The Effects of Herbal Medicines on Cancer Therapy-Induced Oral Mucositis: A Literature Review

Saba Safarzadeh[1], Farinaz Shirban[2], Mohammad Bagherniya[3,4,5], Thozhukat Sathyapalan,[6] Amirhossein Sahebkar[7,8]

[1] Post Graduate Student, Dental Students' Research Committee, Department of Orthodontics, School of Dentistry, Isfahan University of Medical Sciences, Isfahan, Iran.
[2]Department of Orthodontics, Dental Research Center, Dental Research Institute, School of Dentistry, Isfahan University of Medical Sciences, Isfahan, Iran.
[3]Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.
[4]Anesthesia and Critical Care Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.
[5]Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran.
[6]Department of Academic Diabetes, Endocrinology and Metabolism, Hull York Medical School, University of Hull, Hull HU3 2JZ. United Kingdom.
[7]Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad. Iran.
[8]Applied Biomedical Research Center, Mashhad University of Medical Sciences, Mashhad. Iran.

Correspondence: sahebkara@mums.ac.ir; bagherniya@nutr.mui.ac.ir

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Abstract

Cancer-therapy-induced oral mucositis (OM) is one of the most troublesome morbidities after radio-chemotherapy. Age, nutritional status, tumor type, oral hygiene and treatment method are the determinants for OM incidence. Oxygen free radicals can act as a trigger for starting an inflammatory milieu that causes OM. Based on the debilitating nature of OM, it must be cured or at least alleviate; finding a safe and inexpensive agent with anti-inflammatory, anti-microbial and antioxidative properties can be valuable for this situation. Considering the harmful effects of chemical agents, herbal medicine with unique properties such as natural, inexpensive, available and accessible, and well-accepted without any considerable adverse effects has attracted considerable attention. Many studies have illustrated several excellent properties of herbal medicines in recent years, for example, anti-inflammatory, anti-microbial and antioxidative activities in palliation of cancer-therapy-induced OM. This review aimed to evaluate herbal medicines' effects on cancer therapy-induced oral mucositis, mentioned in included studies to approve such aspects. According to this comprehensive review, it is concluded that herbal medicine and medicinal plants can be used as practical agents in palliation of cancer therapy-induced OM without any serious side effects.

Keywords: Herbal medicine; Oral mucositis; Cancer; Radiotherapy; Chemotherapy

Abbreviation

OM, oral mucositis; DNA, deoxyribonucleic acid; WHO, world health organization; TNF, tumor necrosis factor; IFN-γ, interferon gamma; IL, interleukin; NF, nuclear factor; PICO, problem intervention comparison outcome; Gy, Gray; RCT, randomized clinical trial; SUCRA, surface under the cumulative ranking; HaCaT, human keratinocytes cell line; EC, epicatechin; ROS, reactive oxygen species; ALL, Acute Lymphoblastic Leukemia; VAS, visual analog scaling; HST, Hangeshashinto; HOK, human oral keratinocytes; OUM, Oral ulcerative mucositis; KRG, Korean red ginseng; RT, radio therapy; CAPE, capheic acid phenyl ethyl ester; HNC, head and neck cancer; HOPE, honey olive oil–propolis extract and beeswax; FDA, food and drug administration: Common toxicity criteria [CTC]; OAG, oral assessment guide; HNC, head and neck cancer; NRS, numeric rating scale; NM, not mentioned; COM, chemo therapy-induced oral mucositis; COX, cyclooxygenase; LOX, lipoxygenase; PBMC, peripheral blood mononuclear cells.

Introduction

Cancer-therapy-induced oral mucositis (OM) is the most debilitating morbidities after radio-chemo therapy (1, 2). The incidence of OM is 100% after radiotherapy and about 20-40% after chemotherapy (3, 4). The occurrence of OM also is determined by age, nutritional status, oral hygiene and tumor type (5-7). The development of OM is associated with the type of therapy (radiation, chemotherapy, or combined chemoradiotherapy), dosage and how to deliver it (8). The common sites of OM in the oral cavity are in the buccal mucosa, the borders of the tongue, inside of the lips and the floor of the mouth. If the severity of OM is tolerable, it is classified as grade 1 or 2, and if it becomes more severe and impossible to tolerate, it is called grade 3 or more (9). Severe mucositis has several adverse consequences for patients, such as a sense of pain in the mouth, difficulty swallowing, infectious condition, reducing the quality of life and discontinuing cancer treatment. In addition, OM may have several economic impacts on patients' lives (10, 11).

OM can be mild such as erythema, or severe, like ulceration due to inflammation (12). The OM develops after generating oxygen free radicals produced from water within cells due to radiation (13). These species are very destructive for cells because of their high reactivity. They can cause damage due to lipid peroxidation, mitochondrial dysfunction, damage to cellular DNA and death (14). Nowadays, there is no approved treatment for OM (15) and the treatment approaches are mostly palliative, including antibiotics and analgesics (16). It is shown that good oral hygiene and dental care can reduce pain or delay the beginning of OM by controlling the inflammation (17). However, there is a real need for extra treatment options that are focused on reducing the sense of pain and bacterial load and enhance healing procedure at the same time (4). The agents with anti-inflammatory, anti-microbial and antioxidative activities might be helpful for this situation.

Mouthwashes can be chemical or herbal. Nowadays many regular types of mouthwash used during cancer-therapy procedure contain several chemical ingredients which are harmful to oral mucosa and have several side effects. World health organization (WHO) has advised investigating the use of products to manage infection (18).

Considering the harmful effects of chemical agents, herbal medicine with unique properties such as natural, inexpensive, available and accessible, and well-accepted without any considerable adverse effects has attracted considerable attention recently. Several beneficial properties are attributed to the medicinal plants, including anti-inflammatory, antibacterial and antioxidant activities (19-25). Due to these favorable properties, today, herbal medicine is considered a relatively novel approach to managing a large number of diseases, including diabetes mellitus (26-28), arthritis rheumatoid (29), cancer (30, 31), cardiovascular diseases (CVDs) (32-35), hypertension (36-38) and fatty liver disease (39). Similarly, herbal medicine and medicinal plants are traditionally known as safe remedies for dental and oral diseases. Previous reviews showed that these agents have beneficial effects on the prevention and treatment of aphthous stomatitis (40-42), gingivitis (41, 42), and periodontal diseases (43, 44).

The beneficial effects of herbal medicines such as antioxidative and anti-inflammatory activities have been established (45, 46). However, to the authors' knowledge, to date, there is no study to review and summarize the effects of herbal medicines on cancer therapy-induced oral mucositis. We have examined the effects of various herbal medicines on OM. Table 1 to 4 are the summary of the main results of the reviewed studies. In Figure 1. the summary of pathways depicting the possible effects of radio-chemotherapy on the healthy oral mucosa and potential effects of herbal medicine on cancer therapy-induced oral mucositis and its potential related mechanisms are shown.

Curcumin

Curcumin is a rhizomatous herb which is a subbranch of ginger kin, Zingeberaceae (47). This spice also applied as traditional Oriental medicine (4). It is a well-known polyphenol with unique antioxidant, anti-inflammatory, antimicrobial, and anticarcinogenic properties (48-50). In addition, a review reported that curcumin has some effects on pathologic pain in several chronic conditions (51). There are several palliative effects of curcumin on the oral cavity (49, 52). It can reduce the activity of inflammatory cytokines through inhibition of toll-like receptor 4 (TLR4), nuclear factor kappa B (NF-κB), and mitogen-activated protein kinase signaling pathway activation (53-56). Recently, several studies have been done to evaluate the effects of curcumin on OM in patients undergoing various cancer therapies.

A recent systematic review and meta-analysis of clinical trials, which included 5 trials, evaluated the effects of curcumin in the management of OM in patients undergoing chemo and radiotherapy. As presented in Table 2. results showed that turmeric and curcumin could reduce pain, erythema intensity, ulceration area, and degree of severity. Delayed onset of mucositis was reported suggesting preventive activities (4). A meta-analysis reviewed six randomized controlled trials (RCT) claimed that curcumin could be safe and preventive about treatment-induced OM in patients with head and neck cancers (HNC). It can also reduce OM-induced weight loss (57). Moreover, in a network meta-analysis of 28 RCTs, the effects of 9 oral care solutions on preventing OM in cancer patients undergoing radiotherapy and chemotherapy were evaluated. One of these solutions was curcumin. This study concluded that curcumin is the first option for preventive goals, followed by honey base on the SUCRA (surface under the cumulative ranking) scale (58). In a Bayesian network analysis of RCTs, the effects of ten different types of mouthwash on intolerable oral mucositis in cancer patients were evaluated. The number of included studies was 36. Finally, they

concluded that there are no significant differences between most mouthwashes. Based on analysis of rank probabilities, chamomile, honey, curcumin, and benzydamine mouthwashes had the most beneficial effects on severe OM (59).

As shown in table 1, in a double-blind RCT on 32 patients with HNC undergoing radiotherapy, the effect of curcumin in the form of nano-micelle on OM was evaluated. All patients were at least 18 years old, under 50 Gy or more radiation, and patients received radiation at least 50% of their oral mucosa as the field of radiation. The study group (16 patients) was asked to take 1 capsule, which contained 80 mg/day oral nanocurcumin during the radiotherapy and the control group (16 patients) was given placebo lactose tablets. The study completed with 14 patients in the control group and 15 patients in the study group. The severity of OM in patients evaluated for four weeks based on NCI-CTC v.2 scaling. The study showed that nano-micelle curcumin is useful for avoiding OM (the study group showed OM after 2 weeks, whereas the case group showed OM during the first week). It also can reduce the severity of OM. No apparent oral or systemic side effects were observed (60).

In a pilot study, 20 cancer patients (39-71year-old) undergoing 65-70 Gy radiotherapy and chemotherapy for 5-7 weeks evaluated curcumin mouthwash in OM for twenty days to determine the efficacy safety curcumin mouthwash in OM. The patients in the group were asked to wash their mouth with 0.004% curcumin mouthwash in 1:5 dilution for 1 minute, three times daily. In contrast, the control group patients were given chlorhexidine mouthwash 0.2% in 1:1 dilution in a similar fashion. It was concluded that curcumin mouthwash was better than chlorhexidine because it was helpful in more rapid healing and patient compliance with no local or general adverse effects (61).

In a case series study, the effectiveness of curcumal mouthwash was studied. Four pediatric patients with a median age of 15.2 under doxorubicin-containing chemotherapy were asked to use 10 to 30 (one-third of adult's dosage) drops of curcumal (contains 95% curcumin) twice per day. They evaluated patients on days 7, 10, 14 and 21 and concluded that curcumin mouthwash was safe and well-tolerated. Since this study used chlorhexidine mouthwash (0.2%, 30 seconds, twice a day) at the same time, the conclusion might be considered with caution (62).

In a study on rats, a combination of curcumin, a-tocopherol and sunflower oil as a single drug (compound A) was compared with each of the components itself on radiation-induced OM. Although each of the components effectively prevented radiation-induced OM, compound A was more effective (63).

In an *in vitro* study, curcumin's bactericidal effect was evaluated using the LIVE/DEAD Kit and 18 oropharyngeal species. After 4 hours of exposure to 50–200 μM curcumin, 12 species were destroyed. With preincubation between 5 to 60 minutes, almost all inflammatory cytokines such as TNF-α, granulocyte macrophage-colony stimulating factor, monocyte chemoattractant protein 1, interleukin (IL)-6, IL-8, and vascular endothelial growth factor but not interferon-γ and fibroblast growth factor-2 were suppressed. Hence, it was expected that curcumin could help prevent cancer therapy-induced oral mucositis, especially as a daily mouthwash (64).

An *in vitro* study suggested that FITOPROT can have some chemopreventive effects against 5-fluorouracil-induced toxicity. FITOPROT contains curcuminoids from Curcuma longa L (Zingiberaceae) and Bidens pilosa L. (Asteraceae) extract. In this study, at first HaCaT cells had a pretreatment period with FITOPROT for 24 h, and then they were treated with FITOPROT and exposed to 5-FU simultaneously for another 24 h cycle. It was seen that FITOPROT could preserve HaCaT cells from 5-FU-triggered cell damage. The authors concluded that these favorable effects

are due to the antioxidant and anti-inflammatory properties of the intervention agent, so it can use as a prophylactic tool to prevent OM in patients undergoing chemotherapy (65).

Silymarin

Silymarin is a member of the Carduus marianum family and the milk thistle extract with several anti-inflammatories and antioxidative features (66-68). It also has nephroprotective (69, 70) and hepatoprotective effects (70-73). Based on clinical and preclinical studies, silymarin acts as a natural antioxidant by inhibiting lipid peroxidation, mediated by enhancing glutathione accumulation and superoxide dismutase activation (68, 74, 75). In addition, it is shown that silymarin with affecting NF-kB pathway has an immunomodulatory property. It increases proliferation of lymphocytes, interferon-gamma (IFN-γ), IL-4 and IL-10 secretion through activation of lymphocytes and suppressing T-cell activation (12, 66, 76, 77). Moreover, neutrophil migration and leukotrienes and formation of the prostaglandin was inhibited by silymarin which, resulted in anti-inflammatory effects of silymarin (70, 78, 79). Thus, according to these properties, it is hypothesised that silymarin might be useful for treating OM.

One RCT (80) evaluated the effect of oral silymarin administration on preventing radiotherapy-induced OM. In this study, 27 patients were included and assessed in two groups. Patients in the study group were asked to intake 420 mg/of day Silymarin in three divided doses for 6 weeks; patients in the control group were asked to use vitamin B6 three times a day. The investigators use WHO and NCI-CTCAE for scoring OM. They concluded that silymarin could reduce the severity and delay the onset of radiotherapy-induced mucositis.

Tea

Different types of tea benefits patients with cancer therapy-induced OM because of their antiseptic, anti-inflammatory, antimicrobial, antifungal and antiviral properties (81-83). They are also useful for several pathologic conditions such as stomatitis, pharyngolaryngitis, and oral candidiasis (82). Here we review the articles which studied these different types of tea.

A randomized controlled pilot study (84) evaluated the alleviative effect of Sage tea–thyme peppermint hydrosol oral rinse on chemotherapy-induced OM. The investigators selected 60 patients who underwent chemotherapy and divided them randomly into 2 groups; patients in the intervention group were asked to consume Sage tea–thyme peppermint hydrosol oral rinse in addition to basic oral care while the control group only did routine oral care, including brushing twice a day. The instruction for using the mouth rinse was 15ml/qid for 14 days. Patients in both groups were evaluated on days 5 and 14 based on the WHO scale for OM. Results showed that Sage tea–thyme–peppermint hydrosol oral rinse has ameliorative effects on chemotherapy-induced OM, and it is cost-effective and well-tolerated for clinical use.

In another randomized controlled study (85) the efficacy of polyphenol-containing cystus tea mouthwash solution for reducing OM in HNC patients undergoing radiotherapy was compared with sage tea. Patients consumed a tea bag (sage tea or 1.5g Cystus®) steeped for seven minutes. The recommendation consisted of regular mouth rinses of at least 1.5min 3–5 times a day. The patients evaluated twice a week during and 3 months after radiotherapy, and their OM was scored according to RTOG/ EORTC criteria. They did not find any differences in the incidence of mucositis grade 3 between the two interventions. In the period after the radiotherapy, the incidence of dental problems was increased (85).

Another study (86) investigated the effectiveness of epicatechin (EC), a component of green tea extracts, on radiation-induced OM. The intervention *in vitro* arm was performed on HaCaT. After

ensuring cell viability, the investigators treated cells with EC only, radiation only or radiation plus EC in three different groups. In the invivo arm, they tried (2 mM, 100 mL/dose, total 300 mL/day) for 23 days after irradiation on 32 female, 6-week-old rats. The rats were randomized into four groups: the control group received nothing, the EC group treated with only EC, the radiation + epicatechin group and the radiation only group. Results indicated that EC by inhibiting ROS generation could protect the HaCaT cells from radiation and apoptosis. Its effects on reducing radiation-induced OM and healing of the wounds are suggested clinically safe and effective treatment for preventing radiation-induced OM (86).

Calendula

Calendula officinalis (Marigold), is used in Asia and other countries because of its anti-inflammatory activities (87). It also has other antioxidant action, antibacterial, antifungal, and antiviral properties (88). In addition, it has been reported that Calendula can prevent acute dermatitis in cancer therapy irradiated patients (89) and cytotoxic effect on tumor cell lines and anticancer activity *in vivo* (90).

A randomized controlled clinical study (91) investigated the antioxidative and preventive effects of calendula on radiation-induced oropharyngeal mucositis in patients with HNC. The investigators selected 40 patients who underwent cancer therapy and divided them randomly into two equal groups. The intervention group was given oral mouth wash 2% calendula 5 ml twice a day as gel formulation, and the placebo arm was asked to use placebo mouthwashes which were the same in all features. The patients followed for 6 weeks, and OM was measured using Oral Mucositis Assessment Scale (OMAS) scores. The authors claimed that although Calendula could not prevent the occurring of OM during cancer therapy, it could reduce the intensity of OM without any adverse effects (i.e., nausea and vomiting) (91).

Coumarin

There are several activities for coumarin that is described in various studies. A double-blind study showed that it could be useful for patients undergoing cancer therapy suffered from xerostomia (92), similar to another study (93). It has also been claimed that coumarin has a protective effect on endothelial cells by reducing the leucocyte adhesion and thrombocyte aggregation, so it can save the capillary flow (94) and also it has an anti-inflammatory effect by activating proteolysis (95).

One randomized, double-blind study (95) evaluated the prophylactic effect of coumarin/troxerutine on OM in patients who underwent radiotherapy due to head and neck cancers. The study began with 48 patients and finished with 23 (n=11 experimental, 12 placebo). The experimental group was medicated with tablets containing coumarin 15 mg and troxerutin 90 mg; 2 coated tablets used three times a day. The beginning of intervention was 1 week before starting radiotherapy and was continued for 4 weeks after the course. The OM and other acute side effects were measured by Radiation Therapy Oncology Group (RTOG) scoring. The study suggested that coumarin/troxerutine have a desirable activity in relieving radiotherapy-induced mucositis (95).

Quercetin

Quercetin is the most available member of the flavonoid family. It has several recognised benefits such as antioxidative and anti-inflammatory activities (96-100) and alleviative effects on some oral inflammatory conditions like aphthous stomatitis (101). However, it was observed that the administration of quercetin did not have any desirable clinical benefits for oral lichen planus lesions (102). Quercetin has a role in the stabilization of mast cell and cytoprotective

gastrointestinal tract (103). It also has modulating, biphasic and regulatory effects on immunity and inflammation (103). The immunosuppressive effect of quercetin on dendritic cells was also shown. Lipopolysaccharide (LPS)-induced TNF-α production in macrophages and production of IL-8 in lung cells was inhibited by quercetin (103). The production of cyclooxygenase (COX) and lipoxygenase (LOX), known as inflammation-producing enzymes, was inhibited by quercetin. Quercetin treatment resulted in the induction of the gene expression, and the Th-1 derived IFN-γ production and down-regulation of Th-2 derived IL-4 through normal peripheral blood mononuclear cells (PBMC) (103). Considering the immunomodulatory and anti-inflammatory properties of quercetin, its effects on chemotherapy-induced OM was previously evaluated.

Recently a randomized, double-blind clinical study (104) evaluated the preventive and therapeutic effects of quercetin on chemotherapy-induced OM in patients with haematological malignancies. The study involved 20 patients who underwent chemotherapy and randomized them into two equal groups. The intervention group was requested to use 250 mg quercetin capsules two times per day, and the control group was asked to use lactose capsules in the same prescription. They evaluated OM severity by means of WHO scaling. At the end of the study, investigators concluded that although quercetin could reduce the incidence of OM, patients in the study group might experience a more severe condition. In addition, quercetin might have adverse effects at higher doses, such as inhibitory effect on lymphocytes that can influence its therapeutic and preventive effects (104).

Aloe vera

Aloe vera is a warm and dry weather plant that contains several ingredients (105). It has been claimed that Aloe vera has many protective properties such as anti-inflammatory, anti-neoplastic and anti-aging activities (106-109). Because of the anti-inflammatory and antibacterial properties

of Aloe vera, this plant was used for the treatment of periodontal diseases (110, 111). In addition, several studies revealed the radioprotective effect of Aloe vera; for example, two studies on mice demonstrated the reduction of radiotherapy-induced adverse effects on the skin (112) and oral mucosa (113). However, a clinical trial (114) did not confirm the skin improvement. In addition, a review study showed that Aloe vera mouthwash is not only effective and useful treatment in radiotherapy-induced OM but also an antifungal agent in patients with HNC who suffer from candidiasis due to radiotherapy (105).

A triple-blind, randomized controlled trial study (115) compared the efficacy of Aloe vera and benzydamine mouthwashes on radiation-induced OM. They selected 26 patients who underwent radiotherapy and divided them randomly into two equal groups. The study group received 5 ml Aloe vera mouthwash 3 times daily, while the control group was asked to use 0.15% benzydamine mouthwash. Both groups followed for 6 weeks (total of 8 visits), and the OM evaluated based on WHO scaling. Findings showed that both types of mouthwash were beneficial for radiotherapy-induced OM, but Aloe vera was less expensive and could be an excellent alternative treatment (115).

An RCT (116) on children with Acute Lymphoblastic Leukemia (ALL) undergoing chemotherapy evaluated the efficacy of Aloe-Vera use for the prevention of chemotherapy-induced OM. Twenty-six children between 3-6 years old randomly allocated into two groups. The intervention group used 70% Aloe-vera solution topically twice a day, while the control group used sodium bicarbonate 5% with the same administration. After 8 weeks of follow up, the investigators concluded that the Aloe-vera solution could reduce COM (chemotherapy-induced OM) severity and prevent severity in ALL children. The evaluations were done based on the WHO grading scale.

A randomized controlled clinical trial investigated the effect of Aloe vera on chemotherapy-induced stomatitis in patients with lymphoma and leukemia (117). In this study, 64 patients were randomly divided into two groups. The study group was requested to rinse their mouths with 5 ml of aloe vera solution for two minutes tid. The control group used regular mouthwashes used in cancer centers based on the physician's prescription. The WHO grading scale measured the OM severity, and the pain was evaluated by visual analog scaling (VAS). The authors claimed that Aloe vera solution could reduce the pain and intensity of chemotherapy-induced OM.

A phase II double-blind, randomized study (118) compared oral aloe vera versus placebo for preventing radiation-related mucositis in 58 patients with head-and-neck neoplasms, which underwent at least 50 Gy irradiation on the pharyngeal or oral mucosa. They used oral aloe vera solution, which contains 94.5% aloe juice, 5.0% pear juice concentrate, 0.4% lemon-lime flavor, and 0.1% citric acid and a similar solution without aloe vera as a placebo. After 7 weeks of follow up, they concluded that however patients in the study arm had higher quality-of-life scores, but this difference was not statistically significant. They announced that oral aloe vera did not have beneficial effects such as decreasing mucositis and reducing soreness, and it could not be a good adjunct to head-and-neck radiotherapy.

Hangeshashinto

Hangeshashinto (HST), also known as one of the "Kampo" medicines, is a combination of seven different ingredients (119, 120) including Pinellia tuber, ginseng, processed ginger, jujube, Scutellaria root, glycyrrhiza, and Coptisrhizome, used as a traditional medicine in Japan. Several RCTs and preclinical studies have been shown an anti-inflammatory activity for HST in gastrointestinal infections(121-124). In addition, it can inhibit prostaglandin E2 production in human gingival fibroblasts, so it can be useful to manage inflammation in periodontally

compromised patients (125). It was also mentioned that HST has antibacterial and anticancer-therapy induced OM properties (121, 126-129).

One study evaluated the inhibitory effect of HST on prostaglandin E2 production in human oral keratinocytes (HOK) undergoing chemotherapy (130). The investigators tried different concentration (10, 30, 100, or 300 μg/mL) of HST on HOKs. They concluded that HST showed a concentration-dependent inhibitory effect on prostaglandin E2 production, especially at 100 and 300 μg/mL. In addition, they claimed that there is a time/concentration-dependent effect on reduction cell metabolic activity that is optimum in 24 hours with a concentration up to 300 μg/mL; therefore, HST could be a good clinical choice for treatment of chemotherapy-induced OM (130).

Another *in vitro* experiment studied the effect of HST on the growth of oral microorganisms (131). Because of the important role of microorganisms in periodontal pathogenesis (especially gram-negative bacteria) and cancer therapies that lead to OM condition, they worked on 27 microbial species, including 19 oral bacteria and 1 fungus exposed to HST at 10mg/mL concentration. At the end of the study, they suggested that HST inhibiting oral bacteria growth can be useful as a therapeutic antibacterial agent in gram-negative bacterial periodontitis in cancer-therapy induced OM.

Ginger

Ginger (Zingiber officinale Roscoe), is one of the common spices with numerous useful effects, such as anti-inflammatory activities (132). There were no focused studies on the effect of ginger on cancer-therapy OM, but it was evaluated in an *in vivo/in vitro* study (133) as one of Hangeshashinto (HST) major components. HST is a traditional Japanese herbal medicine that contains seven different ingredients in the ratio Pinellia tuber (5): Glycyrrhiza ginseng (2.5): (2.5):

jujube (2.5): processed ginger (2.5): Scutellaria root (2.5): Coptis rhizome (1). This study claimed that “HST facilitates oral keratinocyte migration for rapid wound healing in patients with chemotherapy-induced oral ulcerative mucositis”.

They evaluated the HST effects on human oral keratinocytes (HOKs) as an *in vitro* arm and oral ulcerative mucositis (OUM) healing using rats with OUM as an *in vivo* arm. They concluded that Scutellaria root, processed ginger, and Glycyrrhiza as major active components could improve scratch-induced HOK migration that caused a better wound-healing effect.

In addition, topical application of HST (100 mg/mL) in a chemotherapy-administered OUM rat model showed significantly enhanced healing of wounds. Because of the different components of HST, the results should consider with caution.

Ginseng

There are several medicinal effects exist for ginseng extract such as antibacterial (134), antiviral (135), antioxidative(136, 137), antitumor(138) , antimutagenic(139) ,and immune-modulatory activities(140). In addition, Ginseng extract containing abundant saponin that causes an analgesic effect of ginseng. These effects were investigated in the literature:

An animal study on rats evaluated Korean red ginseng (KRG) effects on radiation-Induced OM in a preclinical rat model. Sixty male rats were randomized into four groups and received nothing, only KRG by the dose of 500 mg/kg/day, or only radiation (RT) 20Gy by the rate of 2Gy/min RT+KRG (With the same dosage as said above), respectively. Follow up was considered for 21 days. Then they claimed that:

1) Survival probability could be increased in KRG-treated rats, but it is not significant.

2) The oral mucositis, circumoral mucosal condition and mucosal ulcers on the tongue were better in the RT+KRG group than the RT only group.
3) The weight difference between the two groups (the KRG+RT and RT only group) was significant (positive effect for KRG).
4) The KRG-treated rats had a significantly lower reduction in oral intake, which took place suddenly.
5) The mean weight of the submandibular gland (SMG) of the RT + KRG group was much higher than RT only group with a histopathological recovery of ductal secretory structures, less fibrotic changes and fewer inflammatory reactions.
6) Enhanced recovery of the oral mucosa and salivary glands was observed in KRG-treated rats.

Finally, the study suggested that KRG can be useful and safe for clinical usage. It might have protective effects on radiation-induced OM, common morbidity after RT in patients with HNC (141).

Another study evaluated the pain-relieving effects of active ingredients of the traditional Japanese medicine hangeshashinto (HST) via action on Na+ channels. One of the ingredients was Ginseng. They selected two types of Ginseng, Rb1 and Rg1, because of their inhibitory effect on capsaicin-induced inflammatory responses in a keratinocyte cell line (142, 143).

After swab application on rat's OUM (oral ulcerative mucositis) areas, it was shown that Ginseng extracts in combination with other ingredients such as Processed Ginger, [6]-gingerol and [6]-shogaol demonstrated sufficient analgesic effects on OUM-induced mechanical pain but applying

Ginseng with swab by itself was not effective. So HST as a combined herbal medicine considered helpful in patients with OUM-induced pain (144).

In an *in vivo/in vitro* study, the protective effects of Korean red ginseng against (KRG) radiation-induced apoptosis in human HaCaT keratinocytes represent squamous epithelium of oral mucosa (145) were evaluated. They tried different concentrations of KRG on irradiated (8 Gy) HaCaT species and concluded that:

1. KRG can enhance HaCaT cell viability in radiated cases, and it is not a dose-dependent effect.
2. KRG preserves the proliferation and migratory ability of HaCaT cells in a decreasing, dose-dependent manner.
3. KRG inhibits radiation-induced apoptosis in HaCaT cells and intracellular generation of ROS
4. It protects mitochondria by stabilizing mitochondrial membrane potential (MMP)
5. "KRG rescues HaCaT cells by inhibiting the caspase-3 pathway and activation of ATM and p53."

Therefore, KRG shows protective effects against radiation-induced oral mucosal epithelium ulceration by promoting wound healing. These effects were approved through an invivo model (zebrafish). This study suggested that KRG might have beneficial effects on radiation-induced OM (16).

An *in vitro* study evaluated the antioxidative function of the radioprotective Japanese traditional (Kampo) medicine, hangeshashinto (combination of seven crude drugs: Pinelliae Tuber (hange),

Ginseng Radix (ninjin), Scutellariae Radix (ogon), Zingiberis Siccatum Rhizoma (kankyo), Zizyphi Fructus (taiso), Glycyrrhizae Radix (kanzo), and Coptidis Rhizoma (oren)), in an aqueous phase (146). They prepared an aqueous reaction mixture containing 30-mM DMPO (5,5-dimethyl-1-pyrroline-N-oxide) and various HST concentrations that were irradiated with 32 Gy X-rays as an •OH source for generating DMPO-OH as reactive oxygen species (ROS). They concluded that a relatively small concentration (0.25%) of HST resulted in a relatively significant reduction in DMPO-OH generation. Ginseng extract can be a scavenger for •OH(137).

Propolis

Propolis is a natural product made of resins from plants produced by honeybees with several antiulcer and antitumor activities (147). The major component of propolis is polyphenols, including capheic acid phenyl ethyl ester (CAPE), artipelin, sequiterpene quinines, galangin, quercetin, luteolin, campferol, vitamin, amino acids, coumarins, steroids and inorganic compounds (147, 148). An anti-inflammatory effect of propolis is useful in curing denture stomatitis (149), recurrent aphthous stomatitis (150) and eosinophilic ulcer conditions (151). It also has antioxidative (152), antibacterial(153), antifungal (154) and antiviral l (155) activities. Propolis can use for internal or external (e.g. in the shape of mouthwashes) purposes (156). Many studies show the effectiveness of propolis in relieving cancer therapy-induced OM.

An RCT (157) based on the anti-inflammatory and wound healing effects of the honey and honey products designed research on 90 children with acute lymphoblastic leukemia (ALL) and chemotherapy-induced oral mucositis with a mean age of 6.9±3.8 years. They divided samples into three groups, 30 patients each. Group 1 was given topical 0.5 g honey/kg (maximum 15 g) on affected oral mucosa three times a day until healing or for 10 days, whichever comes first. Group 2 was given 0.25 g/kg (maximum 5 g) of a 4:2:1 topical mixture of honey, olive oil–propolis extract

and beeswax (HOPE) in the same prescription. Group 3, as the control group, was given benzocaine 7.5% topical gel on affected oral mucosa three times a day. All patients received routine oral and dental, care including brushing and saline rinse just before each topical treatment. According to the NCI-CTC scale, the patients with grade 2 or 3 of chemotherapy-induced OM were included in the study. No adverse effects such as gastrointestinal effects or hypersensitivity reactions were observed. In grade 2 patients, honey groups experienced faster healing compared with other groups. In grade 3 patients who underwent topical treatment of HOPE and honey revealed faster recovery time than the control group but with no differences between them. They recommended that honey and other bee products help rapid healing in patients suffering from grade 2/3 chemotherapy-induced OM.

One systematic review and meta-analysis (158) evaluated the efficacy and safety of propolis mouthwash in cancer patients with severe therapy-induced OM. This study included five RCTs and a total of 209 participants. It was concluded that propolis mouthwash could be effective and safe in treating severe oral mucositis in patients with different cancer therapies. The researchers stated that since propolis is recognized as a food, not a drug, by the FDA and Health Canada, propolis related products could not be safe and effective without medical staffs and health-professionals supervision.

A pilot randomized controlled study evaluated the preventive effect of propolis on OM in breast cancer patients receiving adjuvant chemotherapy. The participants were 60 women with stage II breast cancer. They divided into two groups (30 patients each). The intervention group was given 8–10 mg/kg/day of propolis tablets 2-3 times a day to and the control group sodium was given bicarbonate mouth rinse three times a day. OM was evaluated with the NCI-CTCAE v4.0 on days 5, 10, 15 and 21 of treatment. It was concluded that during the first cycle, propolis could reduce

the severity and incidence of OM. Still, the prospective evaluations showed that significant differences were not found between the two groups (159).

An interventional follow-up phase II study evaluated the preventive effect of mucoadhesive propolis gel on the radiation-induced OM in oral cancer patients undergoing radiotherapy. This study included 24 patients. They were asked to use a special mucoadhesive propolis gel three times a day which contained 5% of propolis and some other chemicals. Then the oral mucositis evaluated based on the WHO scale. However, this study suggested that this type of propolis could be appropriate for avoiding radiation-induced OM. The results should consider with caution because of other components of the gel (160).

A prospective, randomized, double-blind, placebo-controlled study evaluated the safety and efficacy of propolis mouthwash in oral mucositis and dysphagia in patients undergoing head and neck radiotherapy. This study included 30 patients. They divided into two equal groups and evaluated for four weeks. The case group was asked to use 20 ml propolis oral solution (0.8 mg/ml) three times daily. In contrast, the control group was asked to use a 20 ml placebo solution (sterile water with allowable neutral additives) every 8 hours. It was observed that propolis oral solution could reduce the severity and incidence of OM and the severity of dysphagia(161).

A double-blind, randomized clinical study (162) evaluated the benefit of a natural mixture in preventing mucositis in 107 patients undergoing chemoradiotherapy for head and neck squamous cell carcinoma. This mixture contained Propolis, Aloe vera, Calendula, Chamomile, Honey and some other agents named Faringel. The placebo solution was similar to the experimental one in all features except propolis, aloe vera, calendula, and chamomile. Patients in both groups were asked to wash their mouth with 7mL of mouthwash qid (before each main meal and radiotherapy session) during weekdays and 3 times per day during weekends. The study used the CTCAE v3.0 scale for

functional mucositis, mucositis and dysphagia and the Verbal Descriptor Scale for pain. Despite previous studies, they did not report a preventive effect for this four-agent natural solution (calendula, aloe vera, chamomile, and propolis) on developing grade three acute mucositis during chemoradiotherapy for HNC.

A triple-blind, randomized, placebo-controlled trial evaluated preventing and therapeutic effect of propolis in radiotherapy-induced mucositis of HNC (163). 20 patients in this were randomly divided into two equal groups. The patients in the case group were requested to swallow 15 ml of propolis 3% mouthwash 3 times a day for 5 weeks, whereas for patients in the control group, the same placebo mouthwash was prepared. The mucositis measured by the NIC-CTC scale, and after 5 weeks of follow up, it was observed that the mucositis score in the propolis group was significantly lower than the placebo group. In addition, during the radiotherapy course, 8 patients in the propolis group did not show mucositis. Patients in the propolis group had lower weight loss. This study concluded that water-based propolis mouthwash is effective and safe in avoiding and relieving radiotherapy-induced mucositis.

A double-blind, randomized placebo-controlled study (164) evaluated the effectiveness of propolis in treating severe OM in children undergoing chemotherapy. 40 pediatric patients were entered into this study. The active group were asked to apply 0.38 g propolis product on affected areas in the mouth twice a. In contrast, the control group applied an identical product that contained 70% caramel dye alcohol solution as a placebo. They evaluated the OM by OAG scale and concluded that severe OM episodes frequency, OM episodes mean duration. OM episodes mean severity did not have statistically significant differences between the study groups. There were no adverse effects recorded in patients who finished the protocol.

Conclusion and future perspective

This study was a comprehensive review to assess the impact of herbal medicines on cancer treatment-induced OM. Findings of this review showed that almost all herbal medicines have several beneficial effects on the palliation of cancer therapy-induced OM. Curcumin, Aloe vera and propolis showed promising and favorable effects on OM according to both clinical trials and preclinical studies. Other herbs such as calendula, coumarin/troxerutine, quercetin, silymarin, ginseng, green tea, and Hangeshashinto also benefit OM. However, the small number of clinical trials using heterogeneous methodological approaches in terms of dose, duration of the intervention, way of agent administration and OM scaling makes it challenging to draw a definitive conclusion. Altogether, this review highlights the beneficial effects of herbal medicine and medicinal plants as natural, inexpensive, available and accessible agents without any significant side effects on cancer therapy-induced oral mucositis. The studies' results are not uniform, suggesting more well-designed clinical trials should be conducted in the future to make sure about such effectiveness. Future studies should follow similar protocols in terms of duration of intervention, scales and dosage of agents to draw a more definitive conclusion.

Tables

Table 1. The effects of herbal medicines on cancer therapy-induced oral mucositis based on clinical trials

Table 2. Studies the effects of herbal medicines on cancer treatment-induced oral mucositis.

Table 3. The effects of herbal medicines on cancer therapy-induced oral mucositis based *on in vivo* studies.

Table 4. The effects of herbal medicines on cancer therapy-induced oral mucositis based on *in vitro* studies.

Figure

Figure 1. Schematic summary of pathways depicting the possible effects of radio-chemotherapy on the healthy oral mucosa and potential effects of herbal medicine on cancer therapy-induced oral mucositis and its potential related mechanisms are depicted.

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Table 1. The effects of herbal medicines on cancer therapy-induced oral mucositis based on clinical trials

Study characteristics		Population characteristics	Intervention characteristics						
Author, Year	**Study design**	**Sample**	**Intervention**	**Control**	**Administration**	**scale**	**Time**	**Main conclusions**	**Adverse effects**
Delavarian Z at al 2019 (60)	double-blind randomized clinical trial study	Thirty-two patients with HNC undergoing radiotherapy	oral nanocurcumin	Lactose tables	1 capsule of SinaCurcumin® 80mg per day	NCI-CTC v.2	42 days	prevention of OM or reducing its severity	no obvious oral or systemic side effects
Patil K at al 2015 (61)	A Pilot Study	20 adult cancer patients undergoing radio-chemotherapy	curcumin mouthrinse 0.004%	chlorhexidine mouth wash 0.2% to be used for 1 minute, in 1:1 dilution, thrice daily for twenty days	1:5 dilution for one minute, three times daily for 20 days	NRS, OMAS & WHO scores	20 days	better than chlorhexidine in rapid wound healing better patient compliance No complications.	no adverse even
Elyasi S et al 2016 (80)	A Randomized, Double-Blinded, Placebo-Controlled Clinical Trial	27 patients	oral silymarin	vitamin B6	420mg daily in three divided doses	WHO and NCI-CTC	for 6 weeks	delay for mucositis development and progression of OM reduce the severity of radiotherapy induced mucositis	Well tolerated, no adverse effects relevant to silymarin administration
Yayla EM et al 2016 (84)	A randomized controlled	60 patients	Sage tea–thyme–peppermint hydrosol	Basic oral care, brush the	15 mL of sage tea–thyme–peppermint	WHO oral toxicity scale	for14 days	1) alleviative effect 2)well-tolerated	NM

	pilotstudy			teeth two times a day	hydrosolqid			3)cost-effective	
Ebert N et al 2020 (85)	a randomized controlled phase III trial	57 patients n= 27 sage; n= 30 Cystus®	polyphenol-containing cystus® tea mouthwash	Sage tea	a tea bag (1.5g Cystus® or sage tea), should steep for 7min for Cystus® tea and 10min for sage tea. Tea bag was removed and the tea should cool down before use. Regular mouth rinses of at least 1.5min 3–5 times a day	RTOG/ EORTC criteria.	Two times a week during, and 3 months after radiotherapy	There was no significant difference between the groups in latency and frequency of the occurrence of mucositis grade 3.	NM
Babaee N et al 2013 (91)	a randomized controlled clinical study	40 patients	calendula	placebo mouth wash	Mouth wash 2% calendula 5 ml BID as gel formulation	OMAS	For 6 weeks	decreasing the intensity of radiotherapy-induced OM	without any significant side effects (i.e., nausea and vomiting)
Grötz KA et al 2001 (95)	a prospective, randomized, placebo-controlled, double-blind study	23 patients (48 patients in first)	coumarin/troxerutine	NM	coumarin 15 mg and troxerutin 90 mg in each coated tablet 2 coated tablets	RTOG score	one week before radiotherapy and was continued for four weeks after the	Favourable effect in mucositis.	No adverse event

					three times a day		end of the course		
Kooshyar MM et al 2017	A Randomized Placebo-Controlled Double Blind Clinical Trial	20 patients	Quercetin	lactose capsule	250 mg quercetin capsules two times daily	WHO	for four weeks.	Less incidence and more severity in intervention group were recorded	at higher doses, quercetin has an inhibitory effect on lymphocytes.
Sahebjamee M et al 2015 (115)	a triple-blind, randomised controlled trial	26 patients	Aloe vera mouthwash containing pure Aloe vera gel	0.15% benzydamine mouth wash	rinse 5 ml of the solution; not eat or drink for the subsequent 30 min, 3 times a day from the first day of RT to the end of the treatment	WHO	during 6 weeks (total of 8 visits)	Aloe vera mouthwash was as beneficial as benzydamine mouthwash	no side effects
Su CK et al 2004 (118)	Phase II double-blind randomized study	58 head-and-neck patients with cancer	oral aloe vera solution	The placebo solution was taste-matched, with identical astringency, consistency, and ingredients, except that the aloe vera juice was replaced with water.	20cc QID	Radiation Therapy Oncology Group acute toxicity 4-point grading scale	7 weeks	aloe vera was not a beneficial adjunct to radiotherapy	No patients reported adverse effects

Abdulrhman M et al 2012 (157)	A Randomized Controlled Pilot Study	90 children (33 females and 57 males) with (ALL) and chemotherapy-related oral mucositis grades 2 and 3	Honey and a 4:2:1mixture of honey, olive oil–propolis extract and beeswax (HOPE)	benzocaine 7.5% gel applied topically to the affected oral mucosa 3 times daily	0.5 g honey/kg (maximum 15 g) applied topically to the affected oral mucosa 3 times daily until healing or for 10 days and 0.25 g/kg (maximum 5 g) of a 4:2:1mixture of honey, olive oil–propolis extract & beeswax	NCI-CTC	10 days	honey and other bee products can be useful for faster healing in patients with grade 2/3 chemotherapy-induced oral mucositis.	transient burning sensation
M. Pireddda 2017 (159)	A pilot randomized controlled trial	60 patients 20 years or more	propolis	sodium bicarbonate three times a day.	Dry extract of propolis divided into 2–3 times/day between meals. The tablets of propolis were swallowed. Each tablet contained 80 mg of propolis titrated in galangin 8%–12%. The total daily	NCI-CTC AE v4.0	21 days	Propolis plus bicarbonate was safe, well tolerated and promisingly effective in the prevention of OM in patients with breast cancer.	No severe adverse reactions to propolis occurred. Only two mild skin rashes were reported, as suspected reactions to propolis

					number of tablets was calculated according to patient weight and ranged 8–10 mg/kg/day of propolis				
Dastan F et al 2020 (161)	a randomized, double blind clinical trial	30 patients	propolis oral solution	20 ml placebo solution (sterile water with allowable neutral additives) three times a day	20 ml propolis oral solution (0.8 mg/ml) three times a day	For OM: NCI-CTC and For dysphagia: CTC AE	four weeks	propolis mouthwash is an effective and safe medication for alleviation of oral mucositis and dysphagia in patients under head and neck radiotherapy	There is not any serious adverse effect related to propolis or placebo during the study
Maruc ci L et al 2017 (162)	a double-blind, single-institution, randomized clinical trial	107 patients	a mixture of natural agents (Faringel) propolis, aloe vera, calendula, and chamomile	A solution similar to the experimental one in color, flavor, and density, but without propolis, aloe vera, calendula, and chamomile	rinse with 7mL of mouthwash 4 times per day (before each main meal and radiotherapy session) during week days, and 3 times per day (before each	CTC AE v3.0 for functional mucositis, mucositis and dysphagia Verbal Descriptor Scale for pain	Weekly visits and some criteria were defined as end points	The selected natural agents do not prevent mucositis	they did not negatively impact tumor control

					main meal) during weekends				
Bolouri AJ et al 2015 (163)	randomized triple blind clinical trial	20 patients	Propolis	15 ml of placebo mouth wash that swallow three times a day for five weeks	15 ml of propolis 3% mouthwash three times a day for five weeks	NCI-CTC	5 weeks	water based extract of propolis efficiently prevents and heals radiotherapy induced mucositis	NM
Tomaževič T et al 2013 (164)	A double-blind randomized placebo-controlled study	40 Pediatric patients	Propolis	Topical application of 0.38 g placebo (70% caramel dye alcohol solution) 2 times a day	Topical application of 0.38 g propolis 2 times a day	OAG	for the period of the chemotherapy or for the first 6 months of the chemotherapy	propolis cannot be recommended for severe OM treatment	No side effects

Table 2. Summary of reviews on the effect of herbal medicines on cancer therapy-induced oral mucositis

Author, year	Type	Number of included studies	agent	Main outcome
Normando AGC at al 2019(4)	Systematic review & meta-analysis	5	turmeric &curcumin	Reduced pain, erythema intensity, ulceration area, and degree of severity. delayed mucositis lesions
Zhang L at al 2020(57)	A Meta-Analysis of Randomized Controlled Trials	6	curcumin	curcumin can significantly prevent and treat OM and reduce OM-induced weight loss

				effect of curcumin on the incidence of severe OM should be interpreted with caution due to high heterogeneity
Yu YY at al 2020(58)	a network meta-analysis of randomized controlled trials	28	curcumin, honey, benzydamine, chlorhexidine, allopurinol, sucralfate, granulocyte-macrophage colonystimulating factor, povidone-iodine, and aloe	curcumin and honey as the preferred options to prevent OM
Zhang X at al 2020(59)	A Bayesian network analysis of RCTs	36	10 different types of mouthwashes, namely aloe vera, benzydamine, chamomile, chlorhexidine, curcumin, honey, lactobacillus brevis, Na bicarbonate, povidone-iodine, and sucralfate mouthwash	chamomile, honey, curcumin and benzydamine mouthwashes could potentially prevent intolerable OM
Kuo CC et al 2018 (158)	a systematic review and Meta-Analysis of RCTs	5	propolis	Propolis mouthwash effective and safe in the treatment of severe OM

Table 3. The effects of herbal medicines on cancer therapy-induced oral mucositis based *on in vivo* studies

Study characteristics		Population characteristics	Intervention characteristics			
Author, Year	**Study design**	**Sample**	**Intervention**	**Administration**	**scale**	**Main conclusions**
Elad S at al 2013(62)	Case series	4 pediatric	Curcumall mouth wash	10 to 30 drops BID	WHO OMAS VAS	curcumin mouthwash safe and well-tolerated
M. REZVANI and G. A. ROSS 2004(63)	Animal study	rats	Comparing compound A (curcumin, a-tocopherol and sunflower oil) with each of its components	0.5 ml/day From each solution About curcumin it was 200mg/kg/day in each 0.5 ml+10% ethanol	mucosal ulceration	Curcumin and other components of compound A appeared to be effective in the prevention of radiation-induced OM. Compound A has greater effects
Shin YS et al 2013 (86)	Invivo/invitro	HaCaT/Rats	Epicatechin (EC),	EC (100 mM) for HaCaT for 23 days after irradiation for rats	NM	EC significantly inhibited radiation-induced apoptosis in keratinocytes and rat oral mucosa
Miyano K et al 2020 (133)	Invivo/invitro	human oral keratinocytes (HOKs) And Rats	Hangeshashinto (HST) contains: Pinellia tuber (5): Scutellaria root (2.5): processed ginger (2.5): Glycyrrhiza (2.5): jujube (2.5): ginseng (2.5): Coptis rhizome (1)	100 μg/mL	visual oral mucositis score	Markedly facilitated the scratch-induced HOK migration in a dose-dependent manner

Chang JW et al 2014(141)	Animal study	rats	Korean Red Ginseng	500 mg/kg/day each dose was 2.5 ml (total, 5 ml/day) oral gavage and spraying	6-point grading system	KRG can be used safely in the clinical setting as a protective agent against radiation-induced oral mucositis
Hitomi S et al 2017(144)	Animal study	rats	Ginseng	4% and 13.5 mg/mL in saline	NM	Ginseng extract in combination with other ingridients such as Processed Ginger, [6]-gingerol and [6]-shogaol demonstrated sufficient analgesic effects on OUM-induced mechanical pain but the swab application of Ginseng extract alone was not effective
RAS Noronha V et al 2014 (160)	interventional follow-up phase II study	24 oral cancer patients	Propolis	Propolis mucoadhesive gel 5% (10 g) three times a day, starting 24h before the first session and during the period of radiation therapy	WHO classification	propolis gel could be useful for prevention of radiation-induced oral mucositis

Table 4. The effects of herbal medicines on cancer therapy-induced oral mucositis based on in vitro studies

Study characteristics		Population characteristics	Intervention characteristics		
Author, Year	**Study design**	**Sample**	**Intervention**	**Administration**	**Main conclusions**
Lüer S 2012 (64)	invitro	18 oropharyngeal species	curcumin	50–200 µM For 4 h	curcumin can prevent cancer therapy-induced oral mucositis
dos Santos Filho EX 2018 (165)	invitro	HaCaT	FITOPROT	0.005%) for 24 h	has some chemopreventive effects against 5-fluorouracil-induced toxicity
Kono et al 2014 (130)	invitro	human oral keratinocytes (HOK)	Hangeshashinto: Pinellia tuber, Scutellaria root, processed ginger, glycyrrhiza, jujube, ginseng, and Coptis rhizome	HST was added to cultures at final concentrations of 3, 10, 30, 100, or 300 µg/mL.	Promising agent for the treatment of COM
Fukamachi H et al 2015 (131)	invitro	27 microbial species including 19 oral bacteria and one fungus	Hangeshashinto: Pinellia tuber, Scutellaria root, processed ginger, glycyrrhiza, jujube, ginseng, and Coptis rhizome	10mg/mL	Potentially useful treatment for OM in patients undergoing chemotherapy
Jae Won CHANG et al 2014(16)	Invivo/invitro	HaCaT	Korean Red Ginseng	various concentrations of KRG (0, 10, 30, 50 and 100 µg/ml	KRG can be useful against radiation-induced oral mucositis
Matsumoto C et al 2015(146)	invitro	aqueous reaction mixture	Kampo hangeshashinto (HST) contains: Pinelliae Tuber (hange), Scutellariae Radix (ogon), Zingiberis Siccatum Rhizoma (kankyo), Glycyrrhizae Radix (kanzo), Zizyphi Fructus (taiso), Ginseng Radix (ninjin) and Coptidis Rhizoma (oren)	various concentrations (%w/v) of HST (0.25%, 0.5%, 1.0% and 2	Ginseng extract scavenges •OH