



Systematic review of natural and miscellaneous agents, for the management of oral mucositis in cancer patients and clinical practice guidelines — part 2: honey, herbal compounds, saliva stimulants, probiotics, and miscellaneous agents

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Abstract

Objective To update the clinical practice guidelines for the management of oral mucositis (OM) that were developed by the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). This part focuses on honey, herbal compounds, saliva stimulants, probiotics, and miscellaneous agents.

Methods A systematic review was conducted by the Mucositis Study Group of MASCC/ISOO. The body of evidence for each intervention, in each clinical setting, was assigned an evidence level. The findings were added to the database used to develop the 2014 MASCC/ISOO clinical practice guidelines. Based on the evidence level, one of the following guidelines were determined: Recommendation, Suggestion, No Guideline Possible.

Results A total of 78 papers were identified within the scope of this section, of which 49 were included in this review and merged with nine publications that were reported in the previous guidelines update. A new Suggestion was made for honey (combined topical and systemic delivery) for the prevention of OM in head and neck cancer patients receiving radiotherapy with or without chemotherapy. A new Suggestion clarified that chewing gum is not effective for the prevention of OM in pediatric patients with hematological or solid cancer treated with chemotherapy. No guideline was possible for other interventions.

Conclusions Numerous natural products and herbal remedies were studied for the management of OM. Of the agents reviewed in this systematic review, a guideline in favor was made for honey (combined topical and systemic), while a guideline against was made for chewing gum. Additional research is warranted to clarify the potential of other interventions.

Keywords Oral mucositis · Cancer · Management · Natural · Traditional · Complementary · Herbal

Introduction

Among all cancer treatment toxicities, oral mucositis (OM) is a common and significant complication. It is frequently observed in head and neck (H&N) cancer patients undergoing

radiotherapy (RT) with or without concomitant chemotherapy (CT) and in patients undergoing hematopoietic stem cell transplantation (HSCT) [1]. Clinically, it manifests as erythema and/or ulcerations involving the non-keratinized oral mucosa, causing severe pain and/or dysphagia, and may result in treatment breaks and prolonged hospitalization.

"In the search for OM prevention, treatment, or palliation, a broad variety of natural remedies have been suggested. For many generations, natural remedies have been used for the management of oral ulcerations in various cultures across the world. Unlike synthetic drugs, natural remedies are

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generally perceived to have fewer side effects and are therefore attractive as potential therapies. Patient-based access to these products in resource-restricted geographic regions may be an additional advantage as well.

The Mucositis Study Group (MSG) of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) has published clinical practice guidelines for the management of OM [2–4]. In the 2014 guidelines update, the Natural and Miscellaneous section concluded the systematic review with two guidelines regarding honey, herbal compounds, saliva stimulants/inhibitors, probiotics, and miscellaneous agents: (1) a suggestion against the use of systemic pilocarpine administered orally for the prevention of OM associated with RT for H&N cancer and in patients receiving high-dose chemotherapy, with or without total body irradiation, prior to HSCT; (2) a suggestion against the use of systemic pentoxifylline administered orally for the prevention of OM in patients undergoing HSCT. No guideline was possible for any other agents [5,6]. The aim of this systematic review was to review newly reported evidence for the efficacy of natural and miscellaneous agents for the prevention and/or treatment of OM and update the clinical practice guidelines.

In the first part of this systematic review, we focused on the efficacy of vitamins, minerals, and nutritional supplements for the management of OM [7]. This paper includes studies on honey, herbal compounds, saliva stimulants/inhibitors, probiotics, and miscellaneous agents.

Methods

The methods are described in detail in Ranna et al. [8] Briefly, a literature search for relevant papers indexed in the literature from January 1, 2011 to June 30, 2016 was conducted using PubMed/Web of Science/EMBASE, with papers selected for review based on defined inclusion and exclusion criteria.

Papers were reviewed by two independent reviewers and data were extracted using a standard electronic form. Studies were scored for their level of evidence (LoE) based on Somerfield criteria [9] and flaws were listed according to Hadorn criteria [10]. A well-designed study was defined as a study with no major flaws per the Hadorn criteria.

Findings from the reviewed studies were integrated into guidelines based on the overall level of evidence for each intervention. Guidelines were classified into 3 types: Recommendation, Suggestion, and No Guideline Possible.

Guidelines were separated based on (1) the aim of the intervention (prevention or treatment of mucositis); (2) the treatment modality (RT, CT, RT-CT, or high-dose conditioning

therapy for HSCT); and (3) the route of administration of the intervention.

The list of intervention keywords used for the literature search of this section are detailed in the Methods paper [8].

Results

A total of 2653 papers were identified in the literature search: 1863 from PubMed and 790 from Web of Science. After careful assessment of the abstracts, 2563 articles were excluded due to repetition across databases, non-clinical studies, meta-analyses and reviews. Three additional papers were transferred from other sections of the guidelines update leading to a total of ninety-three articles. After review of the full papers, 6 were moved to other sections, and 9 were excluded based on inclusion/exclusion criteria. A total of 78 papers were included in this section. Of them 49 were included in this paper (part 2) (Fig. 1), while 29 papers were included in part 1 [7]. These 49 publications describe 26 various interventions that fall within the scope of honey, herbal compounds, saliva stimulants/inhibitors, probiotics, and miscellaneous agents. These papers were merged with 9 publications that were reviewed in the previous guidelines update.

Honey

Honey has been reported to be effective in promoting wound healing when applied as a dressing [11]. The wound healing effect is considered to be primarily mediated by the low-level hydrogen peroxide generation. Interestingly, compared with diluted honey, full-strength honey has a lower glucose oxidase activity, and thus lower level of hydrogen peroxide generation [12]. There are also non-hydrogen peroxide phytochemical mechanisms which appear to be involved in wound healing. In addition, honey has anti-microbial properties which may be beneficial to prevent secondary infection [13].

Honey (topical) – H&N - RT or RT-CT – prevention

Guideline: No guideline possible (LoE II)

Overall, in the H&N cancer patient population, there were 4 RCTs for topical honey [Table 1] [14–17]. Two of these RCTs demonstrated that honey was effective in preventing OM associated with RT or RT-CT [16,17]; however, these RCTs had a small sample size. Therefore, No Guidelines Possible. Interestingly, the two RCTs that reported honey is ineffective in preventing radiation-association OM were using Manuka honey.

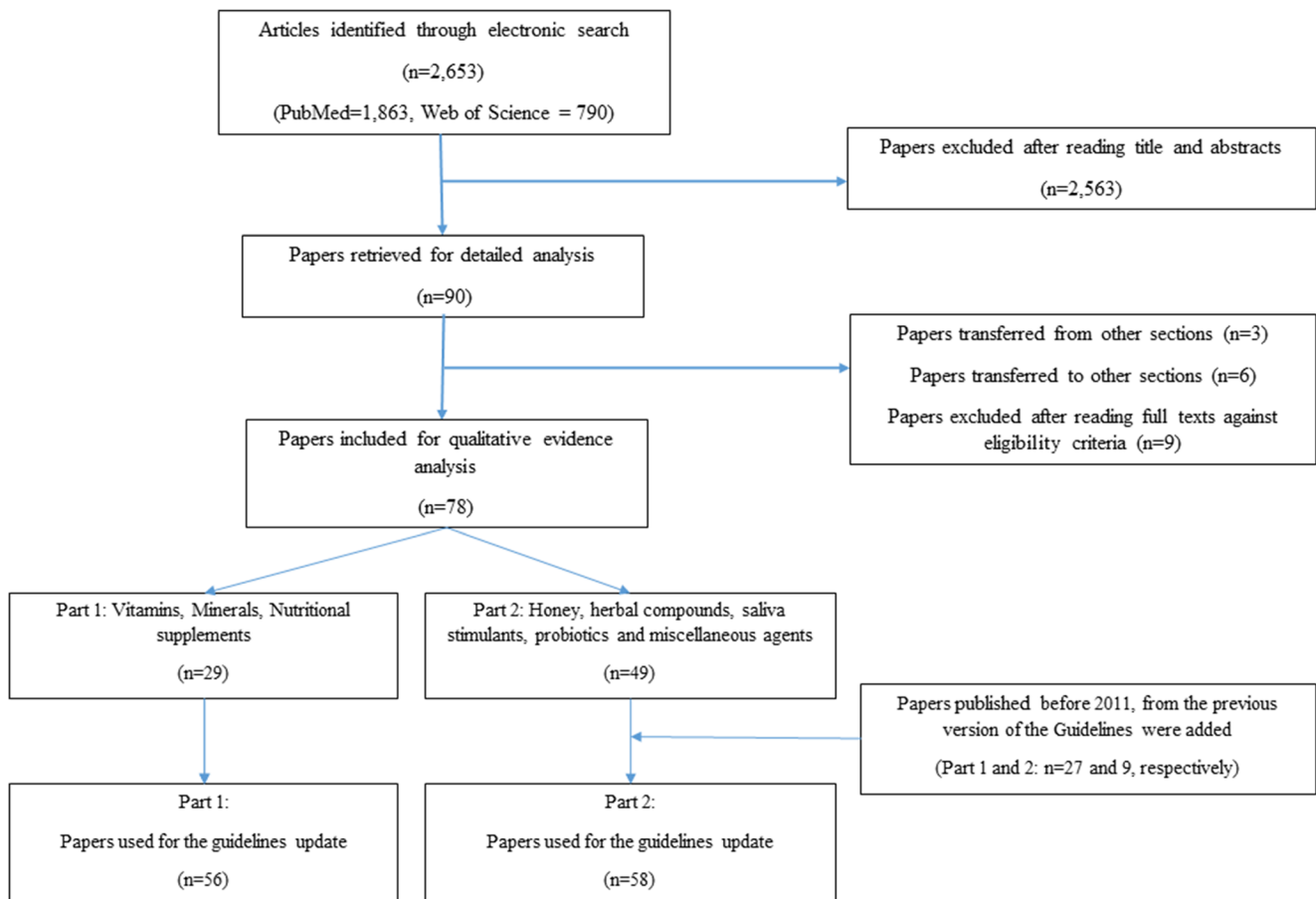


Fig. 1 Article flow chart

Honey (combined topical-systemic) – H&N – RT or RT-CT – prevention

Guideline: Suggestion (LoE III)

Honey (combined topical application and systemic administration) is suggested for the prevention of OM in H&N cancer patients treated with either RT or RT-CT.

There is consistent evidence that topical application combined with systemic administration of honey is beneficial in preventing OM in H&N cancer patients treated with either RT or RT-CT [Table 1] [18–23]. Since some of these RCTs had a mixed patient population (RT and RT-CT), small sample size, and different sources for the honey, only a Suggestion can be made for the present guideline update.

Likewise, a single study had equivocal results as statistical significance was not reported [20]. Of note, there was an additional RCT comparing a combined protocol of honey, benzydamine, and nystatin with a control group that received benzydamine and nystatin only [24]. This latter RCT did not contribute to our analysis because the patient population was not clearly defined.

Two RCTs compared honey with another active agent and are considered comparator studies [25,26]. One RCT compared topical honey with topical lidocaine and found honey to be superior in reducing the OM severity in patients with H&N cancer [25]. In another RCT, honey was applied to prevent OM in an unspecified group of cancer patients treated with CT [26]. This study included 3 arms comparing honey with a mix of honey and caffeine, and with steroids (8 mg betamethasone) [26], and found that the combined honey and caffeine had the greatest reduction in OM severity.

The source of the honey differed between these studies: “natural” honey [16,19], royal jelly [17,24], honey extracted mainly from the tea plant, *Camellia sinensis* [18], honey extracted from *Thymus* and *Astragale* in the Alborz mountains [21], honey extracted from the western Ghats forests [25], honey extracted from the clover plant *Trifolium alexandrinum* [22], or unspecified [20,23].

No data were reported regarding dental caries in the studies about honey-based protocols for the prevention of OM.

Table 1 Studies reported for honey overall level of evidence and guideline determination

Name of agent	Route of administration	Cancer	Treatment modality	Indication	Author, year	Effective	Overall level of evidence	Guideline category	Guideline determination	Non-RCT studies	Comments
Honey	Topical	H&N	RT/RT-CT	P	Hawley 2014 [15] Jayankshmi 2016 [16] Yamauchi 2014 [17] Bardy 2012 [14]	N (1) Y (1) Y (1) N (1)	II	NGP	Honey is suggested for the prevention of OM in H&N cancer patients treated with either RT or RT-CT.	Bahrammezhad 2015 [93]-(3) Y	Hawley 2014 [15]- <i>Manuka honey</i> ; Jayalekshmi 2016 [16]-“natural honey”; Yamauchi 2014 [17]- <i>Royal Jelly</i> ; Bardy 2012 [14]- <i>Manuka honey</i>
	Topical & systemic	H&N	RT	P	Jayachandran 2012 [19] Biswal 2003 [18] Motallebnejad 2008 [21] Samdariya 2015 [23] Maiti 2012 [20] Rashad 2009 [22]	Y (2) Y (1) Y [1] Y (3) (unclear)* Y (1)	III	Suggestion			<i>Biswal 2003 [18]-Honey extracted mainly from the tea plant, Camellia sinensis; Motallebnejad 2008 [21]-Honey extracted from Thymus and Astragale in the Alborz mountains</i>
	Topical & systemic	H&N	RT-CT	P	Abdulrhman 2012 [27]	Y (2)	III	NGP			Rashad 2009 [22]- <i>Honey extracted from the clover plant Trifolium alexandrinum</i>
	Topical	Hematol.	CT	T	Abdulrhman 2012 [27]	Y (2)	III	NGP			Abdulrhman 2012 [27]- <i>honey vs honey and a mixture of honey, olive oil, propolis extract, and bees wax (HOPE)</i>
	Topical & systemic	Hematol. CT & solid	CT	P	Mohamed 2012 [28]	Y (1)	III	NGP			
	Topical & systemic	Not reported	RT or CT	T	Erdem 2014 [24]	Y (2)	III	NGP			Erdem 2014 [24]- <i>Royal Jelly</i>

Non-RCT studies key: 3. Non-RCT, 4. Cohort, 5. Before and after, 6. Case control studies, 7. Cross sectional, 8. Case series, 9. Case report, 10. Expert opinion

Effectiveness key: 1–Mucositis severity; 2–Mucositis duration; 3–Pain severity; 4–Pain duration

HSCCT hematopoietic stem cell transplant; H&N head and neck; RT radiotherapy; CT chemotherapy; hematol hematological; P prevention; Y yes, effective; N no, ineffective; NGP no guideline possible; ^ pediatric

*No statistical analysis reported [20]

Honey (topical) – hematologic cancer – CT – treatment**Guideline: No guideline possible (LoE III)**

This systematic review found a single RCT on honey as a treatment for OM among pediatric patients with hematologic malignancies treated with CT [27]. This study demonstrated that topical honey was effective in reducing the duration of OM but not its severity. Since there is a single RCT in this clinical setting, the guideline category is No Guideline Possible.

Honey (topical) – hematologic or solid cancer – CT – prevention**Guideline: No guideline possible (LoE III)**

A RCT reported on honey for the prevention of OM in a mixed patient population of hematologic malignancies and solid cancers treated with CT [28]. This RCT reported that honey was effective to reduce OM severity. Considering the limited evidence, as well as the lack of placebo and blinding in this study, no guideline is possible.

Propolis

Propolis is a natural wax-like resinous substance collected by honey bees from the tree buds or other botanical sources such as poplar, willow, birch, elm, alder, beech, conifer, and horse-chestnut trees [29]. Propolis is used by Western and European honeybees as a building material in the hive [29]. The chemical composition of propolis varies and depends on the geographical area,

time of collection, seasonality, illumination, altitude, and food availability during propolis [29].

Propolis has been used throughout history as a natural medicine [30]. Its antibacterial, antiseptic, anti-inflammatory, anti-fungal, anesthetic, and healing properties have been reported [30].

Propolis (topical) – hematologic or solid cancer – CT – treatment**Propolis (topical and systemic) – H&N cancer – RT – prevention****Propolis (topical) – H&N cancer – CT – treatment****Guideline: No guideline possible (LoE III)**

Each of the above categories had a single, small RCT [31–33] and an additional cohort study was reported for one of these categories (Table 2) [34]. This evidence was insufficient to determine a guideline for any of these categories.

Traumeel

Traumeel is a homeopathic intervention used to treat a variety of conditions related to inflammation. It contains several medicinal plants and minerals in very low concentrations: *Arnica montana*, *Calendula officinalis*, *Atropa belladonna*, *Aconitum napellus*, *Bellis perennis*, *Hypericum perforatum*, *Echinacea angustifolia*, *Echinacea purpurea*, *Symphytum officinale*, *Matricaria chamomilla*, *Achillea millefolium*, *Mercurius solubilis hahnemanni* [35].

Table 2 Studies reported for propolis, overall level of evidence, and guideline determination

Name of agent	Route of administration	Cancer	Treatment modality	Indication	Author, year	Effective	Overall level of evidence	Guideline category	Non-RCT studies
Propolis	Topical	hematol. & solid	CT	T	Tomazevic 2013 [33]	N (1)	III	NGP	
	Topical & systemic	H&N	RT	P	Javadzadeh Bolouri 2015 [32]	Y (1)	III	NGP	Noronha 2014 [34]–(4) Y
	Topical	H&N	CT	T	Akhavan-Karbassi 2016 [31]	Y (1)	III	NGP	

Non-RCT studies key: 3. Non-RCT, 4. Cohort, 5. Before and after, 6. Case control studies, 7. Cross sectional, 8. Case series, 9. Case report, 10. Expert opinion

Effectiveness key: 1–Mucositis severity; 2–Mucositis duration; 3–Pain severity; 4–Pain duration

HSCT hematopoietic stem cell transplant; H&N head and neck; RT radiotherapy; CT chemotherapy; *hematol* hematological; P prevention; Y yes, effective; N no, ineffective; NGP no guideline possible; ^ pediatric

Table 3 Studies reported for traumeel, overall level of evidence, and guideline determination

Name of agent	Route of administration	Cancer	Treatment modality	Indication	Author, year	Effective	Overall level of evidence	Guideline category	Non-RCT studies
Traumeel	Topical & systemic	hematol.	HSCT ^	P	Oberbaum 2001 [36] ^	Y (1, 2)	II	NGP	
	Topical & systemic	H&N	RT or RT-CT	P	Sencer 2012 [35] ^	N (1)	III	NGP	Steinmann 2012 [37]-(3) N

Non-RCT studies key: 3. Non-RCT, 4. Cohort, 5. Before and after, 6. Case control studies, 7. Cross sectional, 8. Case series, 9. Case report, 10. Expert opinion

Effectiveness key: 1–Mucositis severity; 2–Mucositis duration; 3–Pain severity; 4–Pain duration

HSCT hematopoietic stem cell transplant; H&N head and neck; RT radiotherapy; CT chemotherapy; hematol hematological; P prevention; Y yes, effective; N no, ineffective; NGP no guideline possible; ^ pediatric

Traumeel (topical and systemic) – hematologic cancer (pediatric) – HSCT – prevention

Traumeel (topical and systemic) – H&N cancer – RT or RT-CT – prevention

Guideline: No guideline possible (LoE II and III, respectively)

Two RCTs assessed traumeel as a preventive therapy for OM in HSCT pediatric patients [Table 3] [35,36]. Both studies instructed the patients to swish and swallow. These studies presented conflicting evidence, therefore no guideline is possible.

Another comparative study was performed in H&N cancer patients treated with either RT or RT-CT [37]. This study reported that traumeel was not effective to prevent OM. Due to the limited evidence, no guideline is possible in this setting either.

Saliva stimulation

Saliva contains mucosal protective compounds that are vital for the oral health [38]. Among these salivary proteins are growth factors such as epidermal growth factor (EGF) and fibroblast growth factor (FGF) that promote wound healing and tissue repair. Animal models have shown delayed oral mucosal wound healing when salivary glands were mechanically obstructed, with the connective tissue being much more sensitive to lack of saliva than the epithelium [39]. Therefore, it has been suggested that any decrease in salivary flow may predispose the oral cavity to cytotoxic damage, whereas increasing salivary flow may support mucosal integrity and healing.

Chewing gum is a simple and inexpensive method to increase salivary production by up to 10-fold [40]. Therefore, it is postulated that chewing a gum may be beneficial in the

management of OM. Other modalities that increases the oral cavity moistening, such as electrostimulation of the salivary glands or production of an artificial humid climate, may work in a similar way.

Chewing gum – hematologic/solid cancer (pediatric) – CT – prevention

Guideline: Suggestion (against) (LoE III)

Chewing gum is not suggested for the prevention of OM in pediatric patients with hematological or solid cancer treated with CT.

This review identified 2 large RCTs assessing the potential of chewing gum for the prevention of OM in a mixed patient population of hematologic cancers and solid tumors [Table 4] [41,42]. Both studies were in pediatric patients and reported no difference between the treatment and control groups in regard to the reduction of OM severity. In one RCT, the chewing gum was compared with oral care alone [42] and in the second RCT, a combination of chewing gum and “magic mouthwash” was compared with “magic mouthwash” alone [41]. Considering the consistent evidence from 2 RCTs, a Suggestion against chewing gum was made.

Artificial moistening – Hematologic cancer – HSCT – prevention

Artificial humidification – H&N cancer – RT or RT-CT – prevention

Guideline: No guideline possible (LoE III)

A single RCT was found for chewing gum in patients undergoing HSCT and reported that it was not effective in

Table 4 Studies reported for saliva stimulants, overall level of evidence, and guideline determination

Name of agent	Route of administration	Cancer	Treatment modality	Indication	Author, year	Effective	Overall level of evidence	Guideline category	Guideline determination
Chewing gum	Topical	Hematol./solid ^	CT	P	Eghbali 2016 [41]	N (1)	III	Suggestion	Chewing gum is not suggested for the prevention of OM in pediatric patients with hematological or solid cancer treated with CT
	Topical	Hematol./solid ^	CT	P	Gandemer 2007 [42]	N (1)	III		
Chewing/electric stimulation (TENS)	Topical	Hematol.	HSCT	P	Pimenta 2012 [43]	N (1)	III	NGP	
Domiciliary humidification	Topical	H&N	RT or RT-CT	P	Macann 2014 [44]	Y (1)	III	NGP	
N-acetyl cysteine (NAC)	Systemic	Hematol.	HSCT	P	Moslehi 2014 [45]	Y (1, 2)	II	NGP	

Non-RCT studies key: 3. Non-RCT, 4. Cohort, 5. Before and after, 6. Case control studies, 7. Cross sectional, 8. Case series, 9. Case report, 10. Expert opinion

Effectiveness key: 1–Mucositis severity; 2–Mucositis duration; 3–Pain severity; 4–Pain duration

HSCT hematopoietic stem cell transplant; H&N head and neck; RT radiotherapy; CT chemotherapy; hematol hematological; P prevention; Y yes, effective; N no, ineffective; NGP no guideline possible; ^ pediatric

preventing OM [Table 4] [43]. Interestingly, this RCT included another experimental group in which patients were treated with electrostimulation to increase saliva secretion. However, the study sample was small and the data are limited [43].

Another RCT studied the efficacy of artificial humidification in H&N cancer patients treated with either RT or RT-CT was published [Table 4] [44]. This study concluded that humidification was beneficial for the prevention of OM. Blinding was not applied in the artificial humidification study; however, it is understandable that it is impossible to blind the patient to this treatment modality [44]. Due to the limited data, no guideline is possible.

N-acetyl cysteine (NAC) – hematologic cancer – HSCT – prevention

Guideline: No guideline possible (LoE II)

A single RCT evaluated the effectiveness of intravenous N-acetyl cysteine (NAC) for the prevention of OM in hematologic cancer patients undergoing HSCT [Table 4] [45]. The incidence of severe OM (grades 3–4) was significantly lower and the mean duration of OM was significantly shorter in the NAC group compared with the control group. This evidence did not meet the threshold to determine a guideline.

Curcumin

Curcumin has antioxidant, free-radical scavenging, and anti-inflammatory properties and has been used in traditional natural herbal medicine for management of wound healing and burns [46]. Furthermore, curcumin was reported to have anti-tumor properties [47]. Curcumin is obtained from the rhizome of *Curcuma longa*, a member of the Zingiberaceae family.

Curcumin (topical) – H&N cancer – RT – treatment

Guideline: No guideline possible (LoE III)

A single RCT investigated curcumin in H&N cancer patient treated with RT [Table 5] [48]. This small RCT compared *Curcuma longa* gel with placebo and found it to be effective for reducing the severity of OM. Another RCT in an undefined cancer population compared Indian turmeric combined with honey to a control group that received no treatment [49]. Considering the limited information about the patient population, it is impossible to align these data to any specific clinical setting or to conclude about the efficacy of turmeric.

Two comparator RCTs were conducted in H&N cancer patients. The first RCT compared turmeric with povidone iodine in patients treated with RT or RT-CT and found turmeric to be effective in preventing OM [50]. The second RCT

Table 5 Studies reported for herbal, overall level of evidence and guideline determination

Name of agent	Route of administration	Cancer	Treatment modality	Indication	Author, year	Effective	Overall level of evidence	Guideline category	Non-RCT studies	Comments
Curcumin	Topical	H&N	RT	P	Mansourian 2015 [48]	Y (1)	III	NGP		Mansourian 2015 [48]- <i>Curcuma longa gel</i> Francis 2014 [49]- <i>indian turmeric</i>
Hangeshashinto (TJ14)	Unknown	Unknown	RT or CT	P	Francis 2014 [49]	Y (1)				
	Topical	Hematol.	HSCT	P			IV	NGP	Elad 2013 [94]-(8) NA ^	
	Topical	Solid	CT	P	Matsuda 2015 [52] Aoyama 2014 [54]	Y (2) N (1, 2)	II	NGP		
	Topical	H&N	RT or RT-CT-prevention	P				NGP	Yamashita 2015 [55]-(3) Y	
Chamomile	Topical	Solid cancer	CT	P	Dos Reis 2016 [59] Fidler 1996 [58]	Y (1, 3) N (1, 2)	III	NGP		Dos Reis 2016 [59]-in ice chips
Pycnogenol	Topical	H&N, hematol., solid cancer	RT or CT	P			III	NGP	Carl 1991 [95]-(4) Y	Carl 1991 [95]- <i>Kamomillo-san liquidly</i>
	Topical	Hematol.	HSCT	P	Braga 2015 [60] Khurana 2013 [61] ^ *	Y (1, 2) Y (1)	III	NGP		
olive leaf	Topical	Hematol.	CT	P	Ahmed 2013 [62]	Y (1)	III	NGP		
Kangfuxin	Topical & systemic	H&N	RT-CT	P	Luo 2016 [63]	Y (1)	III	NGP		
Camelia Sinensis leaf and palmitoyl hydrolyzed wheat protein	Topical	Hematol.	HSCT	P	Carulli 2013 [64]	Y (1)	III	NGP		
Clove-based herbal mouthwash	Topical	H&N	RT	P	Kong 2016 [65]	Y (1-3)	III	NGP		
Yashtimadhu ghrita (processed ghee)/licorice	Topical	H&N	RT-CT	T	Das 2011 [66]	Y (1)	III	NGP		
Calendula officinalis	Topical	H&N	RT/RT-CT	P	Babace 2013 [67]	Y (1)	III	NGP		

Table 5 (continued)

Name of agent	Route of administration	Cancer	Treatment modality	Indication	Author, year	Effective level of evidence	Guideline category	Non-RCT studies	Comments
Yarrow plant (also called <i>Achillea millefolium</i>)	Topical	Solid and hematol.	CT	T	Miranzadeh 2014 [68]	Y (1)	NGP		
Date palm pollen	Topical & systemic	H&N	RT-CT	P		IV	NGP	Elkerm 2014 [69]–(3) Y	
Orasol plus (lapacho and hyaluronic acid, green tea, calendula, erisimo, propolis, marigold, plantain, and mauve)	topical	H&N	RT/RT-CT	P		IV	NGP	Giacomelli 2015 [70]–(4) Y	
standardized combination of <i>Vaccinium myrtillus</i> (bilberry), <i>Macleaya cordata</i> fruits, and <i>Echinacea angustifolia</i> roots	Topical and systemic	Hematol.	CT	P		IV	NGP	Bertoglio 2013 [71]–(3) Y	

Non-RCT studies key: 3. Non-RCT, 4. Cohort, 5. Before and after, 6. Case control studies, 7. Cross sectional, 8. Case series, 9. Case report, 10. Expert opinion

Effectiveness key: 1–Mucositis severity; 2–Mucositis duration; 3–Pain severity; 4–Pain duration

*HSC*T hematopoietic stem cell transplant; *H&N* head and neck; *RT* radiotherapy; *hematol* hematological; *P* prevention; *Y* yes, effective; *N* no, ineffective; *NGP* no guideline possible; ^

*Significant reduction of OM severity; efficacy is limited to low-moderate grade OM

compared topical curcumin 0.004% mouthwash with 0.2% chlorhexidine for the treatment of established RT-CT induced OM [51]. Since these studies did not use a placebo group, they were not used for this analysis of curcumin efficacy.

Hangeshashinto (TJ14)

Hangeshashinto is a traditional Japanese herbal medicine. It is a mixture of seven herbs including pinellia tuber, scutellaria root, glycyrrhiza, jujube, ginseng, processed ginger, and Coptis rhizome [52]. It reduces the level of prostaglandin E2 and affects the cyclooxygenase activity in oral keratinocytes in hamsters [53]. These properties were the basis for the hypothesis that Hangeshashinto may prevent OM.

Hangeshashinto (topical)– solid cancer – CT – prevention

Guideline: No guideline possible (LoE II)

This review identified 2 RCTs which assessed topical Hangeshashinto for the prevention of OM in patients with gastric cancer, and presented opposing conclusions [Table 5] [52,54]. Both studies used 2.5 g in 50 mL water three times a day. Considering the conflicting results, no guideline was possible in this clinical setting.

Hangeshashinto was also used in a comparative study in H&N cancer patients to prevent OM associated with

either RT or RT-CT [Table 5] [55]. The study reported that Hangeshashinto was effective in reducing the severity of OM and improved the completion rate of CT cycle. Due to limited evidence, no guideline is possible for this category.

Chamomile

Chamomile is one of the most popular medicinal plants in the world due to its assumed anti-inflammatory properties. Its anti-inflammatory activities are mediated by the inhibition of lipopolysaccharide-induced prostaglandin E [2] release and by reduction of cyclooxygenase (COX)-2 enzyme activity. Interestingly, chamomile does not affect the levels of COX-1 [56,57]. Chamomile was also reported to have antibacterial and anti-fungal properties [58].

Chamomile (topical) – solid cancer – CT – prevention

Guideline: No guideline possible (LoE III)

A RCT was identified about chamomile for the prevention of OM in patients with solid cancer treated with CT [Table 5] [59]. The chamomile was delivered as ice chips and was compared to a control group that was treated with ice chips only. This RCT

Table 6 Studies reported for probiotics and miscellaneous agents, overall level of evidence, and guideline determination

Name of agent	Route of administration	Cancer	Treatment modality	Indication	Author, year	Effective	Overall level of evidence	Guideline category	Non-RCT studies
Lactobacillus brevis cd2 lozenges	Topical & systemic	H&N	RT-CT	P	Sharma 2012 [73]	Y (1)	II	NGP	
Ag013 bacteria	Topical	H&N	CT	P	Limaye 2013 [72]	Y (1, 2)	III	NGP	
Phenylbutyrate gelformulation mouthwash	Topical	H&N	RT/RT-CT	T	Yen 2012 [74]	Y (1)	III	NGP	
Phenytoin	Topical	H&N	RT/RT-CT	P	Baharvand 2015 [75]	N	III	NGP	
Oral beta-glucan	Systemic	Solid	CT	P			IV	NGP	Karaca 2014 [76]–(6) Y
Platelet gel supernatant	Topical	H&N	RT/RT-CT	P			III	NGP	Bonfili 2015 [77]–(3) Y
Ankaferd hemostat	Topical & systemic	Hematol.	CT	T			IV	NGP	Atay 2015 [78]–(8) Y

Non-RCT studies key: 3. Non-RCT, 4. Cohort, 5. Before and after, 6. Case control studies, 7. Cross sectional, 8. Case series, 9. Case report, 10. Expert opinion

Effectiveness key: 1–Mucositis severity; 2–Mucositis duration; 3–Pain severity; 4–Pain duration

HSCT hematopoietic stem cell transplant; H&N head and neck; RT radiotherapy; CT chemotherapy; hematol hematological; P prevention; Y yes, effective; N no, ineffective; NGP no guideline possible; ^ pediatric

Table 7 Interventions for which the evidence and guideline are unchanged, based on existing literature (Adapted from Yarom 2013, Jensen 2013) [5,6]

Aim	Agent	Route of administration	patient population	Treatment modality	Guideline
P	Aloe vera*	Systemic (PO)	H&N cancer	RT or RT-CT	NGP
P	Quing Wei San or Yu Nu Jian	Topical	Hematol.	NS	NGP
P	Indigowood root	Topical & systemic	H&N cancer	RT or RT-CT	NGP
T	MF5232	Systemic (PO)	H&N cancer	RT-CT	NGP
P	Rhodiola algida	Systemic (PO)	Solid cancer	CT	NGP
T	Compound collagen, amino-acids and sodium hyaluronate	Topical	H&N cancer, hematol. cancer, solid cancer	RT or RT-CT or CT	NGP
P	Wobe-mugos E	Systemic (PO)	H&N cancer	RT	NGP
P	Manuka & kanuka oils	Topical & systemic	H&N cancer	RT	NGP
P	Allopurinol	Systemic (PO)	Hematol. cancer, solid cancer	CT	NGP
P	Allopurinol	Topical	Solid cancer	CT	NGP
P	Papayor	Topical	H&N cancer	RT	NGP
P	RT (timing)	NA	H&N cancer	RT	NGP
P	Pilocarpine	Systemic (PO)	H&N cancer	RT	Suggestion against
P	Pilocarpine	Systemic (PO)	Hematol. cancer	HSCT	Suggestion against
P	Propantheline	Systemic (PO)	Hematol. and solid cancers	HSCT	NGP
P	Bethanechol	Systemic (PO)	H&N cancer	RT	
P	Tetrachlorodecaoxide	Systemic (PO)	Hematol. and solid cancers	CT	NGP
P	PTX	Systemic (PO)	Hematol. cancer	HSCT	Suggestion against
P	PTX	Systemic (IV)	Hematol. cancer	HSCT	NGP
P	PTX	Systemic (PO)	Solid cancer	CT	NGP

P prevention, T treatment, H&N head and neck, RT radiotherapy, RT-CT radiochemotherapy, Hematol. hematologic, CT chemotherapy, HSCT hematopoietic stem cell transplantation, NGP no guideline possible, PTX pentoxifylline, PO per os, IV intravenous

*A comparator RCT was published but was not contributory to the efficacy analysis—aloe vera vs benzydamine [96]

demonstrated that chamomile was effective in reducing OM severity and in relieving OM-associated pain. This RCT is added to a previously reported RCT investigating chamomile in a similar clinical setting that also reported no benefit [58]. Due to conflicting evidence, no guideline was possible.

Chamomile (topical) – hematologic cancer – HSCT – prevention

Guideline: No guideline possible (LoE III)

Topical chamomile was studied for the prevention of OM in an additional clinical setting—patients undergoing HSCT [60]. This study compared 3 doses of *Chamomilla recutita* extract (0.5%, 1%, and 2%) with standard of care consisting of self-oral hygiene and 0.12% CHX. The authors reported that chamomile 1% extract significantly reduced the severity and duration of

OM. Due to limited evidence no guideline was possible.

Other herbal remedies

A variety of herbal remedies were reported for the prevention or treatment of OM since the previous guidelines update [Table 5]. This includes pycnogenol [61], olive leaf [62], Kangfuxin [63], Camelia Sinensis leaf and Palmitoyl hydrolyzed wheat protein (Baxidil Onco) [64], clove-based herbal compound [65], Yashtimadhu ghrita (processed ghee)/Licorice [66], Calendula [67], and Yarrow plant (also called *Achillea millefolium*) [68]. Each intervention had a single RCT. Lower levels of evidence were published for date palm pollen [69], mixed compound based on Lapacho and hyaluronic acid, green tea, Erisimo, propolis, Marigold, Plantain, and Mauve (OraSol Plus) [70], and compound based on *Vaccinium myrtillus* (bilberry), *Macleaya cordata* fruits, and *Echinacea angustifolia* roots

(Samital) [71]. Due to the limited evidence, no guideline is possible for these compounds.

Probiotics and miscellaneous agents

Protean interventions were assessed for either prevention or treatment of OM [Table 6]. Two studies on probiotics were focused on lactobacillus and lactococcus that were administered either systemically or topically [72,73]. Both studies showed efficacy in preventing OM in H&N cancer patients. Considering the limited data for each of these probiotics, no guideline is possible.

Miscellaneous agents that were tested for the management of OM and included in this systematic review are Phenylbutyrate gelformulation mouthwash [72–74], phenytoin [75], oral beta-glucan [76] and platelet gel supernatant [77], and ankaferd hemostat [Table 6] [78]. No guideline was possible for any of these interventions.

Interventions for which evidence was reported prior to 2011 (addressed in the previous guidelines), and no new evidence was reported since are listed briefly as summarized in the 2013 Guidelines Update [Table 7].

Discussion

Herbal remedies have been used for centuries for the healing of numerous conditions in different cultures worldwide [79]. They are the imprint of the local cultures, unique regional vegetation, and ancient medicine knowledge. Herbal remedies are becoming more accessible to a larger community as global communication and interest in alternative medicine increases. With modernized industrial techniques, these agents are available for larger populations. This manuscript covers natural agents, probiotics, and modalities that are affecting the moistening in the mouth and a group of miscellaneous agents. Two new guidelines were made based on this systematic review: a Suggestion in favor for honey, and a Suggestion against chewing gum.

Honey, as a combination protocol of topical and systemic administration, is suggested to prevent OM in patients with H&N cancer treated with RT or RT-CT [18–23]. This new guideline is based on several RCTs showing positive effects for honey. However, since some of these RCTs had a mixed patient population, small sample size, and different sources for the honey, the guidelines can only be confined to a Suggestion. Notably, both RCTs studying topical Manuka honey were negative, and it is unclear if a combined topical and systemic application of Manuka honey will be effective in preventing OM in H&N cancer patients.

Importantly, honey has a cariogenic effect and it adheres to the teeth. . Although the prevention of OM is limited for the duration of the RT, if the honey is applied repeatedly on a daily basis for a longer period, such deleterious effects may occur [80,81] Accordingly, patients who are applying honey to prevent OM should be on a strict oral hygiene program to prevent dental caries [82].

The systematic review yielded a new guideline for chewing gum. Based on the evidence available from 2 RCTs in pediatric patients, a suggestion against the use of chewing gum was made for the prevention of OM in patients with hematologic or solid cancer treated with CT. This guideline does not preclude the use of chewing gum for any other purpose: saliva production, flavor, refreshment, or simply joy. This guideline reflects the fact that chewing gum will not prevent OM in this clinical setting.

Other changes in this section compared with the 2013 guidelines update include identifying evidence for new interventions (propolis), artificial humidification, or for a new clinical setting (curcumin, traumeel, Hangeshashinto). Unfortunately, this new evidence did not culminate into a guideline.

The scope of “miscellaneous” treatments for the management of OM may extend to medical devices, such as appliances to reduce RT-associated OM [83,84]. The group felt that this topic would benefit from a dedicated systematic review, although it was touched on in the previous guidelines update [5]. Likewise, impact of cancer treatment modality and radiation technique on outcomes and toxicity of patients are not included in this systematic review as OM was a secondary endpoint. Rarely, studies on the modification to the cancer therapy protocol addressed OM as the primary endpoint [85–87].

Several studies were published since the cut-off date of this literature review, which refers to propolis, honey, Glycyrrhiza aqueous extract and licorice. Propolis was studied in a RCT in breast cancer patients receiving doxorubicin and cyclophosphamide. The results showed that propolis plus sodium bicarbonate was significantly more effective than sodium bicarbonate alone in preventing OM [88]. As this study reports about a clinical setting that was not reported previously, this is considered to be initial information that needs confirmation in the future. Propolis was also studied as part of a mixture of 4 natural agents: propolis, Aloe vera, calendula, and chamomile [89]. In this RCT in H&N cancer patients receiving RT, the mixture was reported to be superior to placebo in preventing OM. A recent RCT investigated honey to prevent OM in a single-blinded design [90]. This study concluded that honey was effective in preventing OM in patients with leukemia treated with CT; however, considering the variation in the mode of application, and the small sample size, the collective evidence about honey in this

clinical setting did not cross the threshold for a guideline. Glycyrrhiza aqueous extract was studied in a single small RCT, and showed positive results. This evidence was too limited to set a guideline [91]. Licorice in mucoadhesive vehicle was reported to be as effective as triamcinolone acetonide in reducing OM severity in H&N cancer patients treated with RT only [92]. As this RCT was designed as a comparator study without a placebo arm, the results are not contributory to the efficacy analysis in this study.

In summary, the MASCC/ISOO guideline update suggests applying honey, combined topically and systemically, for the prevention of OM in H&N cancer patients treated with either RT or RT-CT. Chewing gum is not suggested for the prevention of OM in pediatric patients with hematological or solid cancer treated with CT. These guidelines are subject to further updates pending results of future published studies.

Compliance with ethical standards

Conflict of interest Per MASCC Guidelines Policy, employees of commercial entities were not eligible to serve on this MASCC Guidelines Panel.

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