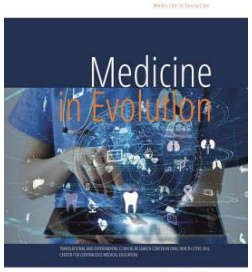
Phytotherapy as an adjuvant in the treatment and prevention of oral cancer



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Abstract

Over time, plant extracts have been used to treat various diseases. Natural products have played an important role in anticancer therapy. Oral cancer is becoming more prevalent in elderly patients. Oral mucositis and xerostomia, induced by cancer therapy, are some of the most distressing morbidities after radio-chemotherapy. Phytochemicals present in fruits, vegetables and grains have a protective effect against the development of cancers. The protective role of phytochemicals may be associated with their antioxidant activity. Herbal remedies are often used alongside conventional treatments to care for cancer patients, with increasing interest in the use of complementary and alternative medicine. Cancer chemoprevention focuses on identifying agents that specifically influence the early stages of cell transformation.

Keywords: Oral cancer, phytochemicals, chemoprevention

INTRODUCTION

Early signs of oral cancer often go unnoticed by the patient and are often discovered during routine dental examinations. The most commonly used treatments for oral cancer include surgery, radiation, and chemotherapy, alone or in combination. Most cancers have the potential for angiogenesis, and their growth, metastasis, and invasion depend on angiogenesis.

Oncology researchers have reported a large number of plant species that have been used in the treatment of cancer since ancient times, and today, the trend toward using and evaluating the therapeutic effects of plants and their compounds as potential anticancer drugs is increasing. More than half of the anticancer drugs in use today are derived from natural resources such as plants, microorganisms and marine life [1].

The mechanisms by which these drugs act on cancer cells are largely unclear. The role of oxidative stress in inducing oral cancer and antioxidants in its prevention and treatment is proven, and most plants are good sources of antioxidants [2,3]. There are more than 25,000 phytochemicals in various plants that have biological effects [4,5].

Diets rich in plant resources provide the body with essential vitamins and minerals. Dietary changes, antioxidant supplementation, high-dose vitamin C therapy, and the use of cannabinoids have been suggested by various researchers to reduce cancer cell replication and increase the chance of remission. The therapeutic capacity of phytonutrients present in medicinal plants holds promise for obtaining natural products and plant compounds that are effective against cancer with low toxicity to healthy tissues [6].

Phytochemicals (Figure 1) can be divided into phenolic compounds, carotenoids, and others. Phenolic acid can be classified into hydroxycinnamic acid and hydroxybenzoic acid. Hydroxycinnamic acid is found in cinnamon, coffee, blueberries, kiwis, plums, apples, and cherries. Hydroxybenzoic acid is found in few consumable plants or can be synthesized chemically [7]. Most of the potent chemopreventive polyphenols disrupt or reverse carcinogenesis [8].

Carotenoids are members of the tetraterpene family that are responsible for the yellow, orange, or red color of fruits, leaves, and flowers. Carotenoid intake inhibits cell proliferation, arrests the cell cycle in different phases, and increases apoptosis and antioxidants in cancer cells [9,10].

Many natural compounds have been widely examined for their potential use in cancer prevention over the years. The growing volume of *in vitro* and *in vivo* data on the chemopreventive and chemotherapeutic outcomes of plant-derived compounds has prompted scientists to conduct clinical trials focused on the pharmacokinetics, efficacy, and safety of phytocompounds.

Aim and objectives

The purpose of this article is to review the current data from the published articles on the role of phytonutrients in the prevention and treatment of oral cancer and oral cavity manifestations after chemo and radiotherapy.

MATERIAL AND METHODS

By screening the literature on medicinal plants used as adjuvants in oral cancer prevention and therapy, we were able to compile a list of the plants most often recommended for the treatment and prevention of oral cancer, and oral discomfort following anticancer therapy.

The screening questions were as follows: "Which medicinal plants are effective in the prevention and treatment of oral cancer"; "Which herbs are effective in the treatment of oral mucositis/xerostomia induced by cancer treatment?" (PubMed, Medline, Web of Science, Scopus). The keywords were the following: phytotherapy; "herbal medicine"; "plant extract"; "medicinal plant"; and: mucositis; xerostomia; chemotherapy; radiotherapy; oral cancer/tumor/neoplasm.

Oral mucositis (OM) induced by cancer therapy is one of the most distressing morbidities after radio-chemotherapy. Age, nutritional status, tumor type, oral hygiene and treatment method are the determinants for the incidence of OM. In addition, oxygen free radicals can act as a trigger for an inflammatory environment that causes OM.

Xerostomia (dry mouth) causes many clinical problems, including oral infections, difficulty speaking, and disturbances in chewing and swallowing food. Many cancer patients have complained of xerostomia induced by cancer therapy.

Treatment methods vary from the local application of ointment, gel and extract, to the oral ingestion of phytotherapeutics.

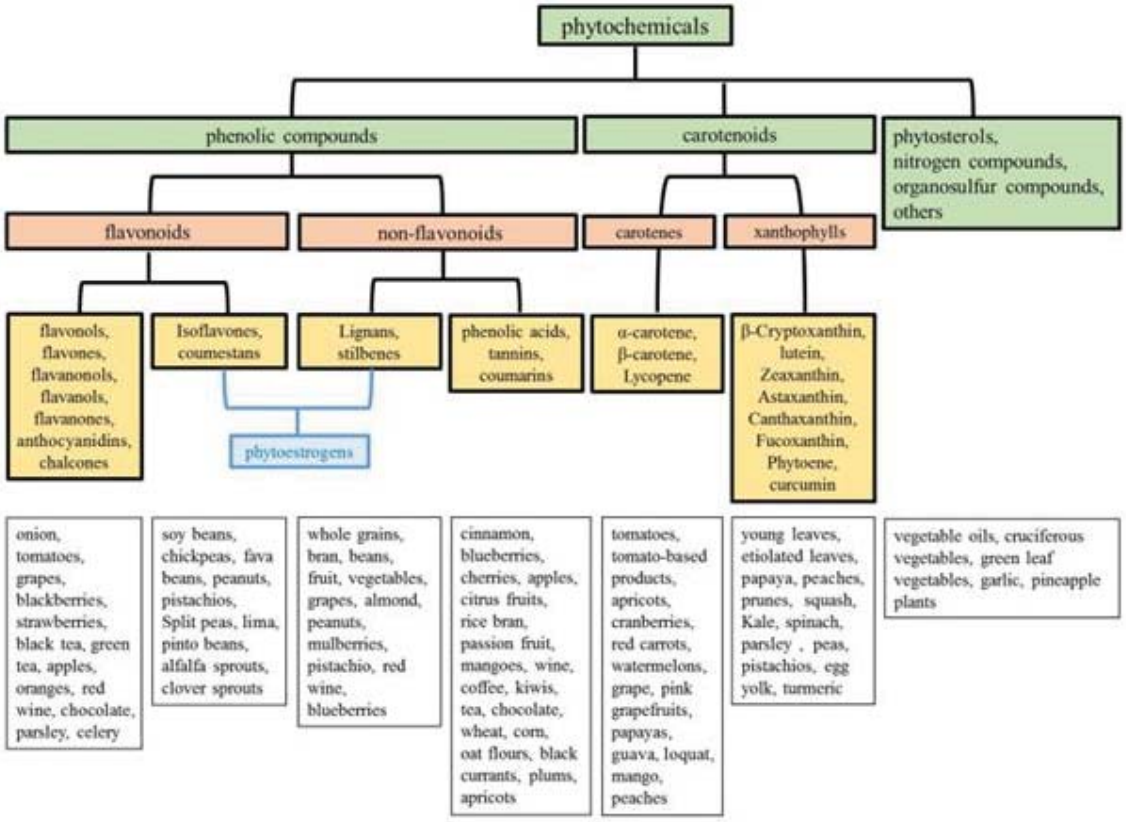

Figure 1. Food sources of phytochemicals [11]

RESULTS

Common phytochemicals for oral cancer chemoprevention and treatment are: green tea, black raspberry, resveratrol, quercetin, curcumin, allium vegetables.

Green tea contains rich flavonoids and other polyphenol antioxidants that protect against cancer. The major constituents of green tea (Figure 2) are EGCG, (-)-epigallocatechin (EGC), and (-)-epicatechin-3-gallate (ECG). EGCG (epigallocatechin gallate) is the major polyphenol that inhibits the growth and interferes with the carcinogenic process of various

cancer cells and inhibits the migration of oral cancer cells [12]. Green tea extract has a dose-dependent chemopreventive effect and an inhibitory effect on oral premalignant lesions (eg: leukoplakia) [13-15].

Clinical studies have shown that drinking more than 10 cups of green tea a day reduces the risk and delays the onset of cancer compared to those who drink less than 3 cups a day. Smokers who took green tea extract (2000–2500 mg/day) for 4 weeks had reduced DNA damage in oral keratinocytes [16,17].

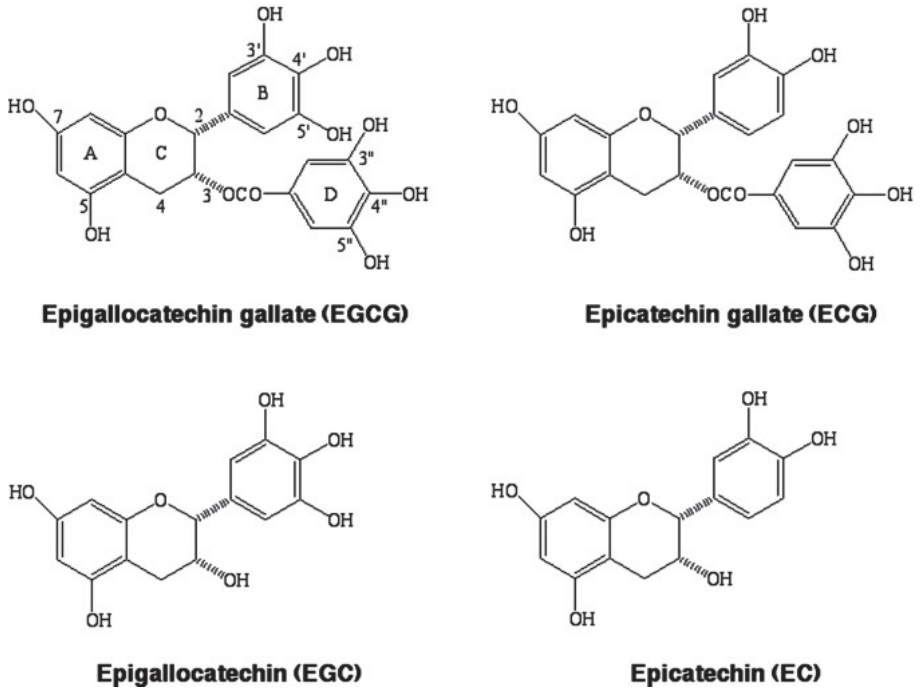

Figure 2. Chemical structure of tea catechins

Black raspberries (BRB) are rich in vitamins, minerals, fiber, anthocyanins, phenolic components and other bioactive components with oral cancer inhibition capabilities [17-20]. Local treatment for 3 months with BRB gel (0.5 g four times a day) on oral premalignant lesions resulted in considerable reductions in lesion size [20-22].

Grape skins, blueberries, raspberries, mulberries, peanuts and many other plant products have powerful polyphenolic compounds and are rich in resveratrol (3, 5, 4'-trihydroxy-trans-stilbene) (Figure 3).

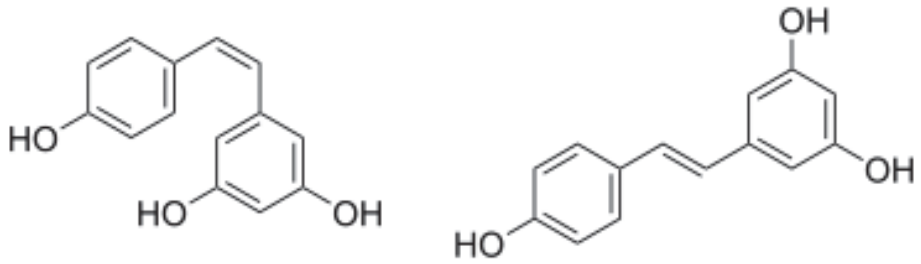

Figure 3. Chemical structure of cis- ((Z)-resveratrol, left) and trans-resveratrol ((E)-resveratrol, right)

Resveratrol, alone or in combination with quercetin, significantly decreases the toxic side effects associated with anticancer therapies and enhances the therapeutic effects against

oral cancer [23-25]. Resveratrol has been found to be safe and reasonably well tolerated at a single dose of up to 5 g/day or as part of a multi-day dosing regimen in healthy subjects [26,27]. The average daily intake of quercetin has been estimated at 25 mg, the serum concentrations of quercetin required for anticancer activity appear to be greater than 10 μM [28,29].

Curcumin (Figure 4), a xanthophyll carotenoid, the main active component of turmeric, which is derived from the rhizome (root) of Curcuma longa, is widely used for the chemoprevention of oral cancer [30-33]. Tetrahydrocurcumin is the key compound of natural curcuminoids and is of great interest in oral cancer research due to its increased water solubility [34].

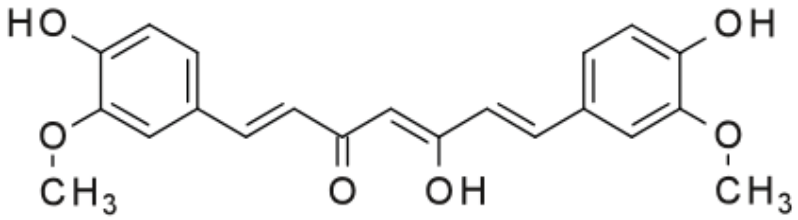

Figure 4. Chemical structure of curcumin

Curcumin is considered to be pharmacologically safe. The safety and tolerability of curcumin administered at a dose of 8 g/day has been demonstrated in clinical trials [35,36]. Curcumin treatment can reduce pain and the size of the tumor lesion [37].

Apigenin (4′, 5, 7, -trihydroxyflavone) (Figure 5) is a flavonoid with chemopreventive action present in fruits and vegetables, parsley, celery and chamomile tea being the most common sources [38,39].

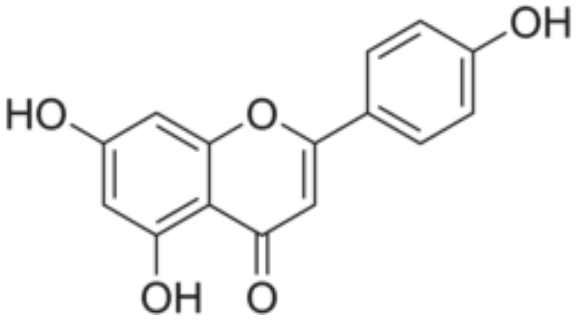

Figure 5. Chemical structure of apigenin

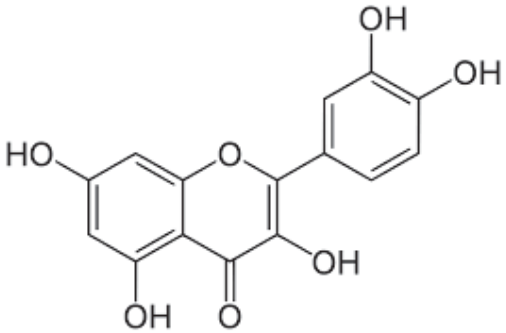

Figure 6. Chemical structure of quercetin

Curcumin and apigenin have an inhibitory effect on cancers related to tobacco smoking and HPV infections [40,41].

Increased consumption of allium vegetables, such as garlic and onions, may reduce the risk of oral cancer [42-46]. Quercetin (Figure 6), the main flavonoid compound in onion, induced cytotoxic effects and reduced cell migration and invasion SAS [47]. Quercetin is available as a dietary supplement, and the recommended dose is 200–1200 mg/day [48,49].

Herbal remedies are good at relieving oral mucositis induced by cancer therapy [50]. Among the herbs most used to treat oral discomfort are: Marticaria recutita L., Zingiber offinicale ROSCOE, Taraxacum Wigg. Calendula officinalis L., Salvia officinalis L., Carum carvi/Cuminum cyminum L., Mentha piperita [51-54]. Matricaria chamomilla (chamomilla) showed a reduction in the severity and incidence of lesions, with improvement in pain

symptoms. Isatis indigótica, Olea europaea, Calendula officinalis, A. digitatae and M. sylvestris plant extracts improved oral mucosal lesions. The herbal drugs MF 5232 (Mucotrol™) and QRLYD decreased the severity of lesions, while SAMITAL® and MUCOSYTE enabled better pain control [55,56].

Herbal medicines significantly improve saliva flow and reduce xerostomia symptoms in cancer patients [57].

DISCUSSIONS

Various studies have provided clinical and preclinical evidence for the use of herbal supplements as complementary treatments for oral cancer. Phytotherapeutic substances are studied as potential in chemopreventive treatment. Antioxidant supplements, high-dose vitamin C therapy, and cannabinoids have been suggested to reduce cancer cell replication and increase the chance of remission [58-61].

Green tea contains polyphenols that induce apoptosis (programmed cell death) in many types of tumor cells, including oral cancer cells, with the extract having a dose-dependent chemopreventive effect [62,63]. Melissa officinalis leaf total extract is a potential agent for the chemoprevention of tongue and pharyngeal cancers [64].

Herbal remedies are often used by cancer patients alongside conventional treatment methods. Herb-drug interactions should not be ignored by healthcare providers in the management of cancer patients. User rates are often underestimated and doctors usually feel unprepared to counsel patients [65,66].

CONCLUSIONS

Chemoprevention through edible phytochemicals is considered as an inexpensive, easy to apply, acceptable and accessible approach for the control and management of oral cancer.

Early detection of tumor lesions and lifestyle changes, the use of dietary supplements in the population at risk, are essential steps in the prevention and successful treatment of oral cancer. The main evidence for the use of herbal supplements is currently in the prevention of cancer rather than its treatment.

Combinations of cytotoxic antitumor agents and phytochemicals could act together to produce inhibitory mechanisms against the development of tumor lesions. The antioxidant effect of dietary phenolic compounds could represent a promising strategy for cancer prevention and reduction of risk factors associated with its progression.

More human clinical trials are needed to demonstrate the anticancer effects of phytochemicals, but their anticancer potential should not be underestimated.

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