Natural Products for Management of Oral Mucositis Induced by Radiotherapy and Chemotherapy

Integrative Cancer Therapies
2016, Vol. 15(1) 60–68

DOI: 10.1177/1534735415596570
ict.sagepub.com
SAGE

Azar Aghamohammadi, MS[1,2,3] and Seyed Jalal Hosseinimehr, PhD[1,2]

Abstract

Oral mucositis is a common side effect of systemic chemotherapy and radiotherapy of head and neck in patients with cancer. Severe oral mucositis is painful and affects oral functions, including intake of food and medications and speech. Prevention of oral mucositis affects the life quality of patients. Recent studies have been focused on natural products to improve or reduce this complication. Many clinical trials have been performed to assess natural products for treatment of mucositis and their results are promising. The authors reviewed the evidence for natural products in the prevention and treatment of oral mucositis induced by radiation therapy and chemotherapy.

Keywords

mucositis, xerostomia, radiation therapy, chemotherapy, cancer, natural products

Introduction

Radiotherapy and chemotherapy are the main strategies for treatment of head and neck cancers.[1,2] Ionizing radiation generates reactive oxygen species (ROS) when it is passing through biological systems. ROS are very reactive, attack the critical macromolecules in the cells such as DNA, and lead to cell damage and death. In head and neck cancer therapy, radiation and anticancer drugs are not only effective on tumor cells but are also absorbed by the buccal and peribuccal tissues.[3,4] Since the mucosal cells of the gastrointestinal tract have high proliferation rates, tumor cells in this region of body are sensitive to radiation and anticancer agents. Although radiotherapy and chemotherapy are effective in treatment of cancers, they have several short- and long-term side effects on normal tissues.[5,6]

Mucositis is an acute injury to the mucosal barrier following head and neck cancer treatment with radiotherapy and/or chemotherapy. Oral mucositis is painful and patients have difficulty swallowing food, and may require feeding tubes. Mouth ulcers can become infected by bacteria; this sepsis can be a life-threatening condition for patients. There is no current Food and Drug Administration–approved medication for the prevention of radiation-induced oral mucositis.[7,8] The protective effect of natural products against toxicity caused by radiation or anticancer agents is probably one of the most promising preventive strategies in patients during therapy. In this review, we have concentrated on the preventive agents in natural products that are used as protective agents against oral mucositis caused by radiation or chemotherapy.

Radiotherapy- and/or Chemotherapy-Induced Mucositis

Mucosal tissue covers respiratory and gastrointestinal tracts. The part of this tissue that covers the mouth is called the oral mucosa. The oral mucosa is one of the most sensitive tissues to chemotherapy and radiation. Mucositis is a condition characterized by pain and inflammation of the surface of the mucous membrane. Almost 80% of patients with head and neck cancer treated by radiotherapy suffer from oral mucositis. About 15% of patients who receive high doses of radiotherapy in the mouth region must be hospitalized because of these side effects. Younger people, because of their high cell proliferation rate, are at high risk of oral mucositis induced by chemotherapy and radiotherapy.[3,9] Various factors that

[1]Traditional and Complementary Medicine Research Center, Mazandaran University of Medical Sciences, Sari, Iran
[2]Department of Radiopharmacy, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran
[3]Department of Midwifery, Sari Branch, Islamic Azad University, Sari, Iran

Corresponding Author:
Seyed Jalal Hosseinimehr, Department of Radiopharmacy, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.
Email: sjhosseinim@yahoo.com

affect the incidence of oral mucositis include mouth hygiene condition before treatment, radiotherapy dosage and plan, the type of treatment used (radiotherapy alone or combination with chemotherapy), and the type of chemotherapy drug administered.[10]

Oral mucositis is an acute mucosal inflammation that starts as redness and progresses to an increased ulceration and pseudomembrane formation, which provides a temporary barrier until cellular repair promotes healing.[11,12] The impaired mucosal tissue often permits bacteria and fungi to penetrate into damaged mucosa and cause infections.[12] Mucositis is divided into 4 phases: an initial inflammatory/vascular phase, an epithelial phase, an ulcerative/bacteriological phase, and a wound healing phase.[13]

In the initial stage, irradiation or chemotherapy, by producing free radicals and ROS, harmfully influences cells and strands of DNA in the basal epithelium and the submucosa and leads to lesions. ROS also activate transcription factors and leads to cell destruction in later stages. In the next stage, not only ROS but also damaged cells and DNA start a cascade of reactions. During these reactions, pro-inflammatory cytokines produce and lead to lesions and basal cell apoptosis. These products have a positive reaction as well, and strengthen the lesions. In this stage, the tissue appears to be normal, with only with slight erythema. In the third stage, painful lesions appear and are colonized by bacteria. Bacterial colonization can lead to the release of new pro-inflammatory cytokines.

After stopping cancer treatment, oral mucositis vanishes little by little. In the healing process, symptoms decrease and the mucosa become normal, but outstanding neovascularization remains.

This tissue is easily broken and it is susceptible to chemotherapy and/or radiotherapy in future periods of cancer treatments.[14] Oral complications remain a major problem despite the use of protective or treatment agents for them.[6] Apoptosis or programmed cell death is responsible for the extension of oral mucositis induced by radiotherapy and chemotherapy.[15] The responsibility of oral fungal and bacterial colonization for the extension of chemotherapy- and radiotherapy-induced oral mucositis is not clear but it is supported by researchers.[16] There is a relationship between neutropenia caused by cancer treatment and existence of oral mucositis, which aggravates the severity or prolongs duration of it in these patients[17]. But other studies have not found the correlation between severity or recovery of neutropenia and grade and recovery of mucositis.[18] Assessments of mucositis are varied in different studies. This diversity in scoring systems may lead to controversies among studies. The most widely used measurements for oral mucositis are the World Health Organization and Radiation Therapy Oncology Group (RTOG) scales. Also, the Oral Mucositis Assessment Scale, and a Visual Analog Pain Scale (patient reporting scale of 0-10) are used for grading of mucositis. Mucosal changes like redness, ulceration with functional outcomes such as inability to eat and pain have been assessed in these scales. Based on clinical examination, 4 distinct grades can be determined for mucositis from 0 to 4 scores. Higher grades of mucositis (grade 3-4) are associated with loss of taste, hemorrhage, decreased intake of food and fluids, ulceration, pain, loss of voice, and low quality of life.[19-21]

Several studies performed on natural product for preventing or reducing chemotherapy- and radiotherapy-induced oral mucositis. Information on their ability to reduce the incidence, severity or the period of oral mucositis was studied in this article. Most points of clinical results are summarized in Table 1.

Natural Products for Prevention and Treatment of Mucositis

Calendula officinalis

Calendula officinalis is a medicinal plant belonging to the Asteraceae family. Extracts of the flower of *C. officinalis* have been used as topical and oral herbal remedies for its bactericidal, antiseptic, anti-inflammatory, antioxidant, hepatoprotective properties, and antimetastatic effects.[42] Several studies reported that *C officinalis* flower extract can reduce the severity of radiation-induced wounds.[43,44] Daily application of *C officinalis* extract in gel form considerably reduces the oral mucositis induced by 5-fluorouracil in mucosa cheek pouches of hamsters.[42] In a clinical trial study, Babaee et al[35] reported that calendula extract was effectively used to decrease the intensity of radiotherapy-induced oral mucositis. Considering the fact that calendula has antioxidant properties, it may act against ROS and prevent or delay the initiation phase of mucositis.[35]

Biological effects of this medicinal plant are mostly related to its chemical compositions such as polyphenols, carotenoids, triterpenes and essential oils. Anti-inflammatory, antitumorigenic, antioxidant, and antimicrobial activities are proposed for calendula to prevent oral mucositis.[45,46] Quercetin is the main flavonoid of this plant. Antioxidant activities of quercetin were demonstrated in recent studies.[35] When quercetin encounters a free radical, it becomes a radical by giving a proton, but the quercetin radical has very low energy because the unpaired electron is delocalized by resonance. The B ring *o*-dihydroxyl groups, the 4-oxo group in conjugation with the 2,3-alkene and the 3- and 5-hydroxyl groups are in quercetin's structure and can donate electrons to the rings, leading to quercetin's antioxidant activity.[47]

Drug interaction: Synergism with sedatives and antihypertensives.[48]
Clinical outcome: Herbs that can be safely consumed when used appropriately.[48]

Table 1. Summary of Treatments With Natural Products for Mucositis in Cancer Patients.

Product	No. Patients	Type of use	Treatment	Results	Reference
Honey	40	Topical and swallow	R	Significant reduction in the frequency of mucositis; Risk of developing intolerable mucositis was 0.05 and 0.75 for honey and lignocaine groups, respectively	22
Honey	40	Topical and swallow	CH-R	Significant reduction in grade 4 mucositis, Candida colonization and positive cultures for aerobic pathogenic bacteria in honey group	23
Honey	40	Topical and swallow	R	Significant reduction in mucositis scales but no significant weight change was found	24
Honey	40	Topical and swallow	R	Significant reduction in symptomatic grade 3/4 mucositis but no significant weight change was found	25
Honey	131	Topical and swallow	R	No improvement in mucositis, but associated with a reduction in bacterial infections	12
Honey	81	Topical and swallow	CH-R	No statistically significant difference between the honey and placebo was reported	26
Propolis (bee glue)	40	Topical and swallow	CH	Not statistically significant	27
Coffee plus honey	75	Topical and swallow	CH	The best reduction in severity was achieved in coffee plus honey group. Honey group and steroid group ranked second and third	28
Matricaria recutita	52	Topical (mouthwash)	CH	Significant reduction in frequency of mucositis	29
Matricaria recutita	1 (case report)	Topical (mouthwash)	CH	Treated case	30
Matricaria recutita	40	Topical (mouthwash)	R	1% extract associated with reduced incidence, intensity, and duration of mucositis	31
Matricaria recutita	164	Topical (mouthwash)	CH	No difference in frequency of mucositis	32
Peppermint	40	Topical (mouthwash)	CH	Significant reduction in frequency of mucositis	33
Aloe vera	61	Oral juice	R	Significant reduction in frequency of mucositis	34
Calendula officinalis	40	Topical (mouthwash)	CH-R	Significantly decreased the intensity of mucositis	35
Olive leaf extract	30	Topical (mouthwash)	CH	Significantly decreased the intensity of mucositis	36
Glycyrrhiza glabra	45	Topical (mouthwash)	R	Result showed better outcome for mucositis	37
Curcuma longa	7	Topical (mouthwash)	CH	Reduction in the WHO, OMAS, and VAS scores of oral mucositis	38
Extract of human placenta	60	Intramuscular	R	Decrease in pain and progression to grade 3 mucositis and improvement in difficulty with swallowing was observed	39
Indigowood root	20	Topical (mouthwash)	R	Reduction in the severity of mucositis, anorexia and swallowing difficulty	40
Dead Sea product	54	Topical (mouthwash)	R	Significantly decreased the intensity of mucositis	41

Abbreviations: R, radiotherapy; CH, chemotherapy; WHO, World Health Organization; OMAS, Oral Mucositis Assessment Scale; VAS, Visual Analog Pain Scale.

Matricaria chamomilla

The flowers of *Matricaria chamomilla* (Chamomile) have been widely used in traditional and herbal medicine for a long time.[30] The plant contains chemical compositions such as chamazulene, alpha-bisabolol, bisaboloxides, spiroethers, and flavonoids that have anti-inflammatory, antibacterial, spasmolytic, sedative, and antifungal activities.[49,50] It has been claimed to promote granulation and epithelialization, which leads to normalization of the oral environment

and accelerates reepithelialization of oral tissue.[51] Recent studies evaluated its effect on prevention and treatment of oral mucositis induced by chemotherapy and radiotherapy.[52] Carl and Emrich[49] showed that chamomile (Kamillosan Liquid oral rinse) can prevent or delay onset and reduce occurrence and severity of mucositis induced by radiotherapy and chemotherapy. Sixty-six patients with head and neck cancer received drops of chamomile in water 3 times a day. Kamillosan Liquid oral rinse delayed the onset of radiation mucositis and in most patients reduced its the intensity. Prophylactic use of the oral rinse prevented the occurrence of severe mucositis in most patients who received systemic chemotherapy.[49] Despite these studies, in the phase III, double-blind, placebo-controlled clinical trial, chamomile mouthwash did not reduce the stomatitis and inflammation of the mouth and lips induced by 5-fluorouracil in patients.[32] Matricine and its transformation product chamazulene are the main compounds of *M chamomilla*. Chamazulene may contribute to the anti-inflammatory activity of chamomile extracts by inhibiting leukotriene synthesis and additional antioxidative effects.[53]

Drug interaction: There is a report of an interaction between warfarin and *M recutita*.[54]
Clinical outcome: Herbs that can be safely consumed when used appropriately.[48]

Aloe vera

Aloe vera is widely used to remedy some skin difficulties, for example dry and burned skin and radiation-induced dermatitis.[55,56] The use of *Aloe vera* in the treatment of irritant contact dermatitis has been reported in the literature since 70 years. Some studies suggested the beneficial effects of *Aloe vera* on prevention and treatment of radiation-induced ulcers and mucositis.[57] Preclinical studies showed that *Aloe vera* enhanced wound healing by reducing vasoconstriction and platelet association at the wound place, increasing collagen formation and wound oxygenation, scavenging free radicals, inhibiting collagenase and metalloproteinase, and activating macrophages.[9,58-60] Also *Aloe vera* has anti-inflammatory property through the inhibition of cyclooxygenase.[60] In a double-blind randomized clinical trial study, significant benefits were not statistically found when adding *Aloe vera* to the standard oral care in the management of radiation mucositis.[9] Radiation-induced mucositis is recognized by exposure of a large region of basal membrane and innervated mesenchymal tissue after erosion of the mucosal layer. Treatment of oral ulcers is needed to regenerate and replace the basal membrane clonogens rather than to inhibit the mediators of inflammation and this maybe one reason for noneffectiveness of *Aloe vera* for radiation-induced mucositis.[9] Puataweepong et al[34] studied a phase III, double-blind, placebo-controlled clinical trial on 61 patients with head and neck cancer, who were under conventional radiation therapy and received oral *Aloe vera* juice or placebo. The incidence of severe mucositis was significantly lower in the *Aloe vera* group compared with the placebo group. In this study, researchers used a fresh *Aloe vera* juice prepared under a well-controlled technique of enzyme deactivation. For this reason, their solution could preserve more essential active compounds, such as glycoprotein, which are powerful substances to promote healing and anti-inflammatory effects.[34] However, more experiments are needed to validate this process. Yagi et al[61] examined the antioxidant activity of *Aloe vera*. They indicated that isorabaichromone exhibited a strong antioxidative activity.

Choi et al[62] showed that other compounds in *Aloe vera*, including β-sitosterol improved the appearance of proteins related to angiogenesis, namely von Willebrand factors, vascular endothelial growth factor (VEGF), VEGF receptor Flk-1, and blood vessel matrix laminin. They suggested that β-sitosterol has curative angiogenic effects on injured blood vessels.[62]

Drug interaction: Synergism with insulin, topical hydrocortisone, and zidovudine.[63]
Clinical outcome: Potassium depletion, hypokalemia, increased hypoglycemic effect.[63]

Isatis indigotica

Isatis indigotica Fort. (Indigowood root) belongs to the Brassicaceae family. Indigowood root is used in Chinese traditional medicine.[64] You et al[40] studied the effect of indigowood root on patients with head and neck malignancy under radiotherapy. Twenty patients were randomly divided into 2 groups. Group 1 served as controls with only normal saline and the second group received indigowood root. They showed that indigowood root significantly reduced the severity of radiation induced mucositis, anorexia, and swallowing difficulty. This extract increased the patients' appetite and swallowing ability and finally their quality of life. The authors suggested that anti-inflammation was the main mechanism for preventive effect of indigowood on mucositis induced by radiation.[40] Chemical analysis of indigowood root illustrated that it contains indirubin and indigotone which have anti-inflammmatory activity.[64] Most studies have shown that the particular structure of indirubin gives it the ability to inhibit cyclin-dependent kinases and glycogen synthase kinases, triggering cell cycle arrest and apoptosis. Kinase inhibitor activity of indirubin is a main cause of cellular proliferation and immune functions. Indirubin is also a strong aryl hydrocarbon receptor (AhR) agonist. The AhR is a cytosolic protein, which, on ligand binding, is translocated to the nucleus and acts as a transcription factor for genes engaged in oxidative stress.[53]

Drug interaction: None reported.[65]
Clinical outcome: A classic textbook in traditional Chinese medicine points out that *Isatis* root is not indicated for feeble patients.[66]

Leptospermum scoparium

Leptospermum scoparium, commonly called manuka, is a species of flowering plant in the myrtle family. The Myrtaceae are native to New Zealand and southeast Australia. This herb contains sesquiterpene hydrocarbons. These compounds have antifungal, antibacterial, and anti-inflammatory activity.[67,68] In a randomized placebo-controlled trial study, 19 adult patients used a gargle containing 2 drops of a 1:1 mix of the essential oils of manuka. Overall, the active gargle was well tolerated by patients with no evidence of toxic or side effects relating to its swallowing. Patients in the essential oil gargle group had a delayed onset of mucositis and reduced pain and oral symptoms relative to placebo. Small sample size was a limitation of this study. They suggested that essential oils had the role in improving oral health by causing lysis of oral bacteria and helping to reduce the bacterial load. As a consequence of the small data in their study, recommendation to using it for mucositis needs large randomized clinical trials to confirm.[69] Recent studies showed that the antimicrobial activity of the manuka oil was related to flavesone and leptospermone.[70,71]

Drug interaction: There is potential synergistic effect with bacitracin, cefadroxil, cephradin, and meropenem but an antagonist effect with ofloxacin, enoxacin, and sparfloxacin.[72] *L scoparium* contains a lipophilic flavonoid that specifically interacts with benzodiazepine receptors (GABA-A receptor-chloride channel complex).[73]
Clinical outcome: Avoid using it during pregnancy because of spasmolytic activity.[68]

Essential Oils

Essential oils have antibacterial and antifungal effects and these natural compounds have been applied to treat the skin and mucosa infections. In a clinical trial, Gravett[74] assessed mixed essential oils as mouthwash for oral mucositis. Gravett[74] combined a mixture of *Melaleuca alternifolia* (1 drop), *Citrus bergamia* (1 drop), and *Pelargonium graveolens* (1 drop) with half of a glass of boiled warm water to gargle for 5 times a day. Although few benefits were found when this mouthwash was added to the routine oral care in the treatment of radiation mucositis, patients preferred to use this plant mouthwash because of less burning discomfort in comparison with routine mouthwash for managing oral mucositis.[74] In a double-blind clinical trial study, 40 patients with colon or rectum cancers were admitted to chemotherapeutic management and randomly divided into 2 equal placebo and peppermint essential oils groups. Patients received 10 drops of oral rinse peppermint essential oils 3 times a day. The incidence of oral mucositis was 15% for the essential oils group, while it was 50% in the placebo group. Mean scores of oral mucositis were 0.2 and 0.8 in essential oils– and placebo-treated groups, respectively. Peppermint essence is an effective, safe, and well-tolerated products for prophylactic treatment of chemotherapy-induced oral mucositis.[33]

Human Placenta

Human placental extract contains a complex mixture of different materials such as polydeoxyribonucleotides, RNA, DNA, peptides, amino acids, enzymes, and other scarce ingredients. These products have anti-inflammatory function and have been used as a remedy for untreatable foot sore and appeared to be effective in the prevention and treatment of chemotherapy- and radiotherapy-induced oral/oropharyngeal mucositis and especially in controlling symptoms.[75] Placentrex is a drug containing peptides (FNP-III, CRF), nucleotides (PDRN, NADPH), and glutamate and is derived from an extract of fresh term, healthy, and human placenta. Each milliliter contains 0.1 g fresh human placenta. Placentrex is used for a number of inflammatory skin diseases.[3] Recent studies have demonstrated that Placentrex stimulates the pituitary and the adrenal cortex and normalizes the tissues metabolism. According to theory, it increases the vascularity of tissues.[47] There are not many studies on the assessment of the effect of human placenta on chemotherapy- and radiotherapy-induced oral mucositis. In a clinical trial study, 120 patients with head and neck cancer under radiation therapy were equally divided into 2 groups. Patients received either Placentrex treatment or standard treatment. Placentrex was given as 2 mL intramuscular injection, 5 days a week for 3 consecutive weeks. The control group received common treatment of aspirin gargles and betamethasone oral drops. A decrease of pain was observed in 80% of patients in the Placentrex group compared with 36.7% in the control group. The progression to grade 3 radiation mucositis was 40% in the Placentrex group compared with 86.7% in the control group. Improvement in swallowing difficulty was seen in 93% of patients in the Placentrex group compared with 15% of patients in the control group. Human placental extract thus reduced the symptoms of mucositis, and the study group had less severe mucositis than standard treatment group.[39] Some studies have suggested that anti-inflammatory effect of this drug was caused by membrane stabilization and reduction of adenosine triphosphate (ATP) synthesis.[76] Investigations about the effect of human placental extract on chemotherapy- and radiotherapy-induced oral mucositis are not sufficient, and the results of this research should to be confirmed by other studies in the future.

Honey and Bee Products

Honey and propolis (bee glue) have been used in the management of mucositis.[25] Golder[77] indicated that propolis is beneficial for the treatment of mucositis induced by radiation therapy. Honey has been used to heal burns, surgical wounds, and oral infections because of its antibacterial and analgesic agents and epithelialization boosting effect.[78,79] The efficacy of pure natural honey for the treatment of mucositis was reported in patients under radiation therapy and/or chemotherapy in several clinical trials. We have found many clinical trials associated with the preventive and therapeutic effects of honey and its relative products for management of radiation- and chemotherapy-induced mucositis. In a randomized single blind clinical trial, 40 patients who suffered from head and neck cancer and required radiation to the oropharyngeal mucosa were randomly divided into 2 groups. Patients received 20 mL pure natural honey from bees fed on thyme and astragale in the Alborz Mountains of Iran, 15 minutes before, then 20 mL doses again at 15 minutes and 6 hours after radiation therapy. They washed their mouths with honey and engorged slowly to cover the oral and pharyngeal mucosa. A significant reduction in mucositis in patients treated with honey was observed as compared with controls.[24] The same results in reduction of mucositis were observed in another study, in which 40 patients received topical applications of 20 mL pure honey before and after radiation therapy.[25] In a clinical trial, the effect of natural honey and 0.15% benzydamine hydrochloride on onset and severity of radiation mucositis was assessed and compared with control. The patients were randomized into three groups of 20 patients. Group 1 patients received topical application of natural honey; groups 2 and 3 received topical application of 0.15% benzydamine hydrochloride and 0.9% normal saline, respectively. The onset of mucositis and the severity of mucositis were graded during the course of the radiotherapy and 2 weeks after radiotherapy. A significant reduction of mucositis in patients treated with honey was compared with 0.15% benzydamine hydrochloride, 0.9% normal saline applied to patients was observed. The differences between the groups were statistically significant.[80] Results of other studies showed that prophylactic use of natural honey was effective in reduction of mucositis subjective symptoms from radiotherapy and/or chemotherapy. Honey reduces wound pain by postponing tissue oxygenation through blocking exposure of the damaged mucosa to oxygen.[3,22-24] Biswal et al[25] suggested that the effectiveness of honey on wound healing might be because of the hygroscopic nature of honey, its viscosity, its acidic pH, which prevents bacteria growth on the mucosa, inhibin (hydrogen peroxide) converted from glucose oxidase and gluconic acid, enzymes which probably are growth factors and tissue nutritive minerals and vitamins that help repair the tissue directly.

A randomized and uncontrolled study was done in 2008. They swished and swallowed 20 mL honey from bees fed primarily on Egyptian clover (*Trifolium alexandrinum*) 3 times per day. Only 3 (15 %) of the honey-treated group had RTOG ≥3 mucositis as compared with 12 (60%) in the control group.[23] A double-blind randomized placebo-controlled trial investigation was done by Hawley et al[26] in 2014. In this study, 81 patients were randomized to swish, hold, and swallow either 5 mL of irradiated organic manuka honey or a placebo gel, 4 times a day throughout radiation treatment, plus 7 more days. Sixty-two percent of subjects received concurrent chemotherapy. They reported that manuka honey was not tolerated well by patients and did not have a significant impact on the severity of radiation-induced oral mucositis.[26]

There are a number of probable reasons why the results of different studies might be different, including differences in the source of honey, patient characteristics, study design, anticancer treatment protocols, and oral mucositis assessment tools.

In 2012, Song et al[81] reported a systematic and meta-analysis review on the use of honey for reduction of radiation-induced oral mucositis. They concluded that the results of clinical trials are promising and further studies are needed to strengthen the current evidence prior to a firm clinical recommendation being given,[81] and Van den Wyngaert[82] confirmed it.

Recent studies have reported that Iranian propolis has flavonoids and phenolic compounds and can manage the radiation-induced mucositis. It found that it postpones the appearance of lesions and substantially reduces the severity of mucositis.[24,83] Because honey is not a generic drug, description of the composition of honey is not easy. The components depend on the plants of the geographical region where honeybees collect pollen. Honey naturally includes <20% water, vitamins, enzymes, proteins, and a high concentration of sugars. Invertase, diastase, and glucose oxidase are the honey enzymes. It is not clear whether the antimicrobial activity of honey is the result of its delay of hydrogen peroxide on exposure to catalase or the result of its high osmolarity.[22]

Some researchers are worried about using honey in irradiated patients. Their concern is that the topical use of honey in the oral mucosa of patients with low motivation for oral hygiene could act in synergy with the other risk factors for radiation-related caries. Honey can be highly cariogenic and certainly should be avoided in certain patients undergoing radiotherapy.[84]

Conclusion

Radiation- and anticancer treatment–induced oral mucositis are severe complications in patients with head and neck cancers. Inflammation and ROS are cellular mechanisms

related to mucositis. Natural products such as herbal medicine have potential to reduce oral mucositis in patients. Many clinical trials have been performed to assess natural products for treatment of mucositis, and the results have been promising. Nowadays, a standard preventive agent for mucositis is not available from natural products that are well documented with several multicenter clinical trials. These natural products were mostly evaluated only once, with small number of patients. Honey has been widely assessed in clinical studies. Several clinical studies support honey for reduction of mucositis in patients during radiation therapy, although a recent trial found no effect of honey. There is, however, a lack of strong evidence for natural products to prevent or treat oral mucositis. Properly designed clinical trials are required to understand natural product efficacy for controlling radiotherapy- and chemotherapy-induced oral mucositis.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. *Cancer Epidemiol Biomarkers Prev*. 2005;14:467-475.
2. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys*. 1995;31:1341-1346.
3. Rodríguez-Caballero A, Torres-Lagares D, Robles-García M, Pachón-Ibáñez J, Gonzalez-Padilla D, Gutierrez-Perez J. Cancer treatment-induced oral mucositis: a critical review. *Int J Oral Maxillofac Surg*. 2012;41:225-238.
4. Levi F, Maisonneuve P, Filiberti R, La Vecchia C, Boyle P. Cancer incidence and mortality in Europe. *Sozi Präventivmed*. 1989;34(suppl 2):S3-S83.
5. Hosseinimehr SJ. Trends in the development of radioprotective agents. *Drug Discov Today*. 2007;12:794-805.
6. Clarkson JE, Worthington HV, Eden OB. Interventions for treating oral mucositis for patients with cancer receiving treatment. *Cochrane Database Syst Rev*. 2007;(2):CD001973.
7. Rosenthal DI, Trotti A. Strategies for managing radiation-induced mucositis in head and neck cancer. *Semin Radiat Oncol*. 2009;19:29-34.
8. Kostler WJ, Hejna M, Wenzel C, Zielinski CC. Oral mucositis complicating chemotherapy and/or radiotherapy: options for prevention and treatment. *CA Cancer J Clin*. 2001;51:290-315.
9. Su CK, Mehta V, Ravikumar L, et al. Phase II double-blind randomized study comparing oral aloe vera versus placebo to prevent radiation-related mucositis in patients with head-and-neck neoplasms. *Int J Radiat Oncol Biol Phys*. 2004;60:171-177.
10. Trotti A, Bellm LA, Epstein JB, et al. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. *Radiother Oncol*. 2003;66:253-262.
11. Scully C, Epstein J, Sonis S. Oral mucositis: a challenging complication of radiotherapy, chemotherapy, and radiochemotherapy: part 1. Pathogenesis and prophylaxis of mucositis. *Head Neck*. 2003;25:1057-1070.
12. Bardy J, Molassiotis A, Ryder WD, et al. A double-blind, placebo-controlled, randomised trial of active manuka honey and standard oral care for radiation-induced oral mucositis. *Br J Oral Maxillofac Surg*. 2012;50:221-226.
13. Sonis S. Mucositis as a biological process: a new hypothesis for the development of chemotherapy-induced stomatotoxicity. *Oral Oncol*. 1998;34:39-43.
14. Bensadoun R-J, Le Page F, Darcourt V, et al. Radiation-induced mucositis of the aerodigestive tract: prevention and treatment. MASCC/ISOO mucositis group's recommendations [in French]. *Bull Cancer*. 2006;93:201-211.
15. Debatin K-M. Cytotoxic drugs, programmed cell death, and the immune system: defining new roles in an old play. *J Natl Cancer Inst*. 1997;89:750-751.
16. Martin M. Irradiation mucositis: a reappraisal. *Eur J Cancer Part B Oral Oncol*. 1993;29:1-2.
17. Eissner G, Lindner H, Behrends U, et al. Influence of bacterial endotoxin on radiation-induced activation of human endothelial cells in vitro and in vivo: protective role of IL-101. *Transplantation*. 1996;62:819-827.
18. Chi K-H, Chen C-H, Chan W-K, et al. Effect of granulocyte-macrophage colony-stimulating factor on oral mucositis in head and neck cancer patients after cisplatin, fluorouracil, and leucovorin chemotherapy. *J Clin Oncol*. 1995;13:2620-2628.
19. Eilers J, Million R. Prevention and management of oral mucositis in patients with cancer. *Semin Oncol Nurs*. 2007;23:201-212.
20. Epstein JB, Epstein JD, Epstein MS, Oien H, Truelove EL. Management of pain in cancer patients with oral mucositis: follow-up of multiple doses of doxepin oral rinse. *J Pain Symptom Manage*. 2007;33:111-114.
21. Biswal BM. Current trends in the management of oral mucositis related to cancer treatment. *Malays J Med Sci*. 2008;15(3):4-13.
22. Khanal B, Baliga M, Uppal N. Effect of topical honey on limitation of radiation-induced oral mucositis: an intervention study. *Int J Oral Maxillofac Surg*. 2010;39:1181-1185.
23. Rashad U, Al-Gezawy S, El-Gezawy E, Azzaz A. Honey as topical prophylaxis against radiochemotherapy-induced mucositis in head and neck cancer. *J Laryngol Otol*. 2009;123:223-228.
24. Motallebnejad M, Akram S, Moghadamnia A, Moulana Z, Omidi S. The effect of topical application of pure honey on radiation-induced mucositis: a randomized clinical trial. *J Contemp Dent Pract*. 2008;9(3):40-47.

25. Biswal BM, Zakaria A, Ahmad NM. Topical application of honey in the management of radiation mucositis. A preliminary study. *Support Care Cancer*. 2003;11:242-248.
26. Hawley P, Hovan A, McGahan CE, Saunders D. A randomized placebo-controlled trial of manuka honey for radiation-induced oral mucositis. *Support Care Cancer*. 2014;22:751-761.
27. Tomaževič T, Jazbec J. A double blind randomised placebo controlled study of propolis (bee glue) effectiveness in the treatment of severe oral mucositis in chemotherapy treated children. *Complement Ther Med*. 2013;21:306-312.
28. Raeessi MA, Raeessi N, Panahi Y, et al. "Coffee plus honey" versus "topical steroid" in the treatment of chemotherapy-induced oral mucositis: a randomised controlled trial. *BMC Complement Altern Med*. 2014;14:293.
29. Renani HA, Keikhai B, Mahani HG, Latifi M. Effect of chamomile mouthwash for preventing chemotherapy-induced ostomatitis in children. *J Mazandaran Univ Med*. 2012;21(86):19-25.
30. Mazokopakis E, Vrentzos G, Papadakis J, Babalis D, Ganotakis E. Wild chamomile (*Matricaria recutita* L.) mouthwashes in methotrexate-induced oral mucositis. *Phytomedicine*. 2005;12:25-27.
31. Braga FT, Santos AC, Bueno PC, et al. Use of *Chamomilla recutita* in the prevention and treatment of oral mucositis in patients undergoing hematopoietic stem cell transplantation: a randomized, controlled, phase II clinical trial. *Cancer Nurs*. 2015;38:322-329.
32. Fidler P, Loprinzi CL, O'Fallon JR, et al. Prospective evaluation of a chamomile mouthwash for prevention of 5-FU-induced oral mucositis. *Cancer*. 1996;77:522-525.
33. Ashktorab T, Yazdani Z, Mojab F, Majd H, Madani H. Preventive effects of an oral rinse peppermint essence on chemotherapy-induced oral mucosistis. *Koomesh*. 2010;12:8-13.
34. Puataweepong P, Dhanachai M, Dangprasert S, et al. The efficacy of oral Aloe vera juice for radiation induced mucositis in head and neck cancer patients: a double-blind placebo-controlled study. *Asian Biomed*. 2009;3:375-382.
35. Babaee N, Moslemi D, Khalilpour M, et al. Antioxidant capacity of *Calendula officinalis* flowers extract and prevention of radiation induced oropharyngeal mucositis in patients with head and neck cancers: a randomized controlled clinical study. *Daru*. 2013;21:18.
36. Al-Jaf HNHF, Ahmed KM, Najmuldeen HH. A microbiological study for evaluating olive leaf extract as a new topical management for oral mucositis following chemotherapy [abstract]. *Bull UASVM*. 2011;1(68):391
37. Ismail AA, Behkite AA, Badria FM, Guemei AA. Licorice in prevention of radiation induced mucositis. *J Clin Oncol*. 2004;22:8268.
38. Elad S, Meidan I, Sellam G, et al. Topical curcumin for the prevention of oral mucositis in pediatric patients: case series. *Altern Ther Health Med*. 2013;19(3):21-24.
39. Kaushal V, Verma K, Manocha S, Hooda H, Das B. Clinical evaluation of human placental extract (Placentrex) in radiation-induced oral mucositis. *Int J Tissue React*. 2000;23: 105-110.
40. You WC, Hsieh CC, Huang JT. Effect of extracts from indigowood root (*Isatis indigotica* Fort.) on immune responses in radiation-induced mucositis. *J Alter Complement Med*. 2009;15:771-778.
41. Matceyevsky D, Hahoshen NY, Asna N, Khafif A, Ben-Yosef R. Assessing the effectiveness of Dead Sea products as prophylactic agents for acute radiochemotherapy-induced skin and mucosal toxicity in patients with head and neck cancers: a phase 2 study. *Chemotherapy*. 2007;9:12.
42. Tanideh N, Tavakoli P, Saghiri MA, et al. Healing acceleration in hamsters of oral mucositis induced by 5-fluorouracil with topical *Calendula officinalis. Oral Surg Oral Med Oral Pathol Oral Radiol*. 2013;115:332-338.
43. Salvo N, Barnes E, van Draanen J, et al. Prophylaxis and management of acute radiation-induced skin reactions: a systematic review of the literature. *Curr Oncol*. 2010;17:94-112.
44. Chandran PK, Kuttan R. Effect of *Calendula officinalis* flower extract on acute phase proteins, antioxidant defense mechanism and granuloma formation during thermal burns. *J Clin Biochem Nutr*. 2008;43(2):58-64.
45. Loke WM, Proudfoot JM, Stewart S, et al. Metabolic transformation has a profound effect on anti-inflammatory activity of flavonoids such as quercetin: lack of association between antioxidant and lipoxygenase inhibitory activity. *Biochem Pharmacol*. 2008;75:1045-1053.
46. Duran V, Matic M, Jovanovć M, et al. Results of the clinical examination of an ointment with marigold (*Calendula officinalis*) extract in the treatment of venous leg ulcers. *Int J Tissue React*. 2004;27:101-106.
47. Anil S, Beena V. Oral submucous fibrosis in a 12-year-old girl: case report. *Pediatr Dent*. 1993;15:120-122.
48. Li TSC. *Medicinal Plants: Culture, Utilization and Phytopharmacology*. Boca Raton, FL: CRC Press; 2000:66-120.
49. Carl W, Emrich LS. Management of oral mucositis during local radiation and systemic chemotherapy: a study of 98 patients. *J Prosthet Dent*. 1991;66:361-369.
50. Avallone R, Zanoli P, Puia G, Kleinschnitz M, Schreier P, Baraldi M. Pharmacological profile of apigenin, a flavonoid isolated from *Matricaria chamomilla. Biochem Pharmacol*. 2000;59:1387-1394.
51. Plevova P. Prevention and treatment of chemotherapy- and radiotherapy-induced oral mucositis: a review. *Oral Oncol*. 1999;35:453-470.
52. Kührer I, Kuzmits R, Linkesch W, Ludwig H. Topical PGE2 enhances healing of chemotherapy associated mucosal lesions. *Lancet*. 1986;327:623.
53. Babcock AS. *The Effects of Indirubin Derivatives on Gene Expression and Cellular Functions in the Murine Cell Line, RAW 264.7* [dissertation]. Clemson, South Carolina: Clemson University; 2008.
54. Segal R, Louise P. Warfarin interaction with *Matricaria chamomilla. CMAJ*. 2006;174:1281-1282.
55. West DP, Zhu YF. Evaluation of aloe vera gel gloves in the treatment of dry skin associated with occupational exposure. *Am J Infect Control*. 2003;31:40-42.
56. Visuthikosol V, Chowchuen B, Sukwanarat Y, Sriurairatana S, Boonpucknavig V. Effect of aloe vera gel to healing of burn wound a clinical and histologic study. *J Med Assoc Thai*. 1995;78:403-409.
57. Williams MS, Burk M, Loprinzi CL, et al. Phase III double-blind evaluation of an aloe vera gel as a prophylactic agent for

radiation-induced skin toxicity. *Int J Radiat Oncol Biol Phys*. 1996;36:345-349.
58. Heggie S, Bryant GP, Tripcony L, et al. A phase III study on the efficacy of topical aloe vera gel on irradiated breast tissue. *Cancer Nurs*. 2002;25:442-451.
59. Barrantes E, Guinea M. Inhibition of collagenase and metalloproteinases by aloins and aloe gel. *Life Sci*. 2003;72: 843-850.
60. Wynn RL. Aloe vera gel: update for dentistry. *Gen Dent*. 2005;53:6-9.
61. Yagi A, Kabash A, Okamura N, Haraguchi H, Moustafa S, Khalifa T. Antioxidant, free radical scavenging and anti-inflammatory effects of aloesin derivatives in Aloe vera. *Planta Med*. 2002;68:957-960.
62. Choi S, Kim KW, Choi JS, et al. Angiogenic activity of beta-sitosterol in the ischaemia/reperfusion-damaged brain of Mongolian gerbil. *Planta Med*. Apr 2002;68(4):330-335.
63. Posadzki P, Leala W, Edzard E. Herb-drug interactions: an overview of systematic reviews. *Br J Clin Pharmacol*. 2013;75:603-618.
64. Gilbert KG, Maule HG, Rudolph B, et al. Quantitative analysis of indigo and indigo precursors in leaves of Isatis spp. and *Polygonum tinctorium. Biotechnol Prog*. 2004;20: 1289-1292.
65. Gardner Z, Michael M. *American Herbal Products Association's Botanical Safety Handbook*. Boca Raton, FL: CRC Press; 2013.
66. Cassileth BR, Lucarelli CD. *Herb-Drug Interactions in Oncology*. Hamilton, Ontario, Canada: BC Dekker; 2003.
67. Lis-Balchin M. *Aromatherapy Science: A Guide for Healthcare Professionals*. London, England: Pharmaceutical Press; 2006.
68. Lis-Balchin M, Hart S, Deans S. Pharmacological and antimicrobial studies on different tea-tree oils (*Melaleuca alternifolia, Leptospermum scoparium* or Manuka and *Kunzea ericoides* or Kanuka), originating in Australia and New Zealand. *Phytotherapy Res*. 2000;14:623-629.
69. Maddocks-Jennings W, Wilkinson JM, Cavanagh HM, Shillington D. Evaluating the effects of the essential oils *Leptospermum scoparium* (manuka) and *Kunzea ericoides* (kanuka) on radiotherapy induced mucositis: a randomized, placebo controlled feasibility study. *Eur J Oncol Nurs*. 2009;13:87-93.
70. Reichling J, Koch C, Stahl-Biskup E, Sojka C, Schnitzler P. Virucidal activity of a β-triketone-rich essential oil of *Leptospermum scoparium* (manuka oil) against HSV-1 and HSV-2 in cell culture. *Planta Med*. 2005;71:1123-1127.
71. Porter NG, Wilkins AL. Chemical, physical and antimicrobial properties of essential oils of *Leptospermum scoparium* and *Kunzea ericoides. Phytochemistry*. 1999;50:407-415.
72. Kim EH, Rhee GJ. Activities of ketonic fraction from *Leptospermum scoparium* alone and synergism in combination with some antibiotics against various bacterial strains and fungi. *J Pharm Soc Korea*. 1999;43:716-728.
73. Häberlein H, Tschiersch KP. 2,5-Dihydroxy-7-methoxy-6, 8-dimethylflavan-3-one a novel flavonoid from *Leptospermum scoparium*: in vitro affinity to the benzodiazepine binding site of the GABAA receptor-chloride channel complex. *Pharmazie*. 1994;49:860.
74. Gravett P. Aromatherapy treatment of severe oral mucositis. *Int J Aromather*. 2000;10:52-53.
75. Ngeow WC, Chai WL, Zain RB. Management of radiation therapy-induced mucositis in head and neck cancer patients. Part II: supportive treatments. *Oncol Rev*. 2008;2:164-182.
76. Banerjee K, Bishayee A, Chatterjee M. Anti-inflammatory effect of human placental extract: a biochemical mechanistic approach. *Riv Eur Sci Med Farmacol*. 1991;14:361-366.
77. Golder W. Propolis. The bee glue as presented by the Graeco-Roman literature [in German]. *Wurzbg Medizinhist Mitt*. 2003;23:133-145.
78. Alam F, Islam MA, Gan SH, Khalil MI. Honey: a potential therapeutic agent for managing diabetic wounds. *Evid Based Complement Alternat Med*. 2014;2014:169130.
79. Belcher J. Dressings and healing with honey. *Br J Nurs*. 2014;23(6):S22.
80. Jayachandran S, Balaji N. Evaluating the effectiveness of topical application of natural honey and benzydamine hydrochloride in the management of radiation mucositis. *Indian J Palliat Care*. 2012;18:190-195.
81. Song JJ, Twumasi-Ankrah P, Salcido R. Systematic review and meta-analysis on the use of honey to protect from the effects of radiation-induced oral mucositis. *Adv Skin Wound Care*. 2012;25:23-28.
82. Van den Wyngaert T. Topical honey application to reduce radiation-induced oral mucositis: a therapy too sweet to ignore? *J Evid Based Dent Pract*. 2012;12:203-205.
83. Ghassemi L, Zabihi E, Mahdavi R, Seyedmajidi M, Akram S, Motallebnejad M. The effect of ethanolic extract of propolis on radiation-induced mucositis in rats. *Saudi Med J*. 2010;31:622-626.
84. Santos-Silva AR, Rosa GB, Eduardo CP, Dias RB, Brandao TB. Increased risk for radiation-related caries in cancer patients using topical honey for the prevention of oral mucositis. *Int J Oral Maxillofac Surg*. 2011;40:1335-1336.