention and suppression of oral cancer are discussed in following sub-section.

4.1 Curcumin

Curcumin is a polyphenol derived from *Curcuma longa* L. (turmeric), a member of the *Zingiberaceae* family, already approved for use as a food additive. The active ingredients of curcumin are volatile, orange-yellowish colored oils, called curcuminoids [42]. Various phytochemical and plant sources targeted for the oral cancer treatment are illustrated in Fig. 2.

Some evidence has shown that curcumin modulates inflammation- and carcinogenesis-involved pathways. Preclinical studies have shown the anti-OC effects of curcumin, when administered in isolation or combined with conventional drugs [42]. Its chemoprophylaxis activity involves the regulation of a number of intracellular signaling transduction pathways at different levels, such as transcription factors. It also influences the expression of many proteins, such as p53, cyclin D1, β-catenin, epidermal growth factor receptor (EGFR), caspases, and improves apoptosis

Table 1. Clinical trials on the effect of curcumin, tea, and soy isoflavone in head and neck squamous cell carcinoma and leukoplakia.

Title	ClinicalTrials.gov	Objective	Number of patients enrolled	Intervention/treatment	Phase
Curcumin biomarker trial in HNSCC	ClinicalTrials.gov Identifier: NCT01160302	To assess the short-term effects of supplementation with a turmeric extract, Curcumin C3 Complex® on HNSCC biomarkers.	33	Microgranular Curcumin C3 Complex®; 4 grams twice daily for 21–28 days	Early phase 1
Phase I chemoprevention trial with green tea polyphenon E (PPE) and Erlotinib in patients with premalignant lesions of head and neck	ClinicalTrials.gov Identifier: NCT01116336	To examine the protective role of a combination of drugs: green tea extracts derived PPE, and Erlotinib. The safety of the combination was also evaluated alongside the effect of the combination on patient's premalignant lesion. The highest dose of each agent without side effects was also formulated.	25	Erlotinib (50 mg, 75 mg, or 100 mg); daily continuously for 6 cycles for each cycle + Green Tea Polyphenon E (200 mg); three times daily for 6 cycles	Phase I
Phase II trial to evaluate the effects of green tea in oral leukoplakia	ClinicalTrials.gov Identifier: NCT00176566	To assess the effects of a green tea preparation on leukoplakia and to find out these effects in reducing the risk of cancer in or around the area of leukoplakia.	8	Green tea lozenges (6 grm), 8 times daily for 12 weeks	Phase II
Soy isoflavonein combination with radiation therapy and Cisplatin in SCC of the head and neck	ClinicalTrials.gov Identifier: NCT02075112	To evaluate the effects of soy supplementation during chemotherapy and radiation therapy in decreasing the side effects caused by the treatments.	24	Genistein (150 mg) daily	Phase I
Soy Isoflavones in Preventing Head and Neck Cancer Recurrence in Patients With Stage I–IV Head and Neck Cancer Undergoing Surgery	ClinicalTrials.gov Identifier: NCT02007200	To determine how well soy isoflavones prevent head and neck cancer in patients who have undergone surgery for stage I–IV.	55	Soy Isoflavones (300 mg); daily for 14 days)	Phase II

HNSCC, head and neck squamous cell carcinoma; SCC, squamous cell carcinoma.

[41,47]. As a matter of fact, the curcumin activity has been investigated in a number of HNSCC cell lines, including CAL27, CCL23 (laryngeal carcinoma), UM-SCC1 and UMSCC14A (oral carcinoma), with curcumin action being fundamentally upon the nuclear factor kappa-B (NF-κB) signaling pathway. In fact, it produces a decrease in NF-κB expression while further inhibits its nuclear localization [48]. In 2017, Borges *et al*. [49] conducted a systematic review on the role of curcumin in HNSCC cell lines, and stated that it inhibits cell proliferation and viability, while induces apoptosis and triggers cell cycle arrest at G2/M phase, thus evidencing its potential as an adjuvant in HNSCC treatment. Preclinical studies on curcumin in rats found that it can inhibit oral carcinogenesis [50,51]. Carcinogenesis was induced by the application of 4-nitroquinoline 1-oxide (4-NQO), and curcumin was administered to rats (100 mg/kg) during 12 weeks, being found a marked reduction in proliferating cell nuclear antigen (PCNA), Bcl2, suppressor of cytokine signaling (SOCS)-1 e-3 and signal transducer and activator of transcription 3 (STAT3) expression [41]. In another study, it was reported the inhibition of oral mucosal tumors in hamsters following dietetic curcumin administration [52]. In another independent study, curcumin administered either alone or with green tea inhibited oral carcinogenesis in hamsters; the authors linked this effect to cell proliferation suppression, apoptosis induction and angiogenesis inhibition [53]. Other researchers assessed the effect of oral dosing of curcumin and piperine in cheek pouch of hamsters with carcinomas induced by 7,12-dimethyl-benzanthracine (DMBA), found that both compounds were able to avoid the tumors formation, probably as a consequence of their antioxidant properties [54]. A group of researchers also reported significant inhibitory effects of curcumin upon SAS cell line (OC cell lines) growth and proliferation, inoculated subcutaneously in mice; the cytotoxic effect of curcumin was found to be targeted at G2/M phase of cell cycle [55]. Other studies have also shown that curcumin exerts *in vivo* suppressive effects upon cell growth, based on nude mouse xenograft models. It was found that curcumin is highly effective in suppressing HNSCC cell xenografts growth in nude mice, suppressing carcinogenesis through inhibition of the AKT/mammalian target of rapamycin (mTOR) pathway [56].

Regarding clinical data, a number of studies have been performed with curcumin. In a study, patients with potentially malignant oral disorders, like leukoplakia, received increasing doses of curcumin extract, starting with 500 mg/day and reaching the highest tolerated dose of 8000 mg/day, over 3 months, and no toxic effects were stated at the highest dose [57,58].

Regarding limiting factors, one that sometimes limits the use of curcumin is its relatively low bioavailability. Accordingly, Boven *et al*., in 2019 [56], applied the substance directly to the oral cavity by means of a chewing gum formulation. Curcumin release and absorption in serum and saliva were assessed after chewing, since contact with the mucosa appears to be critical for improving its release and absorption [59]. Moreover, one of the main research criticisms related to curcumin is that most available data derives from pre-clinical studies. Consequently, the optimum therapeutic dosage remains unclear. On the other hand, there are some agents, like piperine, that can raise the curcumin bioavailability. Therefore, further studies are needed to assess the curcumin usefulness in terms of prevention and treatment [42]. Curcumin has a number of mechanisms of therapeutic action, with main disadvantages of its oral administration being its high metabolic instability and low water solubility that markedly impairs its systemic bioavailability [42]. In this way, new strategies are being investigated to overcome such difficulties, like the use of liposomal formulations containing curcumin and its encapsulation in polymeric nanoparticles.

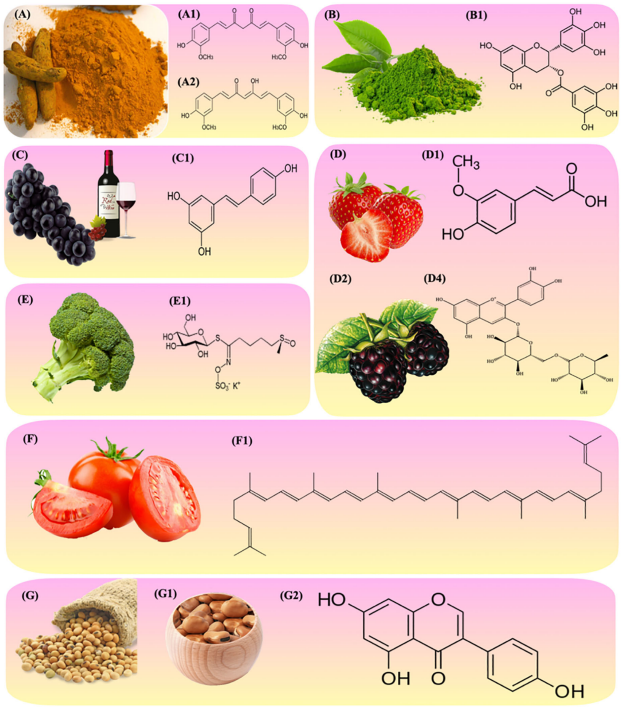

Fig. 2. Illustration showing the plant source of phytochemical reviewed in the current study and structure of specific compound discussed in the current review against oral cancer. Where (A) Turmeric. (A1) Structure of keto form of curcumin. (A2) Structure of keto-enol form of curcumin. (B) Green tea and powder. (B1) Structure of epigallocatechin gallate. (C) Black grapes and red wine. (C1) Structure of resveratrol. (D) Strawberry. (D1) Ferulic acid. (D2) Black raspberry. (D4) Structure of cyanidin-3-rutinoside. (E) Broccoli. (E1) Structure of glucoraphanin. (F) Tomato. (F1) structure of lycopene. (G) Soybean. (G1) Fava beans. (G2) Structure of genistein.

4.2 Green Tea Extract

Green tea (*Camellia sinensis* L. Kuntze) is a popular beverage throughout the world, with a particular attractive aroma, flavor and health potentialities, closely linked to its content in polyphenols. Approximately 80% of commercial tea product found mainly in the western world is black tea, and the remaining corresponds to green tea [60].

Green tea contains 4 main polyphenols, known as catechins: 10–15% (-)-epigallocatechin gallate (EGCG), 6–10% (-)-epigallocatechin (EGC), 2–3% (-)-epicatechin gallate (ECG) and 2% (-)-epicatechin (EC), the first three with antineoplastic properties [43]. Briefly, EGCG is an ester of epigallocatechin and gallic acid, and is the most abundant catechin in green tea. It is also the catechin with the greatest bioactive effects [61]. The most widely used administration route for EGCG is the oral route in the form of tea or capsules, where only 0.1–1% of the administered oral dose reaches the systemic circulation [62,63]. However, the EGCG levels may be far higher in tissues that come into direct contact with the drug, such as oral cavity. Once ingested, the first transformation reactions take place in saliva, in the form of esterase-mediated hydrolysis of EGCG. Metabolization largely occurs in intestine and liver, where glucuronidation, sulphatation of the hydroxyl groups and *O*-methylation of the catechol groups take place mediated by UDP-glucuronyltransferase (UGT), phenol sulfotransferase (SULT) and catechol-*O*-methyl transferase (COMT) [43,63,64].

Laboratory and animal studies have shown that tea-derived polyphenols inhibit tumor cells proliferation while induce apoptosis. Likewise, tea-derived catechins inhibit angiogenesis and tumor cell invasion, while also protect from ultraviolet B (UV-B) radiation, and may possibly modulate the immune system function. In addition, it has been shown that green tea activates enzymes involved in detoxification processes, like glutathione S-transferase and quinone reductase, which may help to protect against tumor formation. Although most beneficial effects of tea have been linked to the remarkable antioxidant effects of polyphenols, the exact mode of action whereby tea could contribute to prevent cancer has not yet been precisely defined [62,65,66].

Regarding clinical data, the green tea extract administration during 4 weeks in smokers led to a reduction in keratinocyte DNA damage. Furthermore, cell growth was inhibited, with a decrease in the percentage of cells at S phase, and an increase in the rate of that in phase G1. Likewise, the diploid DNA content increased, with positive regulation of the apoptosis markers [67]. In a clinical trial involving 59 patients with oral leukoplakia, a 3 g/day of a mixed tea product in the form of oral capsules plus the application of mixed tea ointment with topical glycerin, or placebo plus topical glycerin administered for 6 months, led to a reduction of oral lesions in 38% of patients treated with green tea mixture versus 10% in the placebo group [53]. Another clinical study assessed the chemoprophylactic potential of green tea extract in OC. The authors found that the two arms receiving the highest doses (0.75 and 1.0 g/m^2) evidenced greater clinical response rates (58.8%) compared to those receiving the lower dose (0.5 g/m^2; 36.4%) or placebo (18.2%), stating a dose-response effect. The treatment was well-accepted, being only stated the following side effects at the highest doses: insomnia, diarrhea and oral/neck pain [68]. Lastly, in patients at high risk of developing oral precancerous lesions, the EGCG application in the form of an oral rinse during 7 days triggered a reduction in level of expression of certain oral carcinogenetic biomarkers — though the results failed to reach statistical significance [69]. In 2014, Huang *et al*. [67] studied the association between tea consumption and head and neck cancer in Taiwan, where tea is a commonly used beverage. Surveys were made regarding tea intake (frequency, duration and types) in 396 patients with head and neck cancer and 413 controls. A marked decrease was stated in the risk of head and neck cancer linked to tea consumption, and a significant inverse correlation was recorded between head and neck cancer and tea intake — particularly green tea [70]. Similar inhibitory effects have been stated using EGCG with curcumin and resveratrol in decreasing the tumorigenicity of HPV-positive head and neck tumors [71].

4.3 Resveratrol

Resveratrol is a natural polyphenol found in a broad variety of plant species, including grape, peanut and different types of berries, being also an important constituent of red wine. Currently, resveratrol is known to be a bioactive molecule with potential beneficial health effects thanks to its numerous pharmacological properties and lack of deleterious effects [72,73]. However, the health benefits of resveratrol may be hampered by its low oral bioavailability, which has been attributed to its incomplete intestinal absorption. Nevertheless, different studies have attempted to synthesize resveratrol analogs, ultimately preserving its biological activities [74,75]. The antineoplastic properties of resveratrol have also been tested in different preclinical studies, and for instance, in HNSCC cell lines, the drug is able to inhibit its growth and proliferation [76].

In HNSCC, resveratrol given in combination with curcumin led to a higher inhibition of cancer cells growth than curcumin alone, and the effect of 5-fluorouracil (5-FU) plus resveratrol also revealed to be synergistic in HNSCC cell lines. It was also found that resveratrol (10–1000 μM) reduce cell viability in a tongue SCC cell line [77]. In another study, the effect of resveratrol on signal transducer and activator of transcription (STAT)-3 signaling cascade and its regulated functional responses in squamous cell carcinoma of the head and neck (SCCHN) cells was investigated [78]. Authors concluded that resveratrol attenuates STAT3 cascade by induction of Suppressors of cytokine signaling (SOCS)-1, thus inhibiting STAT3 phosphorylation

and proliferation in SCCHN cells.

However, the low bioavailability and inadequate focalization of the drug is conceived as the main obstacle that blocks the use of these biomolecules in *in vivo* and clinical studies [79]. In this regard, there is a need for nanotechnological developments capable of administering these substances (e.g., EGCG and resveratrol), with a view to boosting their antitumor effects and overcoming the problems posed by their complex pharmacokinetic profile.

4.4 Garcinol

Garcinol (camboginol) is one of another bioactive components explored for the head and neck cancer. This compound is extracted from waste rinds of the *Garcinia indica* fruit. The compounds have also showed their exceptional role in prevention of other types of cancers such as colorectal, beast, gastrointestinal and leukemia [80].

Garcinol mediates its antitumor effects in squamous cell carcinoma of the HNSCC cells and mouse model through the suppression of multiple proinflammatory cascades. Garcinol reduced the growth of HNSCC mouse without exhibiting any significant toxicity, and downregulated the expression of p-signal transducer and activator of transcription (STAT)-3, p65, Ki-67, and CD31 in the treated groups as compared with the control group [80].

4.5 Freeze-Dried Strawberries and Black Raspberries

Strawberries (*Fragaria* $\times$ *ananassa*) contain a number of ingredients with potential chemoprophylactic activities, including vitamins A, C and E, folic acid, calcium, selenium, β-sitosterol, ellagic and ferulic acids, flavonols, like kaempferol and quercetin, and a range of anthocyanins. Strawberry extracts inhibit human cancer cell proliferation and induce apoptosis *in vitro*; furthermore, they inhibit activator protein 1 (AP-1) and NF-κB in cell cultures [81].

Stoner and Casto [82] reviewed the pharmacological and chemoprophylactic activities of the individual components of a number of fruits. The findings referred to strawberries and black raspberries in rodent aerodigestive tract cancer models suggest that the dietetic administration of strawberries could inhibit the development of oral malignant lesions and modify the expression of genes related to OC development [82].

Black raspberries contain anthocyanins, ellagitannins and phenolic acids, that have been found to exert potent inhibitory activity upon aerodigestive tract carcinogenesis [41]. Preclinical findings in animal models indicate that black raspberries inhibit OC through mechanisms linked to cell proliferation, inflammation, angiogenesis and apoptosis [82]. Oghumu *et al.* [81] demonstrated that in a 4NQO OC rat model, black raspberries inhibit oral carcinogenesis through inhibition of proinflammatory and anti-apoptotic pathways. Knobloch *et al.* [83] studied rats exposed to the carcinogen 4NQO, that were fed with a diet supplemented with black raspberries 5 or 10%, or a control diet, during 6 weeks after exposure to the carcinogen. An RNA-seq transcriptome analysis in rat tongue was made, together with mass spectrometry and metabolomic analysis of RNA in rat urine. The authors identified 57 metabolites expressed in different ways, and over 662 modulated genes in rats fed black raspberries. The glycolysis and 5' adenosine monophosphate-activated protein kinase (AMPK) pathways were modulated during OC chemoprophylaxis mediated by black raspberries. The glycolytic enzymes, Aldoa, Hk2, Tpi1, Pgam2, Pfkl and Pkm2, as well as the genes of PKA-AMPK pathway Prkaa2, Pde4a, Pde10a, Ywhag and Crebbp were found to be negatively regulated by black raspberries during OC chemoprophylaxis [84]. Moreover, the glycolysis metabolite glucose-6-phosphate decreased in rats that fed black raspberries. These data evidence new metabolic pathways modulated by black raspberries phytochemicals, which may be directed during OC chemoprophylaxis.

However, translational clinical trials assessing the potential of phytochemicals contained in black raspberries applied to the oral mucosa remain limited [84,85]. For example, a phase 0 clinical trial was carried out in 38 patients in which biopsy confirmed the presence of OSCC. During the time before scheduled surgery (14 days on average), the patients received tablets containing freeze-dried black raspberry powder. The resected cancerous tissue of patients that received black raspberries revealed a significant decrease in the expression of genes encoding proteins of importance for cancer cell survival (AURKA, EGFR o BIRC5), as well as for proinflammatory agents' production, like NFKB1 and PTGS2. Furthermore, the active substances in black raspberries, such as cyanidin-3-rutinoside and cyanidin-3-xylosyl rutinoside, were identified in OSCC tissues, thereby evidencing that they effectively accumulate within the target tissues [84,85]. A study conducted in 40 patients with premalignant oral intraepithelial lesions found that the topical application of a mucoadhesive freeze-dried black raspberry gel significantly reduced the lesion size and histological grade, while the lesions size was seen to increase in the control group [86]. Indeed, the success of local intraoral drug administration strategies mainly depends on the capacity of the polymeric drug vehicles to afford increased solubility and stability in physiological fluids, such as saliva, together with an adequate drug release, good penetration and local distribution of the chemoprophylactic agents, and the capacity to apply the drug at various mucosa oral locations [86,87]. In this sense, further research is necessary to improve our understanding on the ADMET of black raspberries and their respective polyphenols [88].

4.6 Isothiocyanates (ITCs)

Epidemiological studies have indicated that vegetables-rich diets, containing the genus *Brassica* (*Cruciferae* family, e.g., broccoli, cabbage, cauliflower) are linked to a lesser HNSCC risk. Indeed, cruciferous

vegetables, such as broccoli, cabbage and watercress possess a series of bioactive molecules with anticancer properties, mostly attributable to their high contents in glucosinolates, with isothiocyanates (ITCs) being the most potent ones. Briefly, ITCs are able to induce apoptosis and inhibit the NF-κB signaling pathway through a range of mechanisms [89]. In addition, by reducing EGFR signaling, they can suppress both the expression and activity of matrix metalloprotease-2 (MMP-2) and MMP-9 enzymes, resulting in metastasis inhibition [90]. In addition, the topical application of ITCs has shown to exert a potent chemoprophylactic activity against HNSCC in animal models, at same time that can improve the effects of chemotherapy. A pilot study, involving 3 broccoli extract administration regimens in 10 healthy volunteers, was performed to assess the bioavailability and effects upon NRF2 signaling in the oral epithelium. The three groups comprised the intake of glucoraphanin-richbroccoli sprout extracts; sulforaphane-rich broccoli sprout extracts; and the topical exposure to sulforaphane-rich broccoli sprout extracts. As main findings, the authors recorded an adequate bioavailability and chemoprophylactic activity, although further research is needed, since minor changes in the molecular formulas drastically modify the mechanisms of action [91,92].

4.7 Lycopene

Lycopene is a natural liposoluble pigment synthesized by plants and microorganisms, and responsible for the red and orange color of some fruits and vegetables, such as ripe tomatoes, water melon, pink or red grapefruit, and red chili pepper [93]. Lycopene can protect cell components against specific types of damage triggered by reactive oxygen species (ROS), with inhibit cancer cells growth and progression, blocking cell cycle progression from the G0/G1 to the S phase, at same time that can modulate immune responses by decreasing the activity of carcinogen mediators. The mechanisms underlying such effects upon carcinogenesis involve ROS elimination, positive regulation of detoxification systems, interference in cell proliferation, induction of gap-junction communication, and cell cycle progression inhibition. It has also been shown that lycopene raises the p53 protein levels in cancer cells [61]. Other authors also stated that lycopene and tomato paste given to an oral carcinogenesis hamster model, significantly reduced the incidence of oral mucosal tumors, with different mechanisms being involved in their anticancer effects [94]. In addition, Cheng *et al.* [92] analyzed the chemoprophylactic effects of lycopene in a hamster model. The animals in the lycopene or mixed carotenoid groups did not develop carcinomas, in contrast to the controls, and although dysplastic lesions were observed in all groups, though the expression of PCNA was less pronounced in the lycopene group than in the control group [95].

Regarding clinical evidence, the treatment of premalignant oral lesions with lycopene has been linked to significant histological and clinical changes. For example, a case-control study conducted in Japan by Nagao *et al.* [86] with 9536 subjects over the age of 40 stated that among males with leukoplakia, the mean serum lycopene and carotene levels were markedly lower than that of controls [96]. Indeed, lycopene appears to be effective in treating oral leukoplakia, being able to protect cells from damage, while protects from oral dysplasia progression by blocking tumor cell proliferation. Moreover, initial reports on the lycopene efficacy against human oral cancer cells have underlined marked therapeutic effects [94]. Nevertheless, further clinical trials are needed to better address the therapeutic benefits of lycopene for both OC prevention and management.

4.8 Genistein

Genistein is an abundant phytoestrogen in soya and other legumes. To date, no clinical studies have examined the genistein effects in HNSCC, despite the epidemiological data available have underlined the efficacy of genistein intake in breast, prostate and colorectal cancer. However, the routine consumption of soya products was not found to have a significant impact upon HNSCC risk in Chinese adults, though the study in question was hampered by many significant limitations [22,49]. A general mechanism of action of phytochemicals for preventing OC cells growth is illustrated in Fig. 3.

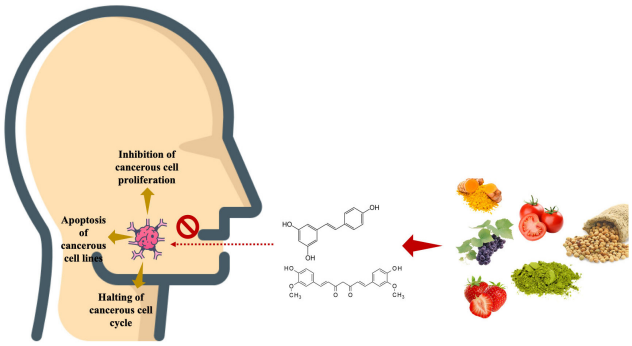

Fig. 3. General mechanism of action of phytochemicals for preventing oral cancer.

4.9 Thymoquinone

Thymoquinone is the main abundant active constituent of the seeds of *Nigella sativa* L.. *N. sativa*, or black cumin, is widely used in Middle Eastern and Far Eastern countries as a spice and food preservation. Thymoquinone has a wide range of pharmacological properties, including its ability to combat oxidative damage, and inflammation [97]. Additionally, the compounds have demonstrated exceptional anticancer properties [98]. The anticancer action of thymoquinone is mediated by a variety of mechanisms. By targeting tumor suppressor genes (p53, p73, PTEN,

Table 2. Role of important bioactive compounds in suppression of oral cancer.

Bioactive compound	Type of extract	Model	Key findings	Reference
Curcumin	Standard curcumin	Human oral cancer cell lines (SCC-25)	Curcumin reduced SCC-25 cells proliferation and invasion through inhibiting the phosphorylation of epidermal growth factor receptor (EGFR) and EGFR downstream signaling molecules Akt, ERK1/2 and STAT3.	[105]
Green tea extract	Epigallocatechin gallate (EGCG) extracts from green tea	Human oral cancer cell lines (SCC)	EGCG inhibited growth, with a decrease in efficacy as cells progressed from normal to cancer. A G1 cell cycle block was induced with an increase in the underphosphorylated form of retinoblastoma protein.	[106]
Resveratrol	Standard resveratrol	Human head and neck squamous cell carcinoma (SCC4 and FaDu cells)	Resveratrol attenuates STAT3 cascade by induction of Suppressors of cytokine signaling (SOCS)-1, thus inhibiting STAT3 phosphorylation and proliferation in SCCHN cells.	[78]
Garcinol	Garcinia indica rind extract	Squamous cell carcinoma of the head and neck cells	Garcinol reduced the growth of HNSCC mouse without exhibiting any significant toxicity, and downregulated the expression of p-signal transducer and activator of transcription (STAT)-3, p65, Ki-67, and CD31 in the treated groups.	[50]
Anthocyanins and other phenolics from berries	Berries extract	Oral squamous cell carcinoma cell lines, CAL-27 and SCC25	Extracts inhibit human cancer cell proliferation and induce apoptosis *in vitro*; furthermore, they inhibit activator protein 1 (AP-1) and NF-κB in cell cultures.	[107]
Isothiocyanates	Benzyl isothiocyanates standard	Human oral cancer OC2 cells	Isothiocyanate derivative inhibits growth, promotes G2/M phase arrest and triggers apoptosis of OC2 cells with a minimal toxicity to normal cells.	[108]
Lycopene	Standard lycopene	OSCC cell lines that included CAL-27 and WSU-HN6 cells	Lycopene drastically induced cell apoptosis suppresses cell migration and tumor growth.	[109]
Genistein	Standard genistein	HSC-3, an oral squamous cell carcinoma cell line	Anti-angiogenic agent, with respect to tumor growth, angiogenesis.	[94]

STAT3), this compound suppressed cancer through cell cycle arrest. Furthermore, thymoquinone suppressed cell proliferation and angiogenesis [99]. Treatment with thymoquinone induces apoptosis and autophagy in human OC cells. Thymoquinone increased number of autophagic vacuoles, LC3-II protein expression, autophagosome accumulation, bax expression, and caspase-9 activation in the HNSCC cell line in a concentration-dependent manner [100]. Thymoquinone/Ca-alg-PVA has the chemopreventive effects against OC. Abdelfadil *et al.* [101], in 2013, demonstrated that thymoquinone induces apoptosis by downregulating the p38MAPK pathway in chemically induced oral squamous cell carcinoma (T28). Pu *et al.* [102], in 2021, showed that thymoquinone down-regulated the inflammatory and PI3K/AKT/mTOR signaling pathway in orally treated 7,12-dimethylbenz[a]anthracene (DMBA)-stimulated hamster oral tumor. In addition to being effective as a treatment for cancer, thymoquinone is also effective as a chemopreventive agent. It also prevents premalignant lesions from progressing to cancer. However, clinical trials are needed to assess the therapeutic benefits of thymoquinone for OC prevention.

4.10 Salvadora Persica L. Extract

Salvadora persica L. is a perennial shrub traditionally called miswa, which has chemo-preventive and anti-oral cancer effects. *S. persica* has been extensively studied for its effect on oral health [103]. *S. persica* root extracts showed significant cytotoxic effects on DOK, oral squamous cell carcinoma (PE/CA-PJ15), and periodontal ligament fibroblast (PDL) cell lines, at concentrations of 11.25, 13.50, and 15.75 mg/mL, respectively [104].

Table 2 (Ref. [50,78,94,105–109]) shows the beneficial role of discussed bioactive compounds in prevention of oral cancer.

5. Conclusions

Although the stated advances, HNSCC requires more effective treatment strategies, with a decrease in therapy-related complications, and in this regard, natural phytochemicals are viewed as possible new chemoprophylactic agents, regarding their tolerability, safety, low toxicity and antioxidant effects. In parallel, preventive strategies have been widely investigated, though the existing data on phytochemicals are still fragmented and inconclusive; nevertheless, the findings from preclinical and clinical trials are becoming more promising in this regard. Besides, pharmacodynamic interactions should also be considered, as well as studies focusing on the pharmacokinetic interactions of different natural products. Also worth of note is that healthcare providers should also monitor herb-drug interactions routinely in cancer patients. In addition, many natural products are limited in their anticancer efficacy for relatively low bioavailability, lack of *in vivo* and clinical evidence, standardization of the optimum dose for treating disease, high metabolic instability and poor aqueous solubility during oral administration, inadequate focalization, complex pharmacokinetic profile, side effects and poor patient adherence. Thus, and in view of the aforementioned, further studies should be done to overcome these constraints and to enhance the absorption, metabolism and bioactivity herbal products throughnanotechnological and related developments, besides attempting for minor changes in molecular formulas to modify their mechanisms of action.

Author Contributions

MB, CQ, JS-R, EP-F, PL-J, WZ, TD, AD, MK, MP, AHE, AU, J-TC, made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. That is, revising or critically reviewing the article; giving final approval of the version to be published; agreeing on the journal to which the article has been submitted; and, confirming to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest. MB is serving as one of the Editorial Board members and Guest Editors, J-TC is serving as one of the Guest Editors of this journal. We declare that MB and J-TC had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to LT.

References

[1] McGuire S. World Cancer Report 2014. Geneva, Switzerland: World Health Organization, International Agency for Research on Cancer, WHO Press, 2015. Advances In Nutrition. 2016; 7: 418–419.

[2] Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, *et al*. Global Cancer Observatory: Cancer Today. 2020. Available at: https://gco.iarc.fr/today (Accessed: 1 February 2021).

[3] Stewart BW, Kleihues P. World Cancer Report. Lyon: WHO International Agency for Research on Cancer. IARC Press: Lyon, France. 2003.

[4] Petersen PE. The World Oral Health Report 2003: continuous improvement of oral health in the 21st century - the approach of the who Global Oral Health Programme. Community Dentistry and Oral Epidemiology. 2003; 31: 3–24.

[5] Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncology. 2009; 45: 309–316.

[6] Kalavrezos N, Scully C. Mouth cancer for clinicians part 2: epidemiology. Dental Update. 2015; 42: 354–359.
[7] Scully C, Bagan J. Oral squamous cell carcinoma: overview of current understanding of aetiopathogenesis and clinical implications. Oral Diseases. 2009; 15: 388–399.
[8] Wong RS. Apoptosis in cancer: from pathogenesis to treatment. Journal of Experimental & Clinical Cancer Research. 2011; 30: 87.
[9] Dissanayaka WL, Pitiyage G, Kumarasiri PVR, Liyanage RLPR, Dias KD, Tilakaratne WM. Clinical and histopathologic parameters in survival of oral squamous cell carcinoma. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. 2012; 113: 518–525.
[10] Meurman JH. Infectious and dietary risk factors of oral cancer. Oral Oncology. 2010; 46: 411–413.
[11] Godsey J, Grundmann O. Review of Various Herbal Supplements as Complementary Treatments for Oral Cancer. Journal of Dietary Supplements. 2016; 13: 538–550.
[12] Butler MS. Natural products to drugs: natural product-derived compounds in clinical trials. Natural Product Reports. 2008; 25: 475.
[13] Lai P, Roy J. Antimicrobial and Chemopreventive Properties of Herbs and Spices. Current Medicinal Chemistry. 2004; 11: 1451–1460.
[14] Caragay AB. Cancer-preventive foods and ingredients. Food Technology. 1992; 46: 65–68.
[15] Craig WJ. Phytochemicals. Journal of the American Dietetic Association. 1997; 97: S199–S204.
[16] Russo M, Spagnuolo C, Tedesco I, Russo GL. Phytochemicals in cancer prevention and therapy: truth or dare? Toxins. 2010; 2: 517–551.
[17] Bhavana SM, Lakshmi CR. Oral oncoprevention by phytochemicals - a systematic review disclosing the therapeutic dilemma. Advanced Pharmaceutical Bulletin. 2014; 4: 413–420.
[18] Newman DJ, Cragg GM. Natural Products as Sources of New Drugs over the 30 Years from 1981 to 2010. Journal of Natural Products. 2012; 75: 311–335.
[19] Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, *et al*. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. International Journal of Cancer. 2019; 144: 1941–1953.
[20] Rivera C. Essentials of oral cancer. International Journal of Experimental Pathology. 2015; 8: 11884–11894.
[21] Petersen PE. Strengthening the prevention of oral cancer: the WHO perspective. Community Dentistry and Oral Epidemiology. 2005; 33: 397–399.
[22] Weinstein S, Sedlak-Weinstein L, Newell J, Lam A. P73 the role of areca nut ("betel nut") in the global epidemiology of oral cancer. Oral Oncology Supplement. 2007; 2: 153–154.
[23] Adeola HA, Bano A, Vats R, Vashishtha A, Verma D, Kaushik D, *et al*. Bioactive compounds and their libraries: An insight into prospective phytotherapeutics approach for oral mucocutaneous cancers. Biomedicine & Pharmacotherapy. 2021; 141: 111809.
[24] Kumar M, Prakash S, Radha, Kumari N, Pundir A, Punia S, *et al*. Beneficial Role of Antioxidant Secondary Metabolites from Medicinal Plants in Maintaining Oral Health. Antioxidants. 2021; 10: 1061.
[25] Maggioni D, Biffi L, Nicolini G, Garavello W. Flavonoids in oral cancer prevention and therapy. European Journal of Cancer Prevention. 2015; 24: 517–528.
[26] Montero PH, Patel SG. Cancer of the Oral Cavity. Surgical Oncology Clinics of North America. 2015; 24: 491–508.
[27] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA: A Cancer Journal for Clinicians. 2019; 69: 7–34.
[28] Hussein AA, Helder MN, de Visscher JG, Leemans CR, Braakhuis BJ, de Vet HCW, *et al*. Global incidence of oral and oropharynx cancer in patients younger than 45 years versus older patients: a systematic review. European Journal of Cancer. 2017; 82: 115–127.
[29] De Felice F, Musio D, Terenzi V, Valentini V, Cassoni A, Tombolini M, *et al*. Treatment improvement and better patient care: which is the most important one in oral cavity cancer? Radiation Oncology. 2014; 9: 263.
[30] Crooker K, Aliani R, Ananth M, Arnold L, Anant S, Thomas SM. A Review of Promising Natural Chemopreventive Agents for Head and Neck Cancer. Cancer Prevention Research. 2018; 11: 441–450.
[31] Pavia M, Pileggi C, Nobile CG, Angelillo IF. Association between fruit and vegetable consumption and oral cancer: a meta-analysis of observational studies. The American Journal of Clinical Nutrition. 2006; 83: 1126–1134.
[32] Lucenteforte E, Garavello W, Bosetti C, La Vecchia C. Dietary factors and oral and pharyngeal cancer risk. Oral Oncology. 2009; 45: 461–467.
[33] Kumar B, Yadav A, Hideg K, Kuppusamy P, Teknos TN, Kumar P. A novel curcumin analog (H-4073) enhances the therapeutic efficacy of cisplatin treatment in head and neck cancer. PLoS ONE. 2014; 9: e93208.
[34] Pezzuto F, Buonaguro L, Caponigro F, Ionna F, Starita N, Annunziata C, *et al*. Update on Head and Neck Cancer: Current Knowledge on Epidemiology, Risk Factors, Molecular Features and Novel Therapies. Oncology. 2015; 89: 125–136.
[35] Helen-Ng LC, Razak IA, Ghani WMN, Marhazlinda J, Norain AT, Raja Jallaludin R, *et al*. Dietary pattern and oral cancer risk - a factor analysis study. Community Dentistry and Oral Epidemiology. 2012; 40: 560–566.
[36] Siemianowicz K, Likus W, Dorecka M, Wilk R, Dziubdziela W, Markowski J. Chemoprevention of Head and Neck Cancers: does it have only one Face? BioMed Research International. 2018; 2018: 1–15.
[37] Zlotogorski A, Dayan A, Dayan D, Chaushu G, Salo T, Vered M. Nutraceuticals as new treatment approaches for oral cancer – i: Curcumin. Oral Oncology. 2013; 49: 187–191.
[38] Zlotogorski A, Dayan A, Dayan D, Chaushu G, Salo T, Vered M. Nutraceuticals as new treatment approaches for oral cancer: II. Green tea extracts and resveratrol. Oral Oncology. 2013; 49: 502–506.
[39] Fathi N, Ahmadian E, Shahi S, Roshangar L, Khan H, Kouhsoltani M, *et al*. Role of vitamin D and vitamin D receptor (VDR) in oral cancer. Biomedicine & Pharmacotherapy. 2019; 109: 391–401.
[40] Atanasov AG, Zotchev SB, Dirsch VM, Supuran CT. Natural products in drug discovery: advances and opportunities. Nature Reviews Drug Discovery. 2021; 20: 200–216.
[41] Iriti M, Varoni EM. Chemopreventive potential of flavonoids in oral squamous cell carcinoma in human studies. Nutrients. 2013; 5: 2564–2576.
[42] Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas P. Influence of Piperine on the Pharmacokinetics of Curcumin in Animals and Human Volunteers. Planta Medica. 1998; 64: 353–356.
[43] Mallery S, Desai K, Holpuch A, Schwendeman S. Optimizing therapeutic efficacy of chemopreventive agents: a critical review of delivery strategies in oral cancer chemoprevention clinical trials. Journal of Carcinogenesis. 2011; 10: 23.
[44] Aggarwal BB, Bhardwaj A, Aggarwal RS, Seeram NP, Shishodia S, Takada Y. Role of resveratrol in prevention and therapy of cancer: preclinical and clinical studies. Anticancer Research. 2004; 24: 2783–2840.
[45] LoTempio MM, Veena MS, Steele HL, Ramamurthy B, Ramalingam TS, Cohen AN, *et al*. Curcumin Suppresses Growth of Head and Neck Squamous Cell Carcinoma. Clinical Cancer Re-

search. 2005; 11: 6994–7002.
[46] Tanaka T, Makita H, Ohnishi M, Hirose Y, Wang A, Mori H, *et al*. Chemoprevention of 4-nitroquinoline 1-oxide-induced oral carcinogenesis by dietary curcumin and hesperidin: comparison with the protective effect of beta-carotene. Cancer Research. 1994; 54: 4653–4659.
[47] de Paiva Gonçalves V, Ortega AAC, Guimarães MR, Curylofo FA, Junior CR, Ribeiro DA, *et al*. Chemopreventive Activity of Systemically Administered Curcumin on Oral Cancer in the 4-Nitroquinoline 1-Oxide Model. Journal of Cellular Biochemistry. 2015; 116: 787–796.
[48] Azuine MA, Bhide SV. Adjuvant chemoprevention of experimental cancer: catechin and dietary turmeric in forestomach and oral cancer models. Journal of Ethnopharmacology. 1994; 44: 211–217.
[49] Borges GÁ, Rêgo DF, Assad DX, Coletta RD, De Luca Canto G, *et al*. *In vivo* and *in vitro* effects of curcumin on head and neck carcinoma: a systematic review. Journal of Oral Pathology & Medicine. 2017; 46: 3–20.
[50] Li N, Chen X, Liao J, Yang G, Wang S, Josephson Y, *et al*. Inhibition of 7,12-dimethylbenz[a]anthracene (DMBA)-induced oral carcinogenesis in hamsters by tea and curcumin. Carcinogenesis. 2002; 23: 1307–1313.
[51] Manoharan S, Balakrishnan S, Menon VP, Alias LM, Reena AR. Chemopreventive efficacy of curcumin and piperine during 7,12-dimethylbenz[a]anthracene-induced hamster buccal pouch carcinogenesis. Singapore Medical Journal. 2009; 50: 139–146.
[52] Lin Y, Chen H, Kuo Y, Chang Y, Lee Y, Hwang J. Therapeutic Efficacy Evaluation of Curcumin on Human Oral Squamous Cell Carcinoma Xenograft Using Multimodalities of Molecular Imaging. The American Journal of Chinese Medicine. 2010; 38: 343–358.
[53] Clark CA, McEachern MD, Shah SH, Rong Y, Rong X, Smelley CL, *et al*. Curcumin Inhibits Carcinogen and Nicotine-Induced Mammalian Target of Rapamycin Pathway Activation in Head and Neck Squamous Cell Carcinoma. Cancer Prevention Research. 2010; 3: 1586–1595.
[54] Cheng AL, Hsu CH, Lin JK, Hsu MM, Ho YF, Shen TS, *et al*. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Research. 2001; 21: 2895–2900.
[55] Kuriakose MA, Ramdas K, Dey B, Iyer S, Rajan G, Elango KK, *et al*. A Randomized Double-Blind Placebo-Controlled Phase IIB Trial of Curcumin in Oral Leukoplakia. Cancer Prevention Research. 2016; 9: 683–691.
[56] Boven L, Holmes SP, Latimer B, McMartin K, Ma X, Moore-Medlin T, *et al*. Curcumin gum formulation for prevention of oral cavity head and neck squamous cell carcinoma. The Laryngoscope. 2019; 129: 1597–1603.
[57] Katiyar SK. Emerging Phytochemicals for the Prevention and Treatment of Head and Neck Cancer. Molecules. 2016; 21: 1610.
[58] Salehi B, Lopez-Jornet P, Pons-Fuster López E, Calina D, Sharifi-Rad M, Ramírez-Alarcón K, *et al*. Plant-Derived Bioactives in Oral Mucosal Lesions: A Key Emphasis to Curcumin, Lycopene, Chamomile, *Aloe vera*, Green Tea and Coffee Properties. Biomolecules. 2019; 9: 106.
[59] Henning SM, Niu Y, Lee NH, Thames GD, Minutti RR, Wang H, *et al*. Bioavailability and antioxidant activity of tea flavanols after consumption of green tea, black tea, or a green tea extract supplement. The American Journal of Clinical Nutrition. 2004; 80: 1558–1564.
[60] Chow H-S, Hakim IA. Pharmacokinetic and chemoprevention studies on tea in humans. Pharmacological Research. 2011; 105–112.
[61] Chu C, Deng J, Man Y, Qu Y. Green Tea Extracts Epigallocatechin-3-gallate for Different Treatments. BioMed Research International. 2017; 2017: 5615647.
[62] Lambert JD, Yang CS. Mechanisms of Cancer Prevention by Tea Constituents. The Journal of Nutrition. 2003; 133: 3262S–3267S.
[63] Chau L, Jabara JT, Lai W, Svider PF, Warner BM, Lin H, *et al*. Topical agents for oral cancer chemoprevention: a systematic review of the literature. Oral Oncology. 2017; 67: 153–159.
[64] Schwartz JL, Baker V, Larios E, Chung F. Molecular and cellular effects of green tea on oral cells of smokers: a pilot study. Molecular Nutrition & Food Research. 2005; 49: 43–51.
[65] Tsao AS, Liu D, Martin J, Tang X, Lee JJ, El-Naggar AK, *et al*. Phase II Randomized, Placebo-Controlled Trial of Green Tea Extract in Patients with High-Risk Oral Premalignant Lesions. Cancer Prevention Research. 2009; 2: 931–941.
[66] Yoon AJ, Shen J, Santella RM, Philipone EM, Wu HC, Eisig SB. Topical Application of Green Tea Polyphenol (-)-Epigallocatechin-3-gallate (EGCG) for Prevention of Recurrent Oral Neoplastic Lesions. Journal of Orofacial Sciences. 2012; 4: 43–50.
[67] Huang CC, Lee WT, Tsai ST, Ou CY, Lo HI, Wong TY, *et al*. Tea consumption and risk of head and neck cancer. PLoS ONE. 2014; 9: e96507.
[68] Piao L, Mukherjee S, Chang Q, Xie X, Li H, Castellanos MR, *et al*. TriCurin, a novel formulation of curcumin, epicatechin gallate, and resveratrol, inhibits the tumorigenicity of human papillomavirus-positive head and neck squamous cell carcinoma. Oncotarget. 2017; 8: 60025–60035.
[69] Aggarwal S, Takada Y, Singh S, Myers JN, Aggarwal BB. Inhibition of growth and survival of human head and neck squamous cell carcinoma cells by curcumin via modulation of nuclear factor-kappaB signaling. International Journal of Cancer. 2004; 111: 679–692.
[70] Baur JA, Sinclair DA. Therapeutic potential of resveratrol: the *in vivo* evidence. Nature Reviews Drug Discovery. 2006; 5: 493–506.
[71] Bishayee A. Cancer Prevention and Treatment with Resveratrol: from Rodent Studies to Clinical Trials. Cancer Prevention Research. 2009; 2: 409–418.
[72] Masuelli L, Di Stefano E, Fantini M, Mattera R, Benvenuto M, Marzocchella L, *et al*. Resveratrol potentiates the *in vitro* and *in vivo* anti-tumoral effects of curcumin in head and neck carcinomas. Oncotarget. 2014; 5: 10745–10762.
[73] Varoni EM, Lo Faro AF, Sharifi-Rad J, Iriti M. Anticancer Molecular Mechanisms of Resveratrol. Frontiers in Nutrition. 2016; 3: 8.
[74] Zhang Q, Tang X, Lu QY, Zhang ZF, Brown J, Le AD. Resveratrol inhibits hypoxia-induced accumulation of hypoxia-inducible factor-1α and VEGF expression in human tongue squamous cell carcinoma and hepatoma cells. Molecular Cancer Therapeutics. 2005; 4: 1465–1474.
[75] Heiduschka G, Bigenzahn J, Brunner M, Thurnher D. Resveratrol synergistically enhances the effect of etoposide in HNSCC cell lines. Acta Oto-Laryngologica. 2014; 134: 1071–1078.
[76] Casto BC, Knobloch TJ, Galioto RL, Yu Z, Accurso BT, Warner BM. Chemoprevention of oral cancer by lyophilized strawberries. Anticancer Research. 2013; 33: 4757–4766.
[77] Stoner GD, Casto BC. Chemoprevention by Fruit Phenolic Compounds. Cancer Chemoprevention. 2004; 55: 419–435.
[78] Baek SH, Ko JH, Lee H, Jung J, Kong M, Lee JW, *et al*. Resveratrol inhibits STAT3 signaling pathway through the induction of SOCS-1: Role in apoptosis induction and radiosensitization in head and neck tumor cells. Phytomedicine. 2016; 23: 566–577.
[79] Warner BM, Casto BC, Knobloch TJ, Accurso BT, Weghorst CM. Chemoprevention of oral cancer by topical application of black raspberries on high at-risk mucosa. Oral Surgery, Oral

Medicine, Oral Pathology and Oral Radiology. 2014; 118: 674–683.

[80] Li F, Shanmugam MK, Chen L, Chatterjee S, Basha J, Kumar AP, *et al*. Garcinol, a polyisoprenylated benzophenone modulates multiple proinflammatory signaling cascades leading to the suppression of growth and survival of head and neck carcinoma. Cancer Prevention Research. 2013; 6: 843–854.

[81] Oghumu S, Casto BC, Ahn-Jarvis J, Weghorst LC, Maloney J, Geuy P, *et al*. Inhibition of Pro-inflammatory and Anti-apoptotic Biomarkers during Experimental Oral Cancer Chemoprevention by Dietary Black Raspberries. Frontiers in Immunology. 2017; 8: 1325.

[82] Knobloch TJ, Ryan NM, Bruschweiler-Li L, Wang C, Bernier MC, Somogyi A, *et al*. Metabolic Regulation of Glycolysis and AMP Activated Protein Kinase Pathways during Black Raspberry-Mediated Oral Cancer Chemoprevention. Metabolites. 2019; 9: 140.

[83] Knobloch TJ, Uhrig LK, Pearl DK, Casto BC, Warner BM, Clinton SK, *et al*. Suppression of Proinflammatory and Prosurvival Biomarkers in Oral Cancer Patients Consuming a Black Raspberry Phytochemical-Rich Troche. Cancer Prevention Research. 2016; 9: 159–171.

[84] Mallery SR, Tong M, Shumway BS, Curran AE, Larsen PE, Ness GM, *et al*. Topical Application of a Mucoadhesive Freeze-Dried Black Raspberry Gel Induces Clinical and Histologic Regression and Reduces Loss of Heterozygosity Events in Premalignant Oral Intraepithelial Lesions: Results from a Multicentered, Placebo-Controlled Clinical Trial. Clinical Cancer Research. 2014; 20: 1910–1924.

[85] Desai KGH, Olsen KF, Mallery SR, Stoner GD, Schwendeman SP. Formulation and in Vitro-in Vivo Evaluation of Black Raspberry Extract-Loaded PLGAPLA Injectable Millicylindrical Implants for Sustained Delivery of Chemopreventive Anthocyanins. Pharmaceutical Research. 2010; 27: 628–643.

[86] Bauman JE, Zang Y, Sen M, Li C, Wang L, Egner PA, *et al*. Prevention of Carcinogen-Induced Oral Cancer by Sulforaphane. Cancer Prevention Research. 2016; 9: 547–557.

[87] Huong L, Shin J, Choi E, Cho N, Kim H, Leem D, *et al*. B-Phenethyl isothiocyanate induces death receptor 5 to induce apoptosis in human oral cancer cells via p38. Oral Diseases. 2012; 18: 513–519.

[88] Solt DB, Chang K, Helenowski I, Rademaker AW. Phenethyl isothiocyanate inhibits nitrosamine carcinogenesis in a model for study of oral cancer chemoprevention. Cancer Letters. 2003; 202: 147–152.

[89] Wolf MA, Claudio PP. Benzyl Isothiocyanate Inhibits HNSCC Cell Migration and Invasion, and Sensitizes HNSCC Cells to Cisplatin. Nutrition and Cancer. 2014; 66: 285–294.

[90] Bhuvaneswari V, Velmurugan B, Balasenthil S, Ramachandran CR, Nagini S. Chemopreventive efficacy of lycopene on 7,12-dimethylbenz[a]anthracene-induced hamster buccal pouch carcinogenesis. Fitoterapia. 2001; 72: 865–874.

[91] Lu R, Dan H, Wu R, Meng W, Liu N, Jin X, *et al*. Lycopene: features and potential significance in the oral cancer and precancerous lesions. Journal of Oral Pathology & Medicine. 2011; 40: 361–368.

[92] Cheng H, Chien H, Liao C, Yang Y, Huang S. Carotenoids suppress proliferating cell nuclear antigen and cyclin D1 expression in oral carcinogenic models. The Journal of Nutritional Biochemistry. 2007; 18: 667–675.

[93] Nagao T, Ikeda N, Warnakulasuriya S, Fukano H, Yuasa H, Yano M, *et al*. Serum antioxidant micronutrients and the risk of oral leukoplakia among Japanese. Oral Oncology. 2000; 36: 466–470.

[94] Myoung H, Hong S, Yun P, Lee J, Kim M. Anti-cancer effect of genistein in oral squamous cell carcinoma with respect to angiogenesis and in vitro invasion. Cancer Science. 2003; 94: 215–220.

[95] Liu YT, Fan YY, Xu CH, Lin XL, Lu YK, Zhang XL, *et al*. Habitual consumption of soy products and risk of nasopharyngeal carcinoma in Chinese adults: a case-control study. PLoS ONE. 2013; 8: e77822.

[96] Bhuvaneswari V, Nagini S. Lycopene: a Review of its Potential as an Anticancer Agent. Current Medicinal Chemistry-Anti-Cancer Agents. 2005; 5: 627–635.

[97] Mekhemar M, Hassan Y, Dörfer C. *Nigella sativa* and Thymoquinone: A Natural Blessing for Periodontal Therapy. Antioxidants. 2020; 9: 1260.

[98] Abdelfadil E, Cheng Y, Bau D, Ting W, Chen L, Hsu H, *et al*. Thymoquinone Induces Apoptosis in Oral Cancer Cells through P38β Inhibition. The American Journal of Chinese Medicine. 2013; 41: 683–696.

[99] Darakhshan S, Bidmeshki Pour A, Hosseinzadeh Colagar A, Sisakhtnezhad S. Thymoquinone and its therapeutic potentials. Pharmacological Research. 2015; 95–96: 138–158.

[100] Chu SC, Hsieh YS, Yu CC, Lai YY, Chen PN. Thymoquinone induces cell death in human squamous carcinoma cells via caspase activation-dependent apoptosis and LC3-II activation-dependent autophagy. PLoS ONE. 2014; 9: e101579.

[101] Abdelfadil E, Cheng Y, Bau D, Ting W, Chen L, Hsu H, *et al*. Thymoquinone Induces Apoptosis in Oral Cancer Cells through P38β Inhibition. The American Journal of Chinese Medicine. 2013; 41: 683–696.

[102] Pu Y, Hu S, Chen Y, Zhang Q, Xia C, Deng H, *et al*. Thymoquinone loaded calcium alginate and polyvinyl alcohol carrier inhibits the 7,12-dimethylbenz[a]anthracene-induced hamster oral cancer via the down-regulation of PI3K/AKT/mTOR signaling pathways. Environmental Toxicology. 2021; 36: 339–351.

[103] al-Otaibi M. The miswak (chewing stick) and oral health. Studies on oral hygiene practices of urban Saudi Arabians. Swedish Dental Journal. 2004; 167: 2–75.

[104] Hammad HM, Al-Qaoud KM, Hammad MM, Mansi MA. Effect of *Salvadora persica* Linn root aqueous extract on oral epithelial dysplasia and oral cancer cell lines. Tropical Journal of Pharmaceutical Research. 2019; 18: 2591–2596.

[105] Zhen L, Fan D, Yi X, Cao X, Chen D, Wang L. Curcumin inhibits oral squamous cell carcinoma proliferation and invasion via EGFR signaling pathways. International Journal of Clinical and Experimental Pathology. 2014; 7: 6438–6446.

[106] Khafif A, Schantz S P, al-Rawi M, Edelstein D, Sacks P G. Green tea regulates cell cycle progression in oral leukoplakia. Head Neck. 1998; 20: 528–34.

[107] Chatelain K, Phippen S, McCabe J, Teeters CA, O'Malley S, Kingsley K. Cranberry and grape seed extracts inhibit the proliferative phenotype of oral squamous cell carcinomas. Evidence-Based Complementary and Alternative Medicine. 2011; 2011: 467691.

[108] Yeh YT, Hsu YN, Huang SY, Lin JS, Chen ZF, Chow NH, *et al*. Benzyl isothiocyanate promotes apoptosis of oral cancer cells via an acute redox stress-mediated DNA damage response. Food and Chemical Toxicology. 2016; 97: 336–345.

[109] Tao A, Wang X, Li C. Effect of Lycopene on Oral Squamous Cell Carcinoma Cell Growth by Inhibiting IGF1 Pathway. Cancer Management and Research. 2021; 13: 723–732.