Review Article

Natural agents in the management of oral mucositis in cancer patients-systematic review

Ravleen Nagi^{a,*}, Deepa Jatti Patil^b, N. Rakesh^c, Supreet Jain^d, Shashikant Sahu^e^a Department of Oral Medicine and Radiology, New Horizon Dental College and Research, Sakri, Bilaspur, Chhattisgarh, India^b Department of Oral medicine and Radiology, Swami Devi Dyal Dental College, Panchkula Haryana, India^c Department of Oral Medicine and Radiology, Faculty of Dental Sciences, MS Ramaiah University of Applied Sciences, MSRIT Post, Mathikere, Bangalore, Karnataka, India^d Department of Oral Medicine and Radiology, New Horizon Dental College and Research Institute, Sakri, Bilaspur, India^e Burn and Cosmetic Surgeon, Burn and Trauma Centre, Bilaspur, Chhattisgarh, India

ARTICLE INFO

Article history:

Received 4 June 2017

Received in revised form 16 August 2017

Accepted 3 December 2017

Available online 6 December 2017

Keywords:

Cancer

Chemotherapy

Natural agents

Management

Radiotherapy

ABSTRACT

Introduction: Oral mucositis is most severe complication of cancer therapy characterized by ulcerative lesions of oral mucosa causing negative impact on patient's quality of life. Wide variety of therapeutic agents are available to reduce the lesions of mucositis. Currently, natural herbal remedies have become popular in treating this condition due to fewer side effects than synthetic drugs.

Aim: The aim of this systematic review is to compile evidence based studies to evaluate the effectiveness of natural agents in the management of oral mucositis induced by chemotherapy or radiotherapy in cancer patients.

Materials and method: Computerized literature searches were performed to identify all published articles in the subject. The following databases were used: PUBMED [MEDLINE], SCOPUS, COCHRANE DATABASE, EMBASE and SCIENCE DIRECT using specific keywords. The search was for limited articles published in English which were read in full by two authors.

Results: Twenty six randomized controlled trials satisfied our inclusion criteria. Most studies showed statistically significant result demonstrating the efficacy of natural agents with minimal side effects except manuka honey which was not tolerated by few patients.

Conclusion: Natural agents proved to be promising in healing cancer induced oral mucositis but future demands further randomized controlled clinical trials on these agents which should also be focused on drug interactions of the natural remedies.

© 2018 Craniofacial Research Foundation. All rights reserved.

Contents

1. Introduction	246
2. Method	246
2.1. Literature Search	246
2.2. Data Collection	246
3. Result	247
3.1. Risk of Bias across individual studies	247
3.2. Adverse effects	248
4. Discussion	248
5. Conclusion	253
Conflict of interest	253
References	253

* Corresponding author.

E-mail address: ravleennagi@yahoo.in (R. Nagi).

1. Introduction

Oral mucositis(OM) is a common devastating, painful side effect of chemo and radiotherapies of various head and neck carcinomas.¹ Incidence of oral mucositis is higher in i) patients with primary tumors of oral cavity, oropharynx and nasopharynx ii) those who receive concomitant chemotherapy iii) those who receive total dose over 5000cGy iv)those who are treated with altered fractionation radiation schedules.² Anticancer therapy and radiotherapy have direct effect on epithelial cells leading to epithelial thinning and loss of barrier. Oxidative stress followed by production of inflammatory cytokines (Tumor necrosis factor TNF α , Interleukin IL 1,6) has been established as the major causative factor of OM.^{2,3}

Sonis ST has proposed hypothetical mechanism for development of OM lesions based on four phases: an initial inflammatory/vascular phase, an epithelial phase, an ulcerative/bacteriological phase, and a healing phase. In the early inflammatory phase, chemotherapy leads to release of cytokines mainly IL-1, TNF- α from the epithelium. Ionizing radiation, at doses which in themselves are not damaging to tissues, also causes release of these cytokines from epithelium and connective tissue. Both IL-1 and TNF- α cause tissue damage and increase subepithelial vascularity. In epithelial phase, cancer chemotherapeutic drugs which are cell phase specific such as methotrexate, 5-Fluorouracil and cytarabine affect DNA synthesis i.e. S phase of cell cycle, takes basal cells out of cell cycle. There is epithelial atrophy, marked erythema thus leading to ulceration. Ulcerative phase is most symptomatic and occurs one week after initiation of drugs along with initial evidence of neutropenia. Severity of neutropenia usually occurs 14 days after initiation of therapy. Secondary infections are common in this phase and oral flora of patient comprises of gram negative organisms along with α hemolytic streptococci. In this phase also production of IL-1 and TNF- α , nitric oxide leads to tissue damage. Final healing phase comprises elements related to cell proliferation, differentiation, normalization of white blood cells and control of bacterial flora.⁴

Clinically, lesions of oral mucositis are atrophic, erythematous or ulcerative. Ulcerative lesions of OM are associated with severe pain, increased risk of severe infections, oral bleeding, compromised oral and pharyngeal function and risk of hospitalization.² OM grading is mainly based on clinical aspects and nutritional state ranging from score 0–4 and several scales are available to grade the mucositis. World Health Organization (WHO) OM toxicity scale is mainly used in daily practice as it is simple and measures both subjective and objective symptoms of OM (Table 1). This scale was used preferably in most of the studies in this systematic review and according to this scale; Grade 3 and 4 OM are considered as severe intolerable mucositis associated with ulcerations and low quality of life.⁵ It requires delay of next chemotherapy (CT) cycle, dose reduction or even discontinuation of planned radiotherapy (RT) treatment.³

It is vital to prevent the pain associated with oral mucositis and to improve nutritional status, hydration and quality of life of

patients to improve cancer prognosis. Wide variety of currently available therapeutic agents comprising of oral health care, anti-inflammatory agents, local anesthetic agents, oral decontamination, benzydamine hydrochloride rinse, low level laser therapy have been tried to reduce the severity of intolerable mucositis pain but there is yet no established effective treatment. Some agents are associated with side effects and higher costs. Therefore, naturally occurring agents such as aloe vera, curcumin, honey, olive oil etc are in progress to target the therapy in more cost effective manner to reduce morbidity of mucositis with fewer side effects as compared to synthetic drugs. Moreover, these agents are easily available without prescription, therefore providing their use by patients without any scientific evidence.^{3,6} The aim of this systematic review was to evaluate the literature for the use of natural agents for the prevention and management of oral mucositis in cancer patients.

2. Method

2.1. Literature Search

A systematic review of scientific literature concerning effectiveness of natural agents or herbal therapies to manage intolerable OM was done in the manuscript. The population, intervention, comparison, outcome (PICO) model was used to develop inclusion criteria and search terms per intervention. Population was cancer patients who developed oral mucositis after radiotherapy or chemotherapy to treat cancer. All types of comparison of natural agents or no comparison were included. Outcome was based on the reduction of severity of mucositis. The electronic retrieval systems and data bases searched for relevant articles were PUBMED (MEDLINE), SCOPUS, SCIENCE DIRECT and COCHRANE DATABASE. The MEDLINE, SCIENCE DIRECT, SCOPUS and COCHRANE DATABASE search was performed from March 2008 till October 2016, interrogated by MeSH terms. The MeSH terms used to evaluate the effectiveness of natural agents were “cancer”, “chemotherapy”, “natural agents”, “management” and “radiotherapy”. Randomized control trials, single and double blind trials, cross sectional and case control studies were included in this review. Studies were eligible only if they were published as full papers in English language. Exclusion criteria were: animal studies, in-vitro studies, review articles, case reports and use of synthetic drugs to manage the lesions of OM.

Two authors searched for articles that met selection criteria and later they reviewed the full title and abstract of the articles retrieved in the initial literature research. Disagreement was resolved by discussion between the two authors.

The articles that were not matching eligibility criteria and duplicate articles were removed from the study. Later, the authors screened the abstracts of the remaining papers individually. The authors tried to obtain the full papers for all the potentially eligible studies and the studies that met the eligibility criteria were included in the systematic review (Table 2).⁷

2.2. Data Collection

On the basis of studies characteristics (title of the paper, author's information, year of study, study design, cancer type and treatment modality used to treat cancer, natural agent used to treat OM, route of administration of agent, results and conclusion) two author's independently extracted data using the standard data extraction form (Tables 3 and 4). Differences were reviewed and resolved by discussion between the authors.

Data was extracted in predefined fashion and assessment of data was done using Jadad score (Table 5).⁸

Table 1
World Health Organization (WHO) Grading of Oral Mucositis.

Definition	Grade
No changes	0
Soreness $\pm$ Erythema	1
Erythema, ulcers, patients can swallow solid food	2
Ulcers with extensive erythema, patients cannot swallow solid food	3
Mucositis to the extent that alimentation is not possible	4

Table 2

Preferred reporting items for systematic review (PRISMA) diagram showing article selection for use of natural agents for management of cancer induced mucositis.

3. Result

Table 2 shows that the initial computerized search strategy and associated hand search yielded 2016 titles. In the first case selection authors screened the articles by reading titles and abstracts of the retrieved publications and 1798 were discarded because these articles did not met the inclusion criteria. Out of those 1798 articles, 1468 were excluded as these were animal studies, case reports, review articles or based on use of synthetic agents. Remaining 330 articles that fulfilled the eligibility criteria were read in full. Among these 330 articles, only 26 clinical trials met our inclusion criteria. Most studies showed statistically significant result demonstrating the efficacy of natural agents in treatment of OM lesions after RT or CT of cancer.

3.1. Risk of Bias across individual studies

All the studies demonstrated low risk bias using COCHRANE BIAS TOOL.⁹ Among twenty Six trials, blinding Bias was observed in

twelve studies and Randomization sequence bias was high in two studies (Table 6).

Table 3 presents clinical trials using natural agents in various doses for the treatment of oral mucositis in different cancer patients. PICO model was designed to evaluate the effectiveness of natural agents in treating OM (Table 4). Out of 26 clinical trials, outcome of 23 trials showed effective reduction in the severity of OM with natural agents as compared to placebo or synthetic agents.^{10–35} Trials by Bardy J et al and Hawley P et al on manuka honey showed no effect on healing of lesions with reduced patient compliance, thus leading to drop outs. Aloe vera (AV) was found to have reverse association with OM lesions.^{14,15} Out of three clinical trials, one trial by Su et al found that AV gel did not reduced soreness or healed lesions and had no impact on patient's quality of life on 58 head and cancer patients, which requires further testing the effectiveness of this agent on OM lesions.¹⁸ Natural herbs such as Indigowood root (*Isatis indigotica* Fort), *Calendula officinalis*, *Achillea Millefolium* and chamomile were reported to have positive therapeutic and preventive effect on OM (Table 4).^{31–33,35}

Table 3

Summarizes various studies using natural agents in various doses for the treatment of oral mucositis in different cancer patients.

Author (Year)	Study Design	Natural Agent	Route of Admins-tration	Cancer type	Treatment modality
Motallebnejad M et al (2008) ¹²	RCT	20 ml of honey	Topical	HNC	RT
Khanal B et al (2010) ¹¹	single-blinded, RCT	Honey with lignocaine	Topical	HNC	RT
Bardy J et al (2012) ¹⁴	Double-blind, placebo-RCT	manuka honey (golden syrup) 20 ml 4 times daily for 6 weeks	Topical	HNC	RT
Abdulrhman M et al (2012) ¹⁰	RCT	honey and a mixture of honey, olive oil-propolis extract, and beeswax (HOPE)	Topical	acute lymphoblastic leukemia	CT
Hawley P et al (2014) ¹⁵	Double blind RCT	5 ml of manuka honey	Topical, PO	HNC	RT
Raessi et al (2014) ¹³	Double-blind RCT	Syrup-like solution. 20 grams of instant coffee" in the Honey,(HC) group, and "300 grams of honey" for the Honey (H) group	PO	HNC	CT
Su CK et al (2004) ¹⁸	Double-blind, RCT	Aloe Vera gel	PO	HNC	RT
Puataweepong et al (2009) ¹⁶	Double blind placebo controlled trial	15 ml of AV solution thrice daily for 8 weeks	PO	HNC	RT
Sahebjamme M et al (2015) ¹⁷	Triple-blind, RCT	Aloe vera	PO	HNC	RT
Elad S et al (2013) ¹⁹	Pilot study	10 drops of Curcuma twice per day in a mouthwash	Oral Rinse	Paediatric cancer	Doxorubicin-containing CT
Rao S et al (2014) ²¹	single-blinded, RCT	Turmeric, 10 ml swishing in mouth for 2 minutes, 6 times a day ie 1 hr prior to radiation, 1, 2 h, 4 h and 6 h after radiation therapy and once before going to bed	PO	HNC	RT
Saldanha (2014) ²²	RCT	50 ml solution of turmeric, Thrice daily for five days	Topical	HNC	CT/RT induced OM
Patil K et al (2015) ²¹	Pilot study	Curcumin mouthwash 0.004%, thrice daily in 1:5 dilution for 1 minutes for 20 minutes	PO	NHC	RCT
Debabrata Das et al (2011) ²³	RCT	<i>Yashthimadhu Ghrita</i> (10 ml twice daily for oral intake), Honey	Topical and oral (PO)	HNC	RCT
Ahmed KM (2013) ²⁴	Double blind RCT	OLE (333 mg/ml), 3–4 times a day for 14 days	PO	Leukemia	CT
Ahmed KM et al (2013) ²⁵	Randomised, Double blind Trial	OLE, 3–4 times a day for 14 days from start of CT	PO	HNC	CT
Noronha VR (2014) et al ²⁷	Phase II open label trial	<i>mucoadhesive gel containing propolis 5.0% three times a day for 2 weeks</i>	Topical	Oral Cancer	RT
Balouri (2015) et al ²⁶	Randomized Triple blind trial	<i>15 ml of propolis mouthwash three times a day for 5 weeks</i>	PO	HNC	RT
Yamouchi (2014) et al ³⁰	Randomized Single blind Trial	<i>RJ (3 g/day), Three times a day</i>	Topical	HNC	CRT
Ashktorab T et al (2010) ²⁸	Randomized double blind clinical trial	<i>PE, 10 drops of oral rinse</i>	PO	Colon/Rectum Cancers	CT
Kaushal V (2001) ²⁹	RCT	<i>placental extract: Inj Placentrex 2 ml by deep im inj 5 days a week for 15 injections</i>	im injections	SCC of HN region	RT
You WC et al (2009) ³¹	RCT	Indigowood root (<i>Isatis indigotica fort</i>)	Topical	Oral Cancer	RT
Babae N (2013) ³²	Prospective placebo controlled trial	2% Calendula mouthwash, three times per day for 6 weeks, minute in the	PO	HNC	RT
Miranzadeh S et al (2016) ³³	RCT, double blind	<i>A. millefolium</i> 4 times a day for 14 days	PO	-----	CT
Mutluay Yayla E et al (2016) ³⁴	RCT	sage tea-thyme-peppermint hydrosol	PO	-----	CT
Dos Reis PE (2016) et al ³⁵	Pilot study, Randomized trial	cryotherapy made with chamomile infusion.	PO	-----	CT

RCT, Randomized Controlled Trial; OM, Oral Mucositis; RT, Radiotherapy; CT, Chemotherapy; HNC, Head and Neck Cancer; PE, Peppermint essence; OLE, Olive Leaf Extract; RJ, Royal Jelly; SCC, Squamous Cell Carcinoma; PO, Per Oral; (—), cancer type not specified; im, intramuscular.

3.2. Adverse effects

Natural therapy was reported to have better patient compliance with fewer side effects. Manuka honey was not tolerated by patients due to nausea and vomiting^{14,15} and it led to 57% drop outs in the study by Hawley et al.¹⁵

4. Discussion

Mucositis is considered to be devastating non haematological complication of anticancer therapy affecting 40–80% of cancer patients receiving chemotherapy and nearly half of the patients undergoing RT of head and neck.^{36,37} Literature reveals that vast majority of synthetic agents have been tried to heal the lesions of mucositis but the main question is safety of these agents. Another major concern is interactions of these agents with other drugs and

most of these agents have provided low level of evidence in most cases according to Somerfield criteria. Therefore, natural remedies have currently emerged for the reduction of symptoms of mucositis.^{37,38}

Very few studies have evaluated the effect of natural remedies on the lesions of OM. This systematic review was an attempt to summarize the literature of the studies conducted to see the effectiveness of natural therapy on OM lesions and our search comprised 26 clinical trials. Honey has been known for its medicinal properties such as tissue repair, wound healing and therapeutic properties in the treatment of various gingival diseases. It has excellent antimicrobial properties, low pH, high osmolality and generates high level of noncytotoxic hydrogen peroxide through the enzyme glucose oxidase. Honey decreases prostaglandin concentration, increases nitric oxide concentration in lesions, has anti-inflammatory and antioxidant properties, thus

Table 4

Population, Intervention, Comparison, Outcome (PICO) model to evaluate the effectiveness of natural agents for treatment of oral mucositis.

Author(Year)	Population	Intervention	Comparison	Outcome
Motallebnejad M et al (2008) ¹²	40 Patients with H&N C	The effect of topical application of pure honey on radiation-induced mucositis	20 ml of saline before and after RT	Significant reduction in mucositis among honey-received patients was observed.
Khanal B et al (2010) ¹¹	40 patients with radiation induced mucositis	Effect of topical honey on limitation of radiation-induced oral mucositis	Lignocaine	1 of 20 patients developed intolerable oral mucositis in honey group than lignocaine
Abdulrhman M et al (2012) ¹⁰	90 patients with acute lymphoblastic leukemia and oral mucositis grades 2 and 3, Mean age: 6.9 years	To evaluate the effect of topical application of honey and a mixture of honey, olive oil-propolis extract, and beeswax in treatment of OM	Honey olive oil-propolis extract, (HOPE) and beeswax & Topical Benzocaine (control)	Honey group overall showed faster healing for Grade 2/3 healing than HOPE and control group. Olive oil and bees wax need future further clinical trials.
Bardy J et al (2012) ¹²	131 Patients with H&N C	To investigate the effect of active manuka honey on radiation-induced mucositis Manuka Honey–20 ml 4 times daily for 6 weeks	placebo (golden syrup)–20 ml 4 times daily for 6 weeks	Manuka honey did not reduced any of the OM symptoms although it reduced bacterial infections
Hawley P et al (2014) ¹³	106 patients with radiation induced mucositis	To investigate whether honey reduced the severity of radiation-induced OM 5 ml of irradiated organic manuka honey	Placebo gel	Manuka honey was not tolerated due to nausea and vomiting and this resulted in 57% drop outs in patients taking honey
Raeessi et al (2014) ¹¹	75 patients with CT induced mucositis	“Coffee plus Honey” versus “topical steroid” in the treatment of Chemotherapy-induced Oral Mucositis “300 grams of honey” in Honey group	28 mg Steroid & Honey plus Coffee(300 grams of honey plus 20 grams of instant coffee” in the Honey plus Coffee group) Placebo	Honey and coffee (0.38 ± 0.50) was found to be highly efficacious than Honey alone (0.90 ± 0.65) to heal OM lesions. Steroid was least effective in healing OM
Su CK et al (2004) ¹⁸	58 H&N C patients	To compare oral Aloe vera (AV) versus placebo to prevent radiation-related mucositis in patients with head-and-neck neoplasms	Placebo	AV gel did not reduce soreness or healed lesions and had no impact on patient's quality of life.
Puataweepong et al (2009) ¹⁶	61 H&N C patients: AV gp – 30 patients & Placebo–31 patients	Efficacy of aloe vera juice for radiation induced mucositis 15 ml of AV solution thrice daily for 8 weeks	Placebo	Incidence of OM severity was less (53%) in OM group.
Sahebamee M et al (2015) ¹⁷	21 H&C cancer patients	To compare the efficacy of an Aloe vera mouthwash with a benzydamine mouthwash in the alleviation of radiation- induced mucositis in head and neck cancer patients	Benzydamine mouthwash	The mean interval between radiation therapy and onset of mucositis was found to be similar for both groups i.e AV, 15.69 ± 7.77 days, benzydamine, 15.85 ± 12.96 days and the mean interval between the start of radiation therapy and the maximum severity of mucositis was also similar in both the groups (AV, 23.38 ± 10.75 days, benzydamine, 23.54 ± 15.45 days).
Elad S et al (2013) ¹⁹	Five pediatric patients	To assess the tolerability of a curcumin mouthwash and to describe oral mucositis in pediatric patients undergoing doxorubicin-containing chemotherapy who were using the curcumin mouthwash 10 drops of Curcuma twice per day in a mouthwash	Placebo	World Health Organization (WHO), Oral Mucositis Assessment Scale (OMAS) and Visual Analog Scale(VAS) were lower than the severity of mucositis for curcumin
Rao S et al (2014) ²¹	80 H&C C patients receiving 70 Gray of RT or chemoRT.	To evaluate the efficacy of turmeric in preventing radiation-induced mucositis turmeric gargle 10 ml 6 times a day	Povidone iodine 10 ml twice a day for 6 weeks	Patients receiving turmeric gargle had reduced incidence of mucositis before, during and at the end of the treatment, and less weight loss.
Saldanha (2014) ²²	40 patients	To compare efficacy of turmeric and saline mouth wash on the treatment induced oral mucositis 50 ml turmeric mouth wash	Saline mouth wash	Significant difference was seen in the score of TIOM between pre-intervention on Day 1 morning and post intervention score on day 5 evening in turmeric and saline group but on comparison it was found that turmeric mouth wash was more effective than saline mouth in all the days except on Day 3.
Patil K et al (2015) ²¹	20 H&N C patients	To evaluate the efficacy and safety of curcumin mouthwash in the management of Oral Mucositis in cancer patients undergoing radioCT. Curcumin mouthwash thrice daily	chlorhexidine mouthwash 0.2%	Curcumin was found to be better agent than chlorhexidine in reducing OM severity mainly due to rapid healing and better patient compliance.
Debabrata Das et al (2011) ²³	75 patients, Four groups i) Group A (local application of the <i>Yashtimadhu</i> powder and honey, along with oral intake of <i>Yashtimadhu ghrita</i> , 10 ml twice daily) ii) Group B (local application of the <i>Yashtimadhu</i> powder and honey), iii) Group C (topical	1 Protective effect of <i>Yashtimadhu</i> (<i>Glycyrrhiza glabra</i>) against side effects of radiation/chemotherapy in head and neck malignancies	Conventional modern medicine	There was marked reduction in the severity of mucositis in group A when compared to group D in the 2nd week of RT. In group B, the results on mucositis as compared to group D were not significant in the 2nd week of RT but were significant in 7th week. In

Table 4 (Continued)

Author(Year)	Population	Intervention	Comparison	Outcome
	application of honey) and iv)GroupD(conv modern med.)			group C, the results on mucositis were insignificant in both the 2nd and 7th week of RT, as compared to group D. <i>Glycyrrhiza glabra</i> proved to be a effective herbal agent in healing of lesions.
Ahmed KM (2013) ²⁴	21 patients	Olive oil leaf extract in decreasing expression proinflammatory cytokines in patients receiving chemotherapy for cancer olive leaf extract (OLE) 333 mg/ml, 3–4 times/day for 14 days	Benzydamine hydrochloride 0.15 mg/100 ml & normal saline, 3–4 times/day for 14 days	Oral mucositis severity decreased after 8 and 15 days with OLE and benzydamine hydrochloride than placebo. TNF α and IL-1 β levels in OLE group (TNF α , 51.9 $\pm$ 56.2; IL-1 β 21.1 $\pm$ 53.3) was less as compared to patients using benzydamine hydrochloride (TNF α , 55.3 $\pm$ 1.2; IL-1 β 66.6 $\pm$ 66.9) and placebo(TNF α , 188.9 $\pm$ 1.2; IL-1 β 112.4 $\pm$ 71.0).
Ahmed KM et al(2013) ²⁵	62 patients	Olive oil leaf extract used as a new topical management for oral mucositis following chemotherapy OLE, 3–4 times/day for 14 days Evaluation on 1,8,15 of each cycle of chemotherapy	Benzydamine hydrochloride and placebo, 3–4 times/day for 14 days	OMAS was low for solutions on day 1 then gradually increased till Day 8. But there was sudden decline in score at day 15 (OLE 0.02 $\pm$ 0.10, benzydamine hydrochloride 0.09 $\pm$ 0.18, placebo 0.39 $\pm$ 0.29). Oral symptoms of mucositis pain, difficulty in swallowing was more in placebo and benzydamine hydrochloride group than OLE group and symptoms were more pronounced at day 8,15.
Noronha VR (2014) et al ²⁷	24 patients	Effectiveness of a mucoadhesive propolis gel in the prevention of radiation-induced oral mucositis. propolis 5.0% w/v three times a day for 2 weeks	NR	Twenty patients did not develop mucositis, two patients developed grade 1 mucositis and two patients developed grade 2 mucositis. Mucoadhesive propolis gel could be considered as a potential topical medication for preventing radiation-induced oral mucositis.
Balouri (2015) et al ²⁶	20 H&NC patients	Therapeutic effect of propolis in radiotherapy induced mucositis in patients with HNC 3% propolis, 3 times a day for 5 weeks	15 ml placebo, 3 times a day for 5 weeks	Mucositis scoring done at beginning, 1 week and after 5 week of treatment was found reduced in propolis group. Weight loss in the propolis group was less (200g) than placebo group (3.4 kg).
Yamouchi (2014) et al ³⁰	13 H&NC patients:7 Royal Jelly group &6 control	Effect of topical application of royal jelly on chemotherapy induced mucositis. RJ three times a day	Controls did not receive Royal jelly	Significant reduction in the signs of mucositis after royal jelly application was seen during and 1 month after the radiation treatment
Ashktorab T et al (2010) ²⁸	20 patients	To determine the effects of an oral rinse Peppermint essence (PE) in the prevention of chemotherapy- induced oral mucositis 10 drops PE, thrice daily for 14 days	placebo	Risk of OM was 3.3 times in placebo group, PE was effective treatment for OM lesions with decrease in pain scores
Kaushal V (2001) ²⁹	60 patients	To evaluate human placental extract in the treatment of radiation mucositis involving theoral/ oropharyngeal region IM Inj Placentrex 2 ml, 5 days a week for 15 injections	Disprin gargles and betamethasone oral drops	In the placentrax group there was a subjective decrease in pain 48/60 (80%), reduced progression to grade 3 radiation mucositis 24/60 (40%), the subjective improvement in difficulty in swallowing 56/60 (93%).
You WC et al (2009) ³¹	20 patients	To evaluate the effect of indigowood root (<i>Isatis indigotica</i> Fort.) on acute mucositis induced by radiation	saline	IR could reduce the severity of radiation mucositis (p = 0.01), anorexia (p = 0.002), and swallowing difficulty (p = 0.002). It was even effective in reducing serum IL-6 levels at first, fifth, seventh weeks of RT.
Babae N (2013) ³²	40 patients	To investigate the effect of <i>Calendula officinalis</i> mouthwash on preventing radiotherapy-induced oral mucositis 2% Calendula mouthwash, three times per day for 6 weeks	5 ml placebo	<i>Calendula officinalis</i> was efficacious in reducing intensity of OM after RT. Total antioxidant, polyphenol and flavonoid contents and quercetin concentration of the 2% extract were 2353.4 $\pm$ 56.5 μ M, 313.40 $\pm$ 6.52 mg/g, 76.66 $\pm$ 23.24 mg/g, and 19.41 $\pm$ 4.34 mg/l, respectively.
Miranzadeh S et al (2016) ³³	56 patients	Effect of adding the herb <i>Achillea millefolium</i> on mouthwash on chemotherapy induced oral mucositis in cancer patients 15 mL of a mixture of routine solution and <i>A. millefolium</i> 4 times a day for 14 days	15 ml routine solution	Severity of OM was found to be reduced, 1.07 $\pm$ 0.85 and 0.32 $\pm$ 0.54 in the intervention group in days 7 and 14.

Table 4 (Continued)

Author(Year)	Population	Intervention	Comparison	Outcome
Mutluay Yayla E et al (2016) ³⁴	60 patients	Severity of OM assessed three times i.e before, 7 and 14 days after intervention. Sage tea-thyme-peppermint hydrosol oral rinse reduces chemotherapy-induced oral mucositis	Basic oral care	Grade I mucositis severity decreased in intervention group (10%) and control group (53.3%) on day 5, symptoms of mucositis totally decreased i.e became grade 0 mucositis for both groups on day 14. Sage tea-thyme-peppermint hydrosol oral rinse is an effective agent to treat OM with good tolerability.
Dos Reis PE (2016)et al ³⁵	38 patients:20 patients-cryotherapy with chamomile &18 patients cryotherapy with water	Chamomile infusion cryotherapy to prevent oral mucositis induced by chemotherapy cryotherapy made with chamomile infusion, Evaluation on days 8, 15, and 22 after the first day of chemotherapy	cryotherapy made only with water	55% of the patients in the control and 30 % in the chamomile group developed OM and on day 22, no ulcerations were observed in chamomile group thus proving its effectiveness in reducing severity of lesions

OM,Oral mucositis;RT,Radiotherapy;CT,Chemotherapy;HOPE,Honey olive oil-propolis extract;TIOM,Treatment induced Oral mucositis;AV,Aloe Vera;PE,Peppermint Essence; NR,No comparison;H&NC,Head and Neck Cancer.

reducing mucosal irritation. Manuka pollen is collected by honey bees from manuka tree, *Leptospermum scoparium* and has potent antibacterial activity due to presence of methylglyoxal.^{15,39} Honey was used in six studies but source of honey was different in all the studies or it was from different geographical areas which posed a difficulty in establishing proper guideline.^{10–15} In four trials, honey proved to be better in reducing ulcerations and lesions of OM and showed low risk bias than manuka honey.^{10–13} It has been reported that too high hydrogen peroxide levels causes cell damage and the effect was more pronounced with diluted honey especially in case of manuka honey. Moreover dilution of the honey also reduces its bioactivity.^{15,39} Safety of manuka honey is questionable as it was not tolerated by patients leading to nausea and vomiting which was major cause of drop outs in the trials. Studies on manuka honey suggested that it possess good antibacterial activity but has low potential in reducing severity of OM lesions and also had low patient compliance.^{14,15}

Caries promoting effect of honey in cancer patients is one of the limitations in OM patients. Major ingredients of honey are glucose, fructose, and sucrose which contribute to its cariogenic properties. Therefore, the patients are advised to rinse their mouth after each topical application, use topical fluoride mouth rinses and maintain proper oral hygiene. Long term follow up is necessary and in future RCT should be carried out to prove the association between honey and caries incidence in OM patients.⁴⁰

AV is natural herb with anti-inflammatory, immunomodulatory, antibacterial, antitumor properties and is used in oral medicine for the treatment of various oral lesions such as oral lichen planus, oral submucous fibrosis, recurrent aphthous stomatitis, pemphigus vulgaris, herpetic stomatitis, leukoplakia and radiation induced mucositis.¹⁶ Out of four RCT by our search, two trials proved efficacy of AV gel on cancer induced mucositis with low risk bias^{16,17} but future, demands further research to test the efficacy of AV components, especially anthraquinone present in the aloe leaves. Dosage of AV gel should be properly managed. Overdosage of AV could result in severe diarrhea and drug interactions should also be kept in mind mainly with corticosteroids and thiazide diuretics which would result in electrolyte imbalance.³⁸ Curcumin, an extract of turmeric has been progressively studied for its various beneficial effects mainly anti-inflammatory, antioxidant, anticarcinogenic, antimicrobial properties. It acts mainly by modulating pro-inflammatory cytokines, apoptotic proteins, nuclear factor- κ B (NF- κ B), cyclooxygenase-2, 5-Lipoxygenase (5-LOX), STAT3, C-reactive protein, and prostaglandin E and has antiapoptotic effect on neoplastic cells.^{20,21} This agent was found to be promising agent in

treating various pro inflammatory diseases and one of them is OM and was found to be useful agent in reversing the signs and symptoms of OM in all the four studies by our search.^{19–22}

Studies evaluating effect of several other herbal agents such as olive oil, PE, placental extract, propolis, indigowood root, *clandulla officinalis*, Glycyrrhiza glabra on OM were also assessed in this review and these natural agents proved to be effective alternative to synthetic therapy for OM lesions after RT/CT. *Olive Oil is a natural leaf extract possessing anti-inflammatory, antioxidant, antibacterial properties* and has been used to treat various ulcerative lesions such as recurrent aphthous ulcers and has gained important role in healing lesions of OM by decreasing proinflammatory cytokines mainly IL-1 β and TNF- α in cancer patients.^{24,25} Propolis is bee glue, natural nontoxic sticky resinous material produced by honey bees which has been used for anti inflammatory purpose in folk medicine since ancient times to cure various diseases. Capheic acid phenyl ethyl ester (CAPE) is a strong antioxidant extracted from propolis to prevent proliferation of neoplastic cells.^{26,27} Yashtimadhu (Glycyrrhiza glabra) is an important medicinal herb with antioxidant, anti-inflammatory properties and has healing properties.²³ Peppermint essence (PE) is used as a natural cure against side effects of cancer therapy. It has been found to protect against radiation induced DNA damage.²⁸ Placental extract is a biological stimulator with therapeutic potential mainly in accelerating wound healing, decreasing fibrosis in oral lesions such as oral submucous fibrosis, healing properties of placental extract has lead to decrease in the severity of OM lesions.²⁹

RJ is secreted by the hypopharyngeal and mandibular glands of worker honeybees between the sixth and twelfth days of their life, and it is an essential food for the development of the queen honeybee. It comprises mainly of proteins (12–15%), sugars (10–12%), lipids (3–7%), amino acids, vitamins, and minerals. It possess antitumor, antioxidant, anti-inflammatory, antibacterial, and anti-allergic, wound healing properties.³⁰ Chinese herbs such as indigowood root and *clandulla officinalis* are also effective in reducing OM lesions. IR is known for its anti-inflammatory properties and *Calendula officinalis* possess anti-inflammatory properties, antioxidant, antifungal and antibacterial properties.^{31,32} The beneficial activities reported for the plant are mainly due to the contents of various secondary metabolites such as polyphenols, carotenoids, triterpenes and essential oils.³² *Achillea millefolium*, known as yarrow is a member of Asteraceae family and contains chamazulene, cineol, and borneol, thus contributing to its antibacterial, anti-inflammatory and anti-spasmodic properties.³³ Chamomile is a member of daisy family and contains chamazulene,

Table 5
Illustrates Jadad Scores of individual studies.

Authors	Kaushal V	Su CK et al	Motallebnejad M et al	Puatawee-pong et al	You WC et al	Khanal B et al	Ashktorab T et al	Debabrata Das et al	Bardy J et al	Abdulrhman M et al	Elad S et al	Ahmed KM	Babee et al	Ahmed KM et al	Hawley P et al	Raessi et al	Rao S et al	Saldanha	Noronha VR et al	Yamauchi K et al	Sahebamee M et al	Patil K et al	Balouri et al	Miranzadeh S et al	Mutluay Yayla E et al	Dos Reis PE et al
Year	2001	2004	2008	2009	2009	2010	2010	2011	2012	2012	2013	2013	2013	2013	2014	2014	2014	2014	2014	2014	2015	2015	2015	2016	2016	2016
Natural Agent Used	PE	AV	Honey	AV	IR wood	Honey	PE	<i>Glycyrrhiza glabra</i>	Manuka Honey	Honey	curcumin	OLE	Clandulla	OLE	Manuka Honey	H & C	curcumin	Turmeric	Propolis	Royal Jelly	AV	curcumin	Propolis	<i>Achillea millefolium</i>	Sage tea-thyme-peppermint hydrosol	Chamomile
Randomization	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1
Concealment	1	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1
Study Drop Out	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Method of randomization	1	1	0	1	1	1	1	0	0	1	0	1	0	0	1	1	1	0	0	1	1	0	1	1	1	1
Method of Blinding	0	1	1	1	0	1	0	0	1	1	0	1	0	0	1	1	1	0	0	1	1	0	1	1	0	0

Reporting Quality: Poor Jadad Score (<3) = 8 trials, Good Jadad Score (≥ 3)=18 trials.

Table 6
Risk of Bias assessment across individual studies.

Authors	Kaushal V	Su CK et al	Motallebnejad M et al	Puatawee-pong et al	You WC et al	Khanal B et al	Ashktorab T et al	Debabrata Das et al	Bardy J et al	Abdulrhman M et al	Elad S et al	Ahmed KM	Babee et al	Ahmed KM et al	Hawley P et al	Raessi et al	Rao S et al	Saldanha	Noronha VR et al	Yamouchi et al	Sahebamee M et al	Patil K et al	Balouri et al	Miranzadeh S et al	Mutluay Yayla E et al	Dos Reis PE et al
Year	2001	2004	2008	2009	2009	2010	2010	2011	2012	2012	2013	2013	2013	2013	2014	2014	2014	2014	2014	2014	2015	2015	2015	2016	2016	2016
Natural Agent Used	PE	AV	Honey	AV	IR wood	Honey	PE	<i>Glycyrrhiza glabra</i>	Manuka Honey	Honey	curcumin	OLE	Clandulla	OLE	Manuka Honey	H & C	curcumin	Curcumin	Propolis	RJ	AV	curcumin	Propolis	<i>Achillea millefolium</i>	Sage tea-thyme-peppermint hydrosol	Chamomile
Randomization sequence	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–
Allocation Concealment	–	–	–	–	–	–	–	–	–	–	+	–	+	+	–	–	–	–	–	–	–	–	–	–	–	–
Blinding of Participants	+	–	–	–	+	–	+	+	–	–	+	–	+	+	–	–	–	+	+	–	–	+	–	–	+	+
Blinding of Patient reported outcome	+	–	–	–	+	–	+	+	–	–	+	–	+	+	–	–	–	+	+	–	–	+	–	–	+	+
Blinding of outcome assessment	+	–	–	–	+	–	+	+	–	–	+	–	+	+	–	–	–	+	+	–	–	+	–	–	+	+

(+), High Risk, (–), Low Risk; RJ,Royal Jelly; PE,Peppermint; AV, Aloe vera; IR, Indigoroot; OLE,Olive leaf extract;H&E,Honey and coffee.

alpha bisabolol, bisabolol oxides, spiroethers, flavanoids (apigenin, luteolin, patuletin, and quercetin), coumarins (herniarin and umbelliferone), terpenoids, and mucilage. It has anti-inflammatory, antioxidant, anticancer, mild astringent, wound healing and antifungal properties. It has been tried in the lesions of OM as demonstrated by the positive results in the trial by Dos Reis PE et al.³⁴ Although 8 trials showed low Jaded scoring (0–2) (Table 5) but the overall methodological quality of these studies was found to be good according to Jadad score thus establishing these agents as effective therapeutic agents to treat OM.

Several studies in the literature have compared the natural agents with other treatment modalities to heal the OM lesions. One of the most common treatment of OM is steroids but this therapy is expensive and is associated with side effects. Raessi MA compared the effects of topical steroid with 'coffee and Honey' on OM lesions. Results demonstrated coffee plus honey as an effective alternative agent in reducing OM lesions than steroids in terms of rapid healing and good tolerability.¹³ Propolis gel was compared with topical anti-inflammatory agent, benzydamine hydrochloride (HCL) in alleviating the symptoms of OM, green propolis gel has anti-inflammatory, antimicrobial, antifungal and antioxidant properties due to presence of flavanoids such as galangin and artemillin C, and was found to be better in reducing OM severity after 17th session of RT than alcoholic solution of benzydamine HCL, that requires combination with antifungal agent such as fluconazole.⁴¹ Another antibacterial agent chlorhexine gluconate gel 0.2% was evaluated for the effectiveness in OM lesions and showed no clinical improvement in lesions. Moreover, this agent had several disadvantages such as bitter taste, discoloration of teeth and unpleasant sensation.⁴² Recently low level laser therapy (LLLT) has been introduced to treat and shorten the duration of OM lesions. LLLT accelerates wound healing, detoxifies free radicals, has anti-inflammatory effects and also reduces secondary infections but results are conflicting mainly in CT patients. In a trial by Djavid GE et al, LLLT on CT induced OM lesions gave positive results by reducing grade 3 and 4 mucositis but further clinical trials are required to test the effectiveness of this modality. Moreover as compared to natural therapy, LLLT is expensive and is contraindicated in certain systemic diseases.⁴³ Although natural agents proved to be better alternative yet future demands more trials on exploration of new herbal agents and also trials should be focused on adverse reactions mainly drug interactions with use of these agents.

5. Conclusion

Our analysis on the various natural agents used in this systematic review, favors the use of these new traditional alternative medicines in the treatment of cancer induced mucositis. Dentists must be familiar and should use these agents in the clinical practice during the course of treatment. Future researchers are required to explore new herbal medicines to treat the OM pain and lesion.

Conflict of interest

None.

References

- 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.
- Lalla RV, Sonis ST, Peterson DE. Management of oral cancer in patients with cancer. *Dent Clin North Am*. 2008;52(1) 61–viii.
- Hondt D, Lonchay L, Andre C, Canon M, Luc J. Oral mucositis induced by anticancer treatments: pathophysiology and treatments. *Ther Clin Risk Manage*. 2006;2(2):159–168.
- Sonis. Mucositis as a biological process: a new hypothesis for the development of chemotherapy-induced stomatotoxicity. *Oral Oncol*. 1998;34:39–43.
- Peterson DE, Bensadoun RJ, Roila F. Management of oral and gastrointestinal mucositis: ESMO clinical practice guidelines. *Ann Oncol*. 2011;22(Suppl 6): vi78–vi84.
- Matsuda C, Munemoto Y, Mishima H, et al. Double-blind, placebo-controlled, randomized phase II study of TJ-14 (Hangeshashinto) for infusional fluorinated-pyrimidine-based colorectal cancer chemotherapy-induced oral mucositis. *Cancer Chemother Pharmacol*. 2015;76:97–103.
- Welch V, Petticrew M, Tugwell P, et al. PRISMA-equity 2012 extension: reporting guidelines for systematic reviews with a focus on health equity. *PLoS Med*. 2012;9(10):e1001333.
- Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17:1–12.
- Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane's collaborations' tool for assessing risk of bias in randomized trials. *Br Med J*. 2011;343.
- Abdulrhman M, Elbarbary NS, Ahmed AD, Saeid ER. Honey and a mixture of honey, beeswax, and olive oil-propolis extract in treatment of chemotherapy-induced oral mucositis: a randomized controlled pilot study. *Pediatr Hematol Oncol*. 2012;29(April 3):285–292.
- 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(December 12):1181–1185.
- Motallebnejad M, Akram S, Moghadamnia A, Moulana Z, Omid S. The effect of topical application of pure honey on radiation-induced mucositis: a randomized clinical trial. *J Contemp Dent Pract*. 2008;9(March 3):40–47.
- Raessi MA, Raessi N, Panahi Y, Gharaie H, Davoudi SM, Saadat A. Coffee plus Honey versus topical steroid in the treatment of chemotherapy-induced oral mucositis: a randomised controlled trial. *Complement Altern Med*. 2014;14:293.
- Bardy J, Molassiotis A, Ryder WD, Mais K, Sykes A, Yap B, 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(April 3):221–226.
- 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(March 3):751–761.
- 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.
- Sahebamee M, Mansourian A, Mohammad MH, et al. Comparative efficacy of aloe vera and benzydamine mouthwashes on radiation-induced oral mucositis: a triple-blind, randomised, controlled clinical trial. *Oral Health Prev Dent*. 2015;13(4):309–315.
- 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(September 1):171–177.
- 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(May-Jun 3):21–24.
- Patil K, Gulegdud MV, Kulkarni PK, Keshari D, Tayal S. Use of curcumin mouthrinse in radio-chemotherapy induced oral mucositis patients: a pilot study. *J Clin Diagn Res*. 2015;9(August 8):ZC59–ZC62.
- Rao S, Dinkar C, Vaishnav LK, et al. The Indian spice turmeric delays and mitigates radiation-induced oral mucositis in patients undergoing treatment for head and neck cancer: an investigational study. *Integr Cancer Ther*. 2014;13:201–210.
- Saldanha SP, Almeida VD. A comparative study to assess the effectiveness of turmeric mouth wash versus saline mouth wash on treatment induced oral mucositis (tiom) in a selected hospital at mangalore. *J Clin Res Bioeth*. 2014;5:200.
- Das D, Agrawal SK, Chandola HM. Protective effect of *Yashtimadhu* (*Glycyrrhiza glabra*) against side effects of radiation/chemotherapy in head and neck malignancies. *Ayu*. 2011;32(Apr-Jun 2):196–199.
- Ahmed MK. The effect of olive leaf extract in decreasing the expression of two pro-inflammatory cytokines in patients receiving chemotherapy for cancer. A randomized clinical trial. *Saudi Dent J*. 2013;25:141–147.
- Ahmed MK, Talabani N, Altaei T. Olive leaf extract as a new topical management for oral mucositis following chemotherapy: a microbiological examination, experimental animal study and clinical trial. *Pharmaceut Anal Acta*. 2013;4:9.
- Bolouri AJ, Pakfetrat A, Tonkaboni A, et al. Preventing and therapeutic effect of propolis in radiotherapy induced mucositis of head and neck cancers: a triple-blind, randomized, placebo-controlled trial. *Iran J Cancer Preven*. 2015;8(October 5):e4019.
- Noronha VR, Araujo GS, Gomes RT, et al. Mucoadhesive propolis gel for prevention of radiation-induced oral mucositis. *Curr Clin Pharmacol*. 2014;9(4):359–364.
- Ashktorab T, Yazdani Z, Mojab F, Majd HA, Madani H. Preventive effects of an oral rinse Peppermint essence on chemotherapy-induced oral mucositis. *J Semnan Univ Med Sci*. 2010;12:1–7.

29. Kaushal V, Verma K, Manocha S, Hooda HS, Das BP. Clinical evaluation of human placental extract (placentrex) in radiation-induced oral mucositis. *Int J Tissue React.* 2001;23(3):105–110.
30. Yamauchi K, Kogashiwa Y, Moro Y, Kohno N. The effect of topical application of royal jelly on chemoradiotherapy-induced mucositis in head and neck cancer: a preliminary study. *Int J Otolaryngol.* 2014;1–5.
31. You WC, Hsieh CC, Huang JT. Effect of extracts from indigowood root (*Isatis indigotica* Fort.) on immune responses in radiation-induced mucositis. *J Altern Compl Med.* 2009;15(July 7):771–778.
32. Babae N, Moslemi D, Khalilpour M, Vejdani F, Moghadamnia Y, Bijani A, 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 J Pharm Sci.* 2013;21:18.
33. Miranzadeh S, Adib-Hajbaghery M, Soleymanpoor L, Ehsani M. Effect of adding the herb *Achillea millefolium* on mouthwash on chemotherapy induced oral mucositis in cancer patients: a double-blind randomized controlled trial. *Eur J Oncol Nurs.* 2015;19:207–213.
34. Mutluay Yayla E, Izgu N, Ozdemir L, Aslan Erdem S, Kartal M. Sage tea-thyme-peppermint hydrosol oral rinse reduces chemotherapy-induced oral mucositis: A randomized controlled pilot study. *Compl Ther Med.* 2016;27:58–64.
35. Dos Reis PE, Ciol MA, de Melo NS, Figueiredo PT, Leite AF, Manzi Nde M. Chamomile infusion cryotherapy to prevent oral mucositis induced by chemotherapy: a pilot study. *Support Care Cancer.* 2016;24(10):4393–4398.
36. Treister N, Sonis S. Mucositis: biology and management. *Curr Opin Otolaryngol Head Neck Surg.* 2007;15(April 2):123–129.
37. De Smet PA. Herbal remedies. *N Engl J Med.* 2002;347:2046–2056.
38. Surjushe A, Vasani R, Saple DG. Aloe vera: a short review. *Ind J Dermatol.* 2008;53(4):163–166.
39. Parsons E, Begley A, Herst P. Manuka honey mouthwash does not affect oral mucositis in head and neck cancer patients in New Zealand. *J Radiother Pract.* 2012;11:249–256.
40. 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.
41. Noronha VRAS, Abdo EN, Persio FPCL, Santos VR. *Propolis gel versus benzydamine in preventing oral mucositis for patients irradiated in head and neck: a preliminary study.* .
42. Diaz Sanchez RM, Pachón-Ibáñez J, Marín-Conde F, Rodríguez-Caballero A, Gutierrez-Perez JL, Torres-Lagares D. Double-blind, randomized pilot study of bioadhesive chlorhexidine gel in the prevention and treatment of mucositis induced by chemoradiotherapy of head and neck cancer. *Med Oral Patol Oral Cir Bucal.* 2015;20(3):e378–85.
43. Djavid GE, Emami A, Ataie-Fashtami L, et al. Low Level Laser Therapy in Management of Chemotherapy-induced Oral Mucositis: Prophylaxis or Treatment. *J Lasers Med.* 2011;2:12–17.