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REVIEW ARTICLE

Systematic review of natural agents for the management of oral mucositis in cancer patients

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Abstract
Purpose The aim of this study was to review the available literature and define clinical practice guidelines for the use of natural agents for the prevention and treatment of oral mucositis.
Methods A systematic review was conducted by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology. The body of evidence for each intervention, in each cancer treatment setting, was assigned an evidence level. Based on the evidence level, one of the following three guideline determinations was possible: recommendation, suggestion, and no guideline possible.
Results A total of 49 papers across 15 interventions were examined. A new suggestion was developed in favor of systemic zinc supplements administered orally in the prevention of oral mucositis in oral cancer patients receiving radiation therapy or chemoradiation (Level III evidence). A recommendation was made against the use of intravenous glutamine for the prevention of oral mucositis in patients

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receiving high-dose chemotherapy prior to hematopoietic stem cell transplant (Level II evidence). No guideline was possible for any other agent, due to inadequate and/or conflicting evidence.
Conclusions Of the various natural agents reviewed here, the available evidence supported a guideline only for two agents: a suggestion in favor of zinc and a recommendation against glutamine, in the treatment settings listed above. Well-designed studies of other natural agents are warranted.

Keywords Oral mucositis · Natural agents · Glutamine · Zinc · Guidelines

Introduction

Oral mucositis is a significant and often dose-limiting complication of cancer therapy. Ulcerative lesions of oral mucositis can be very painful, with negative impact on diet, oral hygiene, and quality of life. These lesions can also be secondarily infected and potentially lead to systemic sepsis in immunocompromised patients. A wide variety of agents have been tested to prevent oral mucositis or reduce its severity. Among these, there has been significant interest in the use of naturally occurring compounds as agents for mucositis. Since mucositis is a toxicity of cancer therapy, the use of naturally occurring compounds is attractive as they are generally perceived to have fewer side effects as compared to synthetic drugs; however, this is not always true. Different naturally occurring agents can theoretically act on different aspects of the pathogenesis of mucositis. For example, natural agents such as glutamine may help to mitigate the damage caused by reactive oxygen species that are believed to play a critical role in the initiation of oral mucositis. Other natural agents such as honey may have anti-inflammatory effects, while vitamins and herbs may promote healing.

The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) has published evidence-based clinical practice guidelines for mucositis [1], in order to facilitate evidence-based patient care and improve outcomes. The last guidelines update in 2006 examined the evidence to date for the following natural agents: glutamine, milk-derived protein extract, vitamins, and aloe vera. However, no guideline was possible for any of these agents due to insufficient and/or conflicting evidence [2]. Since then, there has been an increase in the published literature on these agents as well as several additional natural compounds tested for oral mucositis. As part of a comprehensive update of the MASCC/ISOO clinical practice guidelines for mucositis, the aim of this project was to systematically review the available literature and define evidence-based clinical practice guidelines for the use of natural agents for the prevention and treatment of oral mucositis.

Methods

The methods are described in detail in Bowen et al. [3] and Elad et al. [4]. Briefly, a literature search for relevant papers indexed in Medline until 31 December 2010 was conducted using OVID/MEDLINE, with papers selected for review based on defined inclusion and exclusion criteria. The list of intervention keywords used for the literature search of this section included: alternative, complementary, homeopathic, aloe vera, beta-carotene, chamomile, chinese herbal, folic acid, glutamine, hydrolytic enzyme, MF 5232 (mucotrol), multivitamin, natural, polaprezinc, traumeel, tretinoin, vitamin, zinc, honey, manuka & kanuka oil, *Rhodiola algida*, vitamin A, vitamin E, Wobe-Mugos E, retinoid, and indigo wood root. This literature search was combined with a search for miscellaneous interventions for oral mucositis. This paper presents the results for the natural interventions while those for the miscellaneous interventions are reported elsewhere in this issue [5].

The selected papers were reviewed by two independent reviewers, and data were extracted using a standard electronic form. Studies were evaluated based on the list of major and minor flaws published by Hadorn [6]. A Level of Evidence was assigned for each intervention based on the Somerfield criteria [7]. A well-designed study was defined as a study with no major flaws as 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 three 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 (radiotherapy, chemotherapy, chemoradiotherapy, or high-dose conditioning therapy for hematopoietic stem cell transplant), and (3) the route of administration of the intervention.

Results

The literature searches for this section identified 99 papers for which the abstracts were reviewed. Of these, 18 articles were removed after evaluation of the full article based on the inclusion/exclusion criteria described in Bowen et al. [3]. Of the remaining 81 papers, 49 papers describing only natural interventions were included in the present systematic review, while the remaining 32 papers addressing miscellaneous agents were assessed in a separate systematic review [5]. Tables 1, 2, 3, 4, and 5 summarize the details of the articles reviewed.

Glutamine

Glutamine is the most abundant free amino acid in the body and is known to play a regulatory role in several cell-specific

Table 1 Summary of findings for glutamine

Name of agent	Route of administration	Cancer type	Treatment modality	Indication	Author, year (citation number from reference list) of papers reviewed	Efficacy	Overall level of evidence	Guideline determination	Comments
Glutamine	IV	Hematological cancer	HSCT	P	Van Zaanen 1994 [11]	N	II	IV glutamine is not recommended for prevention of oral mucositis in HSCT patients	Piccirillo 2003 [9]—1/27 with osteosarcoma
			HSCT	P	Pytlik 2002 [13]	N			Pytlik 2002 [13]—4/40 with solid tumors
			HSCT	P	Piccirillo 2003 [9]	Y			
			HSCT w/ TBI	P	Blijlevens 2005 [12]	N			
			HSCT w/ TBI	P	Kuskonmaz 2008 [10]	N			
Glutamine	IV	Hematological cancers	CT	P	Sornsuvit 2008 [14]	N	III	No guideline possible	
Glutamine	PO and S&S	GI	CT	P	Jebb 1994 [19]	N	III	No guideline possible	Ward 2005 [22]—pediatric population
		Solid cancers	CT	P	Skubitz 1996 [20]	N			
		Solid cancers	CT	P	Anderson 1998 [21]	N			
		Breast cancer	CT	P	Rubio 1998 [15]	Y			
		NS	CT	P	Okuno 1999 [8]	N			
		Solid and hematological cancers	CT	P	Cockerham 2000 [16]	Y			
		Solid and hematological cancers	CT	P	Ward 2005 [22]	N			
		Solid cancers	CT	P	Choi 2007 [17]	Y			
		Breast cancer	CT	P	Peterson 2009 [18]	Y			
Glutamine	PO and S&S	Solid and hematological cancers	HSCT w/ TBI	P	Anderson 1998 [23]	N	III	No guideline possible	Anderson 1998 [23] —effectiveness was reported positive for pain relief but not for mucositis prevention. Mixed population.
		Hematological cancer	HSCT w/ TBI	P	Coghlin 2000 [24]	N			Aquino 2005 [25]—age<21 effectiveness demonstrated as reduction of IV narcotics and TPN consumption but not for mucositis prevention
		Solid and hematological cancers	HSCT w/ TBI	P	Aquino 2005 [25]	N			
Glutamine	IV+PO	Solid and hematological cancers	HSCT w/ TBI	P	Schloerb 1999 [26]	N	III	No guideline possible	
Glutamine	MW	H&N cancer	RT	P	Huang 2000 [27]	Y	III	No guideline possible	

IV intravenous, *CT* chemotherapy, *HSCT* hematopoietic stem cell transplant, *w/* with, *TBI* total body irradiation, *RT* radiotherapy, *P* prevention, *T* treatment, *N* no, *Y* yes, *PO* per os, *S&S* swish and swallow, *GI* gastrointestinal, *TPN* total parenteral nutrition, *NS* not specified

Table 2 Summary of findings for vitamins

Name of agent	Route of administration	Cancer type	Treatment modality	Indication	Author, year	Effectiveness	Overall level of evidence	Guideline determination	Comments
Vit A	PO	Solid and hematological cancer	CT	P	Kokkonen 2002 [32]	N	III	No guideline possible	Pediatric patients. Acitretin. Small sample, $n=10$ for study and control each.
Vit A	PO	H&N cancer	CT and RT	P	Mills 1988 [30]	Y	III	No guideline possible	Beta-carotene. Small sample, $n=10$ for study and control each.
Vit A	Paste	Hematological cancer	HSCT w/wo TBI	P	Cohen 1999 [31]	Y	III	No guideline possible	Tretinoin. Small sample $n=6$, 5 for study and control, respectively
Vit E	PO or S&S	NS	CT	T	El-Housseiny 2007 [36]	Y	IV	No guideline possible	Pediatric patients. Control group was treated with systemic vitamin E.
Vit E	S&S	H&N cancer	RT	P	Ferreira 2004 [34]	Y	III	No guideline possible	
Vit E	MW	Combination	CT	P	Sung 2007 [37]	N	IV	No guideline possible	Pediatric patients.
Vit E	Topical application of vitamin E oil	Solid and hematological cancer	CT	T	Wadleigh 1992 [35]	Y	IV	No guideline possible	Small sample, $n=9$ for study and control each.
Vit and dietary supplements	Dietary supplement	Solid cancer breast	CT	P	Branda 2004 [38]	N	IV	No guideline possible	The study referred to combination of vitamins, minerals and nutraceuticals[a]

Vit vitamin, *PO* per os, *H&N* head and neck, *CT* chemotherapy, *RT* radiotherapy, *HSCT* hematopoietic stem cell transplantation, *TBI* total body irradiation, *w* with, *w/o* without, *P* prevention, *T* treatment, *Y* yes, *N* no

[a] Vitamins: vitamin A, folic acid, B complex, vitamins C, D, and E; Minerals: mineral complex, calcium, iron, magnesium, selenium, zinc; Nutraceuticals: *Gingko*, *Echinacea*, Coenzyme Q, glutamine, and others

Table 3 Summary of study findings for honey

Name of agent	Route of administration	Cancer type	Treatment modality	Indication	Author, year	Effective	Overall level of evidence	Guideline determination	Comments
Honey	MW	H&N cancer	RT	P	Khanal 2010 [39]	Y	III	No guideline possible	Honey compared to lignocaine MW Honey extracted from beehives of the Western Ghats forests
Honey	S&S	H&N cancer	RT	P	Biswal 2003 [41]	Y	III	No guideline possible	Honey extracted mainly from the tea plant, *Camellia sinensis*
Honey	S&S	H&N cancer	RT	P	Motallebnejad 2008 [40]	Y			Honey extracted from Thymus and Astragale in the Alborz mountains
Honey	S&S	H&N cancer	C/RT	P	Rashad 2009 [42]	Y	III	No guideline possible	Honey extracted from the clover plant *Trifolium alexandrenum*

MW mouthwash, *S&S* swish and swallow, *H&N* head and neck, *RT* radiotherapy, *C/RT* chemo-radiotherapy, *P* prevention

processes including metabolism, cell integrity, protein synthesis, and extracellular matrix synthesis [8]. Table 1 summarizes the details of studies reviewed on glutamine.

Intravenous glutamine in patients undergoing hematopoietic stem cell transplant

Five studies have evaluated the effectiveness of intravenous (IV) glutamine in preventing oral mucositis among patients with hematological malignancies receiving high-dose chemotherapy [with or without total body irradiation (TBI)] prior to hematopoietic stem cell transplant (HSCT). Of these, only one study reported a slight benefit of glutamine. In this study of 22 subjects, the 10 subjects receiving glutamine had a marginally significant (p=0.047) lower mucositis score (combination of subjective and objective scores), as compared to 12 subjects receiving placebo [9]. In contrast, the other four randomized controlled trials (RCTs) consistently found no significant differences in the severity of oral mucositis between IV glutamine and placebo or no treatment [10–13]. Moreover, in one study, IV glutamine made mucositis worse and was significantly associated with more relapses (p=0.02) and higher mortality (p=0.05) [13]. The available body of evidence was adequate to support a new recommendation against the use of IV glutamine for prevention of oral mucositis in this setting.

Guideline The panel recommends that IV glutamine should not be used for the prevention of oral mucositis in patients receiving high-dose chemotherapy (with or without TBI) prior to HSCT (Level II evidence).

IV glutamine in patients receiving standard dose chemotherapy

Only one pilot study evaluated the efficacy of IV glutamine in mucositis secondary to conventional chemotherapy [14]. There was no statistically significant difference in mucositis duration or severity between the glutamine and control groups (n=8 in each group). No guideline was possible due to insufficient evidence in this setting.

Oral glutamine in patients receiving standard dose chemotherapy

The effectiveness of oral glutamine (including mouthwash—swish and swallow) for the prevention of oral mucositis due to chemotherapy was studied in various solid tumors and hematological cancer patients. Four studies found glutamine to be effective in preventing oral mucositis (15–18), while five studies found it to be ineffective [8, 19–22]. No guideline was possible due to the conflicting evidence.

Oral glutamine in patients undergoing HSCT

The effectiveness of oral glutamine (including mouthwash—swish and swallow) for the prevention of oral mucositis during HSCT conditioning (high-dose chemotherapy and TBI) was evaluated in three studies [23–25]. Although none of the studies found glutamine to be effective in objectively reducing severity of mucositis lesions, glutamine was found to reduce intravenous narcotic and total parenteral nutrition (TPN) use in one study [25]. In another study, the glutamine group had a

Table 4 Summary of study findings for zinc

Name of agent	Route of administration	Cancer type	Treatment modality	Indication	Author, year	Effectiveness	Overall level of evidence	Guideline determination	Comment
Zinc (Polaprezinc)	S&S	H&N	RT or RT&CT	P	Watanabe 2010 [46]	Y	III	Suggestion: *The panel suggests that systemic zinc supplements administered orally may be of benefit in the prevention of oral mucositis in oral cancer patients receiving radiation therapy or chemoradiation.*	Effectiveness referred to incidence of mucositis, incidence of pain score, and reduced use of analgesics.
Zinc	PO	H&N cancer & lymphomas	RT or RT&CT	P	Ertekin 2004 [45]	Y			Effectiveness refers to mucositis score (RTOG), mucositis onset, and time to start of healing.
Zinc	PO	H&N	RT or RT&CT	P	Lin 2006 [44], Lin 2010 [43]	Y (in oral cancer patients)			Lin 2006 [44]; Effectiveness refers to mucositis score and onset.

PO per os, *S&S* swish and swallow, *H&N* head and neck, *CT* chemotherapy, *RT* radiotherapy, *P* prevention, *Y* yes

lower duration and severity of mouth pain [23]. Due to the mixed data, no guideline was possible.

Combined IV and oral glutamine in patients undergoing HSCT

The combination of IV and oral glutamine in hematologic cancer patients during conditioning for HSCT was studied in a single RCT of 66 subjects. The use of glutamine did not reduce mucositis severity or days of TPN, as compared to controls receiving glycine [26]. No guideline was possible due to insufficient evidence in this setting.

Topical glutamine in head and neck cancer patients undergoing radiotherapy

A pilot study with 17 subjects was conducted to test topical glutamine (mouthwash that is not swallowed) in preventing oral mucositis in head and neck (H&N) cancer patients treated with radiotherapy [27]. The duration and severity of objective mucositis were lower in the glutamine group, although there was no difference in the duration and severity of subjective symptoms and analgesic use. No guideline was possible due to insufficient evidence in this setting.

Vitamins

Table 2 summarizes the results of the systematic review on the use of vitamins for prevention or treatment of mucositis associated with cancer therapy. Out of eight publications reviewed, three were on the effect of vitamin A, four on vitamin E, and one on a combination of vitamins, minerals, and dietary supplements.

Vitamin A

Although the exact mode of action is not well understood, it has been thought that vitamin A can promote mucosal cell turnover and therefore could prevent mucositis [28, 29]. A single RCT demonstrated that supplementation with beta-carotene reduced the severity of oral mucositis in H&N cancer patients receiving chemoradiation [30]. Another RCT testing tretinoin in patients undergoing HSCT also indicated a beneficial effect [31]. In contrast, another RCT has found a lack of effectiveness of systemic administration of vitamin A derivative acitretin in pediatric patients receiving chemotherapy for various cancers [32]. The sample size used in all these studies was small, with ten subjects or less in each group. No guideline was possible due to insufficient and conflicting evidence.

Vitamin E

Vitamin E can protect the oral mucosa through its antioxidant and membrane stabilization properties and by interfering with

Table 5 Summary of study findings for other agents

Name of agent	Route of administration	Cancer type	Treatment modality	Indication	Author, year	Effectiveness	Overall level of evidence	Guideline determination	Comment
Aloe vera gel	PO	H&N	RT or RT&CT	P	Su 2004 [47]	N	III	No guideline possible	
Chamomile	MW	NS	CT	P	Fidler 1996 [48]	N	III	No guideline possible	All subjects received cryotherapy.
Kamillosan Liquidum	MW	H&N, hematological and other solid cancers	RT or RT&CT	P	Carl 1991 [49]	Y			An uncontrolled study. Mix of prevention and treatment protocols
Chinese herbal (Qing Wei San or Yu Nu Jian)	MW	Hematological cancer	NS	P	Zhu 1993 [50]	Y	V	No guideline possible	
Indigowood root	S&S	H&N cancer	RT or RT&CT	P	You 2009 [51]	Y	III	No guideline possible	
Manuka & kanuka oils	S&S	H&N cancer	RT	P	Maddocks-Jennings 2009 [52]	Y	III	No guideline possible	Three groups: active treatment, placebo, and control ("usual care"). Efficacy refers to onset of mucositis.
MF 5232 (Mucotrol)	PO	H&N cancer	RT&CT	T	Naidu 2005 [53]	Y	III	No guideline possible	Gel wafer formulation to chew and slowly dissolve. Effectiveness refers to mucositis severity scores.
Rhodiola algida	PO	Breast cancer	CT	P	Loo 2010 [54]	Y	III	No guideline possible	Effectiveness refers to ulcer's quantity, size and duration as well as pain. Control group was treated with honey water.
Spray compound (collagen, amino acids, and sodium hyaluronate)	Topical	H&N, solid, and hematological cancer	RT or RT&CT or CT	T	Colella 2010 [55]	Y	IV	No guideline possible	Effectiveness refers to pain relief and time to healing.
Traumeel S	MW	hematologic cancer & other	HSCT	P	Oberbaum 2001 [56]	Y	III	No guideline possible	Pediatric population. Effectiveness refers to area under the curve for mucositis scores
Wobe-Mugos E	PO	H&N cancer	RT	P	Gujral 2001 [56]	Y	III	No guideline possible	Papain 100 mg, trypsin 40 mg, chymotrypsin 40 mg. Effectiveness refers to mucositis scores
Wobe-Mugos E	PO	H&N cancer	RT	P	Dorr 2007 [57]	N	II		Same composition

PO per os, *MW* mouthwash, *S&S* swish and swallow, *H&N* head and neck, *CT* chemotherapy, *HSCT* hematopoietic stem cell transplantation, *RT* radiotherapy, *P* prevention, *T* treatment, *N* no, *Y* yes, *NS* not specified

the inflammatory damage caused by the chemotherapy and radiotherapy [33, 34]. Of three small studies testing topical vitamin E in chemotherapy-induced oral mucositis, two reported a beneficial effect [35, 36], while one did not [37]. A single RCT in patients undergoing H&N radiotherapy reported a modest reduction in number of events of symptomatic mucositis [33]. No guideline was possible due to insufficient and conflicting evidence.

Combination of vitamins and other supplements

One cohort study evaluated the effectiveness of a combination of vitamins, minerals, and other dietary supplements on the prevention of chemotherapy-induced mucositis in breast cancer patients. No beneficial effect was seen [38]. No guideline was possible due to insufficient evidence.

Honey

Honey has been studied for the prevention of oral mucositis because of evidence suggesting a positive effect on healing of wounds, such as burns and pressure wounds. Four studies assessed honey for the prevention of mucositis in head and neck cancer patients. Table 3 summarizes the details of these studies.

One study focused only on the topical effect of honey [39], and three studies combined the topical and systemic effects [40–42]. Although results were generally promising, the data were insufficient to reach a consensus about a suggestion. Therefore, no guideline was possible.

Zinc

Zinc is an essential element for normal growth, wound healing, maintenance of the immune systems, and other vital functions [43–45, 46]. Table 4 summarizes the details of the studies reviewed for zinc.

A small unblinded RCT investigated the use of a zinc-containing molecule called polaprezinc (zinc L-carnosine) as a mouthrinse (swish and swallow) in patients undergoing radiotherapy or chemoradiation for H&N cancer. Compared to the control group receiving azulene rinse, the zinc group had a lower incidence of oral mucositis, pain, and analgesic use [46]. Another RCT in the same population tested the use of systemic zinc sulfate capsules as compared to placebo. The zinc sulfate group had a lower severity, delayed onset, and shorter time to healing of oral mucositis [45]. A larger double-blind, placebo-controlled RCT also tested systemic zinc supplementation in H&N cancer patients undergoing radiotherapy or chemoradiation. Zinc supplementation was found to result in a lower severity and delayed onset of oral mucositis [44]. A subsequent sub-group analysis of the results of this study found that the benefit was limited to patients with oral cancer, while patients with nasopharyngeal cancer did not have any benefit [43]. Based on the consistently positive results of three RCTs testing zinc, the panel supported a new suggestion in favor of this agent.

Guideline The panel suggests that systemic zinc supplements administered orally may be of benefit in the prevention of oral mucositis in oral cancer patients receiving radiation therapy or chemoradiation (Level III evidence).

Aloe vera gel

Aloe vera has been used historically to assist with wound healing, and has been used to treat radiation-induced dermatitis where anecdotally the patients have found it helpful [47]. One RCT evaluated the efficacy of aloe vera as a swish and swallow mouthwash in the prevention of radiation-induced mucositis in head and neck cancer patients [47]. The aloe vera gel was comprised of 94.5 % aloe juice, 5 % pear juice concentrate, 0.4 % lemon-lime flavor, and 0.1 % citric acid. The study did not demonstrate any advantage of this treatment. No guideline was possible due to insufficient evidence.

Chamomile mouthwash

Chamomile has been used as a traditional and herbal medicine for centuries. Chamomile contains compounds that have anti-inflammatory, anti-fungal, and anti-bacterial properties, as well as antiseptic, and sedative effects [48].

Two studies evaluating the use of chamomile to prevent oral mucositis were reviewed. First, a RCT that enrolled 164 patients receiving 5FU compared chamomile to placebo [48]. All patients received 30 min of cryotherapy during their infusions in addition to the study mouthwash. The results of the trial determined that chamomile mouthwash was not effective in lessening 5FU-induced mucositis. The second study evaluated the use of Kamillosan Liquidum ® as an oral rinse in 98 patients undergoing treatment for head and neck, hematological, and other solid tumors [49]. Kamillosan oral rinse, which is based on the same active agent, was used prophylactically in the 20 patients being treated with radiation therapy alone for head and neck cancer, as well as 46 patients being treated with chemotherapy alone. Further, 32 patients received Kamillosum Liquidum therapeutically following the development of mucositis. Sixteen of the patients of the latter group went on to receive prophylactic and therapeutic Kamillosan Liquidum rinse with their next course of chemotherapy. All patients were asked to mix 10–15 drops of Kamillosan Liquidum rinse in 100 ml of warm water and to rinse vigorously at least three times per day. Only one patient in the radiation group developed a grade 3

mucositis in the final week of treatment. Thirty-six patients undergoing chemotherapy alone did not develop clinically noticeable mucositis [49]. Although this study reported positive results, it was an uncontrolled study. Overall, no guideline was possible for chamomile due to insufficient and conflicting evidence.

Chinese herbal drug mouthwash

In a case series of 31 leukemia patients [50], Chinese herbal drug mouthwashes were evaluated for stomatological complications of leukemia or its treatment. Fourteen patients determined to have "exuberance" were treated with a mouthwash of Qing Wei San ® (powder for clearing stomach heat). An additional 17 patients determined to have "deficiency" were treated with a mouthwash of Yu Nu Jian ® (gypsum decoction). The authors reported that these treatments were markedly effective in resolving oral ulcerations in 7 cases and effective in 19 cases. They concluded that these herbal drugs "replenish ying and clear the heat." No guideline was possible due to insufficient evidence.

Indigowood root

Indigowood root is a commonly used Chinese herb thought to have some antiviral and anti-inflammatory effects [51]. One small RCT has evaluated the use of Indigowood root for the prevention of oral mucositis in head and neck cancer receiving medium-dose radiotherapy (45 Gy). Patients gargled with a 30-ml indigowood root solution for 3 min and then swallowed it before meals daily. The study reported a reduced severity of radiation mucositis assessed by the maximum mucositis grade, as well as a reduction in anorexia, and swallowing difficulty. However, no guideline was possible due to insufficient evidence.

Manuka and kanuka oils

Manuka (*Leptospermum scoparium*) and kanuka (*Kunzea ericoides*) honeys native to New Zealand have been used medicinally by both Maori and early European colonists. The essential oils of manuka and kanuka are known to have antibacterial and antifungal activity as well as anti-inflammatory and analgesic actions [52].

One RCT feasibility study in a small sample of patients undergoing radiation therapy for head and neck cancers was reviewed [52]. The analysis included six patients in the treatment arm (manuka–kanuka oils), six patients in the control group (water rinse), and seven patients in the "usual care" (no rinse). The results of the study support the potential for a mix of manuka and kanuka essential oils as a gargle to prevent mucositis. The small sample size is a limitation of this study. No guideline was possible due to insufficient evidence.

MF 5232 (Mucotrol®)

Mucotrol is a concentrated oral polyherbal gel wafer which consists of sorbitol, *Cyamopsis tetragonolobus*, stearic acid, magnesium stearate, aloe, natural and artificial flavors, acesulfame K, extracts of glycyrrhizin, *Centella asiatica*, *Polygonum cuspidatum*, *Angelica* sp., and *Camellia sinensis*. The mechanism of action of Mucotrol is not known; however, it is presumed to have local analgesic, anti-oxidant, immunomodulatory activity, and wound-healing properties [53].

One pilot RCT was reviewed which evaluated patients receiving radiation treatment and chemotherapeutic cisplatin for oral and oropharyngeal cancers [53]. A decrease of 34.63 % in the WHO mucositis score was seen in the 11 evaluable subjects in the treatment arm, as compared to 11 evaluable subjects in the placebo arm. No guideline was possible due to insufficient evidence.

R. algida

R. algida is a Tibetan plant used in traditional Chinese medicine to stimulate the immune system by nourishing and invigorating *Qi* and activating blood circulation against stasis. A RCT involving 130 breast cancer patients treated with chemotherapy and surgery was reviewed [54]. Half of the patients were given a solution of *R. algida*, while the controls received honeybee water. The test group was given 200 ml of boiled *R. algida* solution for seven consecutive days after they received chemotherapy. The findings of the study were that *R. algida* reduced pain, the quantity of oral ulcers, and shortened the duration of mucositis compared to the control group. No guideline was possible due to insufficient evidence.

Spray compound (based on collagen, amino acids, and sodium hyaluronate)

One study tested a spray compound that consists of sodium hyaluronate combined with a pool of collagen precursor synthetic amino acids (L-proline, L-leucine, L-lysine, and glycine). This composition is thought to promote wound healing and reduce pain by forming a muco-adherent barrier on the mucosa. An open-label before-and-after study tested the spray compound in patients undergoing chemotherapy, radiation therapy, or combined chemotherapy and radiation therapy for the treatment of a variety of cancers [55]. Results showed that painful symptoms of oral mucositis were significantly reduced after spray administration compared with baseline measurements. No guideline was possible due to insufficient evidence.

Traumeel S ®

Traumeel S is a homeopathic complex mouthwash agent made up of *Arnica montana*, *Calendula officinalis*, *Achillea*

millefolium, *Matricaria chamomilla*, *Symphytum officinale*, *Atropa belladonna*, *Aconitum napellus*, *Bellis perennis*, *Hypericum perforatum*, *Echinacea angustifolia*, *Echinacea purpurea*, *Hamamelis virginiana*, *Mercurius solubilis*, and *Hepar sulfuris*. It has been used to treat trauma, inflammation, and degenerative processes. The mechanism of action remains unknown [56].

A randomized, placebo-controlled, double-blind clinical trial in 30 patients was reviewed [56]. Patients undergoing hematopoietic stem cell transplantation between the ages of 3–25 years were included. Traumeel S was assigned to 15 patients on day 2 after transplantation and continued for a minimum of 14 days. Five patients (33 %) in the treatment group did not develop mucositis, while only one (7 %) in the placebo group did not develop mucositis. No guideline was possible due to insufficient evidence.

Wobe-Mugos E/proteolytic enzymes

Wobe-Mugos E is made up of proteolytic enzymes comprising of papain 100 mg, trypsin 40 mg, and chymotrysin 40 mg. It is postulated that the enzymes degrade toxic metabolic and inflammatory substances, thereby having anti-inflammatory and analgesic effects [57, 58].

Two studies, both RCTs, were evaluated to test the efficacy of preventing acute radiation side effects of head and neck cancer patients undergoing radiation therapy alone. One study [57] enrolled 36 patients in the treatment arm and 33 in the placebo arm. This study found no difference in mucositis severity and an earlier onset of mucositis in the Wobe-Mugos E arm [57]. The second RCT [58] enrolled 53 patients in the study arm and 47 in the control arm (no treatment). This study found that the severity and duration of oral mucositis were less in the study arm. No guideline was possible due to the conflicting evidence.

Discussion

The use of "herbal" and "natural" remedies for various indications is gradually increasing during the last few decades mainly because of the popular belief that they are totally safe. Since most such agents are poorly regulated and available without a prescription, widespread adoption can occur in the absence of scientific evidence. However, these remedies can pose serious health risk either directly by causing adverse effects or indirectly by their interaction with some medications [59]. These risks may be particularly relevant in cancer patients during active antineoplastic treatment when mucositis usually occurs. A number of different natural agents have been tested for prevention or treatment of oral mucositis. The members of the panel systematically reviewed the available literature regarding the use of natural remedies used as interventions for oral mucositis. Unfortunately, very few studies were available for most remedies with low level of evidence in most cases (according to the Somerfield criteria).

The most studied product among this group of natural remedies was glutamine with 20 papers that fulfilled the entry criteria for this review. With regard to the pathogenesis of oral mucositis, glutamine can help mitigate the damaging effects of reactive oxygen species. Deamidation of glutamine results in formation of glutamate, which in turn can be converted into glutathione, a major antioxidant [60]. Glutamine may also reduce the production of pro-inflammatory cytokines and cytokine-related apoptosis, and promote wound healing by increasing fibroblast number and collagen synthesis [18]. Various routes of administration were used to assess the beneficial effect of glutamine on oral mucositis in different cancer patient populations. Five studies have evaluated the efficacy of IV glutamine in preventing mucositis among cancer patients undergoing high-dose chemotherapy (with or without TBI) prior to HSCT [9–13]. Only one study has found glutamine to be effective, while four RCTs failed to demonstrate its efficacy. Moreover, in one study glutamine was thought to made oral mucositis worse, and was associated with more relapses and worse mortality rate [13]. Therefore, the panel has decided that there is sufficient body of evidence to recommend that IV glutamine should not be used for the prevention of oral mucositis in patients receiving high-dose chemotherapy (with or without TBI) prior to HSCT. Studies examining the use of glutamine in other cancer treatment settings provided mixed results, and therefore, no other guidelines were possible for this agent. It is worthwhile mentioning that in the systematic review of interventions for the management of gastrointestinal mucositis, the previous negative guideline for glutamine was reversed as no severe toxicities were found in the recently published studies [61].

A number of studies examined the use of various vitamin preparations on oral mucositis. While vitamins are widely believed to be beneficial to human health, a specific positive effect on oral mucositis has not been clearly established. The studies reviewed here provided conflicting data on the benefit of vitamins for mucositis, and no guideline was possible. A number of factors may account for these conflicting results. One factor is that various studies tested different forms of the same vitamin, which may have different levels of bioavailability and activity against mucositis. For example, of the three studies testing vitamin A, one tested acitrecin, the second tested beta-carotene, and the third tested tretinoin. Another potential confounding factor in vitamin studies is the contribution of vitamins from the patients' diet, which can complicate the interpretation of such studies.

Honey is a natural product believed to have medicinal value in some cultures. It is hypothesized that the beneficial

effect on wound healing is due to the capability of honey to inhibit bacterial growth and to activate immune responses [40]. Interestingly, all the four studies reviewed here reported a beneficial effect. However, each study used a different source of honey which is thought to have a significant impact on its properties. The composition of honey is difficult to define since it is not a generic product. The ingredients and their relative amounts are dependent on the flora of the geographical area from which honeybees collect pollen. Considering that the four studies used different types of honey, it becomes challenging to compare between the studies even if the clinical setting is identical. These factors and limitations in the studies reviewed did not allow the development of a guideline. A potential concern with the use of honey in xerostomic H&N radiotherapy patients with salivary gland hypofunction is a possible caries-promoting effect, although the use is typically short term over the period of radiotherapy. It is also relevant to note that a recently published abstract of a large double-blind, placebo-controlled trial of manuka honey in H&N cancer patients undergoing radiotherapy or chemoradiation found no evidence of a beneficial effect [62].

Zinc is an essential trace element that is required for some tissue repair processes. Zinc also induces metallothionein, which can act as a scavenger for damaging free radicals. In an animal model of methotrexate-induced intestinal mucositis, the presence of metallothionein reduced histological damage and neutrophil infiltration [63]. We reviewed three discrete studies testing zinc supplementation in patients with H&N cancer, all of which found a positive effect. The strongest of these studies was a double-blind, placebo-controlled RCT that found a lower severity and delayed onset of oral mucositis in oral cancer patients receiving systemic supplementation [44]. Interestingly, a subgroup analysis found that these benefits did not extend to nasopharyngeal cancer patients [43]. Based on these findings, we developed a new suggestion in favor of zinc in oral cancer patients receiving radiation therapy or chemoradiation.

In conclusion, of the various natural agents reviewed here, the available evidence supported a guideline only for two agents: a suggestion in favor of zinc and a recommendation against glutamine, in the treatment settings listed above. Well-designed studies of other natural agents are warranted. These studies should also examine the potential adverse events associated with the use of such agents, including drug interactions.

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