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Review

Medicinal Plants for Chemoradiotherapy-Induced Oral Mucositis: A Review of Clinical Studies

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Abstract

Oral mucositis is one of the severe complications of chemoradiotherapy in patients with cancer. Current treatments such as artificial saliva, antimicrobial agents, and local analgesics could not fully satisfy patients and thus, further investigations are essential. Medicinal plants, containing a wide variety of phytochemicals may be suitable suggestions to be investigated for the management of this complication in cancer patients. To review current literature regarding the effectiveness of herbal preparations in chemoradiotherapy-induced oral mucositis, electronic databases including PubMed, Scopus, and Cochrane library were searched using "mucositis" or "xerostomia" or "dry mouth" in the title/abstract, and "plant" or "extract" or "herb" or "phytochemical" keywords in the whole text up to August 2017. A total of 14 clinical trials were finally included. *Aloe vera* (aloe), *Matricaria chamomilla* (German chamomile), *Malva sylvestris* (high mallow), and *Alcea digitata* (hollyhock) are the most evident medicinal plants useful for the management of oral mucositis and *xerpstomia*. Mucilage, flavonoids, flavonolignans and terpenoids are the active ingredients which show soothing effect on the lesions of oral cavity. Herbal preparations could reduce the duration of ulceration, ulcer severity, pain and use of analgesics, as well as dysphagia and the need for total parenteral nutrition. In conclusion, medicinal plants are capable of improving chemoradiotherapy-induced oral mucositis and xerostomia in patients with cancer. Future well-designed clinical trials are required for further confirmation of the safety and efficacy of medicinal plants for the management of oral mucositis.

Keywords: chemotherapy, radiotherapy, tumor, medicinal plant, herbal medicine

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Introduction

Today, cancer is a global concern since a numerous number of people are dying each year due to different types of malignancies which imposes a heavy burden to several countries all over the world. Cancer is the final result of a series of complicated cellular and subcellular malfunctions which destroys cell cycle check points during proliferation and produce a mass of abnormal cells with uncontrollable proliferation rate [1].

Treatment of cancer can be categorized into chemotherapy, radiotherapy, surgery, stem cell therapy and immunotherapy, utilized individually or in combination, all of which are accompanied with severe adverse effects which may sometime make patients quit their treatment [2]. One of the most unpleasant side effects of chemotherapy or radiotherapy is oral mucositis.

Oral mucositis is caused due to the damage to the epithelial cells of the oral cavity which is especially common in radiotherapy of head and neck region. The incidence of oral mucositis varies from 40% in patients under radiotherapy for head and neck cancer, to 90% in those treated with concomitant chemo- and radiotherapy [3]. Unpleasant taste in the mouth, xerostomia (dry mouth), erythema, painful lesions in the oral cavity, and, in severe cases, disability to swallow and need for total parenteral nutrition (TPN), as well as secondary infections are the consequences of chemoradiotherapy-induced mucositis. These adverse effects can lead to patient hospitalization, as well as delay in receiving the next dose of chemoradiotherapy which increases the risk of tumor recurrence [4]. Current available treatments for the management of chemoradiotherapy-induced mucositis include artificial saliva, antimicrobial mouthwashes (chlorhexidine), anti-inflammatory and analgesic agents (benzydamine), sucralfate, and low-energy laser therapy; however, a significant number of patients are not fully satisfied with the effectiveness of these treatments and thus, further investigations is required to find better treatment options [4].

Medicinal plants have long been used for the treatment of different types of wounds, ulcers, inflammation, and other types of tissue damage [5-7]. Plant secondary metabolites have demonstrated beneficial effects for the management of different complications in patients with cancer [8]. Several categories of phytochemicals have been identified which are capable of showing beneficial effects for the treatment of tissue injuries [9] and thus, may be suitable choices for the management of lesions in the oral cavity.

The aim of the present review is to summarize current clinical evidence regarding the efficacy of medicinal plants for the management of chemoradiotherapy-induced oral mucositis and xerostomia.

Search strategy

Electronic databases including PubMed, Scopus, and Cochrane library were searched from the date of inception until August 2017 using the keywords “mucositis” or “xerostomia” or “dry mouth” in the title/abstract, and “plant” or “extract” or “herb” or “phytochemical” in the whole text to find clinical trials evaluating the effectiveness of herbal preparations in

chemotherapy/ radiotherapy-induced mucositis. Only articles with English full-text were included in this study. Also, polyherbal preparations in which the identity of the ingredients was not clearly defined, as well as the studies in which the scientific names of the plants were not mentioned were excluded from our study. References of the finally included papers were also reviewed to find further relevant studies. Final included articles were screened regarding the scientific name of the plant, dosage form, administered dose, duration of treatment with herbal material, design of the study, sample size and patients' characteristics, concomitant treatments for mucositis, type of control drug, and outcomes of the trial, and the obtained data are summarized in the form of a table (Table 1).

Table 1: Clinical trials on the effectiveness of medicinal plants for chemoradiotherapy-induced oral mucositis and xerostomia

Plant name and dosage	Dosage form	Study design	Control	Jadad score	Concomitant therapy for xerostomia and mucositis	Duration	Outcome	Reference
Achillea millefolium + routine mouthwash (15 ml, QID)	Mouthwash	Randomized controlled trial in 56 cancer patients with chemotherapy-induced oral mucositis	Routine mouthwash (dexamethasone + lidocaine + sucralfate + diphenhydramine)	5	Dexamethasone	14 days	↓Severity of mucositis	[12]
Aloe vera gel (80%, 15 ml, TDS)	Oral juice	Randomized, double-blind, placebo-controlled trial in 61 H & N cancer patients with oral mucositis	Placebo	5	_	During 3-4 weeks of radiotherapy and continuing to the end of the 8th week follow-up	↓Incidence of severe mucositis, percentage of weight loss and radiation breaks due to mucositis (NS) No effect on the onset of severe mucositis	[18]
Aloe vera gel (94/5%, 20 ml, QID)	Oral juice	Randomized, double-blind, placebo-controlled trial in 58 H & N cancer patients with oral mucositis	Placebo	5	Baking soda mouth rinse, swishing and swallowing Benadryl and nystatin, viscous lidocaine	Throughout radiotherapy courses	No effect on the severity or occurrence of mucositis, quality of life, weight loss, treatment breaks, and oral infection	**[16]**

Aloe vera gel (PRN)	Gel	Randomized, crossover trial in 120 patients with xerostomia after radiotherapy in the H & N region	Glandosane® spray (containing carmellose), Saliva medac spray (mucin extracted from pig stomach)	2	_	1 week	↓Frequency of saliva substitute use, saliva viscosity, xerostomia at rest or while speaking, ↑Sleep quality, No effect on difficulties with eating, need to drink while eating, or impaired sense of taste Best efficacy: Aloe gel Best taste: Carmellose spray	[17]
Calendula officinalis flower (2%, 5 ml, BID)	Mouthwash gel	Randomized, double-blind, placebo-controlled trial in 40 H & N cancer patients with oral mucositis	Placebo	4	None	7 week	↓OMAS score	[21]
Isatis indigotica (0.5 g root powder in 30 ml double distilled water, before each meal)	Gargle and swallow	Randomized, placebo-controlled trial in 20 H & N cancer patients with oral mucositis	Normal saline	3	_	7 week	↓Severity of maximal mucositis, anorexia, swallowing difficulties, IL-6 ↓Weight loss (NS) ↑IL-1β (only by the end of the 3rd week)	[22]
Leptospermum scoparium + Kunzea ericoides (1:1 essential oils, 2 drops in 10-15 ml warm tap water, up to 5 times)	Gargle and swallow solution	Randomized, double-blind, placebo-controlled trial in 19 H & N cancer patients with oral mucositis	Water (as placebo), standard care (as active control)	3	_	Throughout radiotherapy courses	↑Delay in mucositis development, Prevention of weight loss, ↓Pain & analgesics use	[25]
Malva sylvestris + Alcea digitata (1:1, 4 g sachet, TDS)	Suspension	Randomized, controlled trial in 62 H & N cancer patients with xerostomia	Artificial saliva (Hypozalix)	2	None	4 week	↓VAS & degree of xerostomia	[30]
Malva sylvestris + Alcea digitata (1:1, 4 g sachet, TDS)	Suspension	Randomized, open-label, controlled trial in 60 H & N cancer patients with xerostomia	Artificial saliva (Hypozalix)	3	None	4 week	↓EORTC QLQ-H&N 35 scores	[31]
Matricaria chamomilla (Chamomilla recutita) (0.5%, 1%, 2%, 10 ml, BID)	Mouthwash	Randomized, phase II trial in 40 patients undergoing allogenic HSCT with oral mucositis	Standard care alone	5	Standard care	From the first day of conditioning until oral mucosa was reestablished or the granulocyte count exceeded 500 mm3 for 3 consecutive days in patients without mucositis	↓Severity, duration, and incidence of mucositis, ↓analgesics and TPN, Best results observed with 1%	[33]

Matricaria chamomilla (Matricaria recutita) + Mentha piperita (1% in ethanol, 1:50 dilution in water, TDS)	Mouthwash	Randomized, double blind, placebo controlled trial in 60 patients undergoing hematopoietic stem cell transplantation with oral mucositis	Placebo	5	In severe cases: morphine, nystatin oral suspension, Diphenhydramine + lidocaine + alumi-	First day of chemotherapy until discharge	↓Mucositis duration and severity, but not onset, ↓Pain, dryness, dysphagia, & analgesics use	[34]
Phoenix dactylifera pollen (2 g in 125 ml water, nightly)	Suspension	Controlled trial in 20 H & N cancer patients with oral mucositis	Miconazole oral gel, rebamipide, local and oral analgesics (PRN)	0	Standard care was allowed	6 weeks	↓OMAS, severity and incidence of mucositis, ↑ability to swallow	[37]
Rhodiola algida (200 ml, 50 mg/l)	Oral solution	Randomized controlled trial (preclinical trial) in 130 breast cancer patients with oral mucositis	Honey bee water	1	Chlorhexidine	14 days after each cycle of chemotherapy	↓OMAS ↑WBC and neutrophils	[40]
Silybum marianum (140 mg, TDS)	Tablet	Randomized, double-blind, placebo-controlled trial in 27 H & N cancer patients with oral mucositis	Placebo	5	-	6 weeks	↓NCI-CTC and WHO oral mucositis grading score, severity of mucositis ↑Delay in mucositis development	[42]

Results

Total of 14 papers met the inclusion criteria (Table 1).

Achillea millefolium L. (Yarrow)

A. millefolium is a perennial plant from the family Asterceaceae [10] which has been widely studied due to its wound-healing, anti-inflammatory, and antiulcer activities. The most important secondary metabolites of yarrow include flavonoids and sesquiterpenoids, as well as different types of monoterpenes in the essential oil [11].

In a clinical trial in patients with chemotherapy-induced oral mucositis, *A. millefolium* mouthwash was mixed with a routine extemporaneous analgesic mouthwash to a 1:1 ratio in the experimental group, which was compared to the routine mouthwash as control. While the experimental group sowed a reduction in the severity of mucositis during the 2-weeks treatment period, patients in control group had an increase in the mean severity score of mucositis [12].

Aloe vera (L.) Burm. f. (Aloe)

Aloe is a plant from the family Xanthorrhoeaceae [10] which is mostly found in hot and dry

climates. The leaves, which are commercial part of the plant, are divided into two parts: the green rind, containing anthraquinones which act as laxatives, and the parenchyma composed of polysaccharide structures which contain a high amount of water and is often used in cosmeceutical industries [13]. Aloe gel (parenchyma) has been widely investigated as a soothing agent for different types of injuries of skin and oral mucosa and has shown promising effects in several cases [14, 15].

In a group of patients with stage II-IVM0 head and neck cancer, oral aloe swish and swallow solution or a taste-matched placebo was administered four times a day from the first day of their radiotherapy. By the end of the study, there were no significant difference in any of the assessed parameters including the severity of mucositis and quality of life [16]. Another study with a prospective crossover design compared the effect of a commercial oral aloe gel in patients suffered from xerostomia more than four weeks after radiotherapy, with three other saliva substituents including carmellose spray, rape oil, and a mucin spray. Amongst all evaluated materials, aloe gel showed the best efficacy for the management of xerostomia and carmellose spray had the least effectiveness; however, most patients chose carmellose as the preferred preparation due to its pleasant taste. All products improved the xerostomia compared with baseline values; though, none of the interventions could improve sensation of taste or dysphagia [17]. Another placebo-controlled trial compared the effect of aloe juice with placebo during radiotherapy in patients with stage II-IVM0. Despite no difference in the onset of mucositis, the number of patients with mucositis were significantly lower in the intervention group. Weight loss and radiation breaks was observed to a fewer extent in the aloe treated patients; however, these differences were not statistically significant [18]. Considering the positive results of the two latter studies, negative results reported by Su et al. might be explained due to the short type of aloe juice exposure to the damaged area which shows the importance of type of formulation in the final obtained results.

Calendula officinalis L. (Marigold)

C. officinalis from the family Asteraceae is widely cultivated as an ornamental plant [10]. Several pharmacological activities have been attributed to this plant including anti-inflammatory and wound healing properties based on which several medicinal and cosmetic topical preparations are introduced into the market [19]. In addition, *C. officinalis* is considered as a safe topical treatment in radiation-induced dermatitis [20].

In 40 patients with head and neck cancer receiving telecobalt radiotherapy, *C. officinalis* flower gel was administered from the first day of radiotherapy. By the end of the second week, the intensity of oral mucositis was significantly lower in intervention group compared with the placebo. Patients in the intervention group needed no further treatment for mucositis, nor did they need radiotherapy interruption because of mucositis. Also, three patients in *C. officinalis* group did not develop mucositis during the whole treatment [21].

Isatis indigotica Fort. (Indigowood)

I. indigotica is a plant from Brassicaceae family and its root is widely used in traditional Chinese medicine (TCM) remedies for the diseases caused by elevation of heat in the blood [22]. The plant contains several different classes of phytochemicals including alkaloids [23] and polysaccharides [24].

A group of patients under treatment with radiotherapy or chemoradiotherapy, were instructed to gargle an aqueous solution of *I. indigotica* root powder for 3 min and then swallow, before each meal. In comparison to the control group who only received normal saline, patients in the intervention group had lower rate of severe mucositis, anorexia, and dysphagia. Regarding the systemic effects, *I. indigotica* could reduce weight loss and the serum level of the pro-inflammatory cytokine interleukin-6 (IL-6). Another pro-inflammatory cytokine, IL-1β level, was slightly higher in the intervention group; however, this difference was only significant by the end of the third week [22].

Leptospermum scoparium J.R. Forst. & G. Forst. (Manuka) and Kunzea ericoides (A. Rich.) Joy Thomps. (Kanuka)

In a controlled clinical trial, patients under radiotherapy for head and neck area were treated with a 1:1 mixture of kanuka and manuka essential oils in water. The preparation was first gargled, then swallowed by patients to reach all areas prone to mucositis. Results showed that patients in the intervention group had delayed mucositis and less need to use analgesics in comparison to placebo-treated and untreated patients [25].

Malva sylvestris L. (high mallow) + Alcea digitata (Boiss) Alef (hollyhock)

These two plants are both members of the family Malvaceae that are widely grown at many parts of the world. All parts of the plants, especially flowers and roots, are rich in mucilaginous compounds which produce a jelly-like substance in the presence of water and thus, is traditionally used for the treatment of different types of dry coughs, as well as constipation [27, 28]. In the view of Persian medicine, both plants have cold and wet nature and can be used for the treatment of diseases with hot/ dry pathology [29].

In a controlled clinical trial in 62 patients with radiotherapy-induced xerostomia, a mixture of the flowers of *M. sylvestris* and *A. digitata* powder were prepared and patients in the intervention group were instructed to mix each sachet with water and swallow the whole mixture. Patients in the control group received Hypozalix (a commercial artificial saliva). Based on the assessments using visual analogue scale (VAS), the herbal preparation could significantly improve the intensity of xerostomia in comparison to the artificial saliva [30]. Additionally, Heydarirad et al. (2017) reported a significant improvement in the quality of life of patients using the same preparation in comparison to Hypozalix [31].

Matricaria chamomilla L. (German chamomile)

*M. chamomilla (*Syn*: Chamomilla recutita, Matricaria recutita)* is one of the well-known medicinal plants from the Asteraceae family which has long been used in traditional medicine of different nations all over the world.

The plant has remarkable anti-inflammatory activities and contains secondary metabolites amongst which the most important ones are flavonoids (apigenin), terpenoids (bisabolol and azulene derivatives), and coumarins (herniarin and umbelliferone) [32].

In a group of 40 candidates for allogenic hematopoietic stem cell transplantation (HSCT), three concentrations (0.5%, 1%, and 2%) of chamomile extract were administered as mouthwash. Patients in the intervention groups had lower severity and duration of mucositis based on WHO scale in comparison to control group who only received standard care. Also, patients in chamomile group 1% had shorter period of analgesics and TPN use [33]. In another study in patients undergoing HSCT, Tavakoli-Ardakani et al. assessed the effect of a mixture of chamomile extract and peppermint *(Mentha x piperita)* oil as mouthwash for the prevention of oral mucositis. In comparison to placebo group, patients in the intervention group showed lower severity and duration of mucositis and xerostomia; however, the onset of mucositis was not significantly postponed in the intervention group [34].

Phoenix dactylifera L. (Date palm)

Date palm is a tree from the Arecaceae family which is native to tropical and subtropical climates. Different parts of the plant, especially the fruit and the pollen, has been widely used for different indications since ancient times [35]. The pollen, is a folk remedy for male infertility in several countries all over the world. The pollen is a rich source of amino acids, vitamins and minerals, as well as phenolic acids and flavonoids like rutin [36].

In a pilot study by Elkerm *et al*. (2014), patients with head and neck cancer were treated with date palm pollen in the form of a suspension which was administered once per night. The preparation was compared to a standard treatment including analgesics and antifungal agents in the control group. Based on oral mucositis assessment scale (OMAS), date palm pollen could decrease the severity and incidence of mucositis. Additionally, date palm pollen reduced dysphagia in comparison to control group [37].

*Rhodiola algida Fisch. & C.A.Mey. (Stonecrop***)**

R. algida is a Tibetan medicinal plant from Crassulaceae family which is used in the traditional remedies of Asian and European countries [38]. *Rhodiola* genus contain compound such as salidroside and polyphenols (tyrosol) and are demonstrated to improve the activity of immune system [39].

In a preclinical trial by Loo et al. (2010), 130 breast cancer patients with were administered with *R. algida* extract of placebo. After two weeks of administration, patients in the intervention group has significantly lower pain and fewer number of ulcers in the oral cavity. Also, patients received *R. algida* extract experienced shorter period of ulceration [40].

Silybum marianum (L.) Gaertn. (Milk thistle)

Milk thistle is a plant from the family Asteraceae which is well-known since ancient times due to the hepatoprotective activity. The fruits are rich in flavonolignans, mostly silibinin and its

derivatives, which are responsible for most of the therapeutic activities reported from the plant such as antioxidant, anti-inflammatory, and anticancer properties which is demonstrated in a significant number of clinical studies [41].

Elyasi *et al*. assessed the effect of oral silymarin (*S. marianum* standardized extract) in patients with head and neck cancer treated with radiotherapy. Silymarin tablets were administered from the first day of radiotherapy and were continued for six weeks. In comparison to placebo-treated group, patients received silymarin had delayed onset and lower severity of mucositis based on National Cancer Institute Common Toxicology Criteria (NCI-CTC) and World Health Organization (WHO) oral mucositis grading scale. Additionally, none of the patients in the intervention group showed grade 4 mucositis [42].

Discussion and conclusions

Oral mucositis is one of the most disturbing complications in patients under chemoradiotherapy. Current treatments, including artificial saliva, antimicrobial agent and analgesics, cannot sufficiently control the condition [4]; thus, further researches are necessary to find better options to control chemoradiotherapy-induced oral mucositis.

In this paper, we have summarized current clinical evidence regarding the medicinal plants assessed for the primary and secondary prevention of oral mucositis. The most promising plants include aloe and German chamomile which have more than one study demonstrating their efficacy. There are also several plants from the family Asteraceae including yarrow, marigold, and milk thistle which suggest this family of plants to contain secondary metabolites beneficial for the treatment of inflammation and tissue damage in the oral cavity. Polyphenolic compounds like flavonoid can be considered as active ingredients of plants from Asteraceae family and thus, other plants containing such secondary metabolites might also be useful for oral mucositis. Additionally, hollyhock and high mallow both contain mucilaginous compounds, a common constituent of the plants from the family Malvaceae, which shows the potential of this family for further investigation of medicinal plants for soothing effect on chemoradiotherapy - induced oral mucositis. Other plant families from which high mucilaginous compounds are reported including Curcurbitaceae [43], Plantaginaceae, Brassicaceae (Cruciferae), and Crassulaeeae [44] may possibly be effective for pain relief and can be future candidates for clinical studies in patients with oral mucositis.

The most important limitation of the included studies are small sample size and inappropriate study design. The latter problem, however, is due to the ethical consideration which allows patients in the placebo or untreated arms to use standard care to control their mucositis. Thus, it is hard to make a definite conclusion about the efficacy of herbal medicines in such studies.

Another problem is regarding the dosage forms used in the above mentioned studies. Several studies used suspensions which should be prepared by the patient right before use which is not as comfortable as mouthwashes or gargles and may cause errors in dose measurements. Thus,

to introduce these herbal preparations into the market, more comfortable dosage forms should be provided in order to improve the compliance of patients and reduce the risk of possible errors in drug delivery. Also, dosage forms like gel which have a longer period of exposure compared with liquids can provide better chance for the local delivery of phytochemicals to the damaged tissues of oral cavity.

According to reviewed studies, medicinal plants have shown promising effects for the management of chemoradiotherapy-induced oral mucositis which suggest these preparations as future candidates for the management of complications of patients with cancer. Well-designed clinical trials with appropriate sample size and proper methodology are essential for further confirmation of the safety and efficacy of medicinal plants in oral mucositis.

Conflict of Interest

None declare.

Acknowledgment

None.

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