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Honey in the management of side effects of radiotherapy- or radio/chemotherapy-induced oral mucositis. A systematic review

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ABSTRACT

Background: and purpose: In spite of several trials, systematic reviews and meta-analyses, honey is not considered as a viable candidate for the prophylaxis and treatment of radiotherapy-induced oral mucositis in the practice guidelines for supportive care. The purpose of this study was to analyse the value of honey in this treatment situation based on randomized trials acknowledging the fact that manuka honey which is used in some trials distinguishes itself from other honey due to the presence of methylglyoxal.

Methods: On the basis of a literature search, we identified and analysed 17 randomized trials on the topic. Participants in these trials received radiotherapy or a combination of radiotherapy and chemotherapy for head and neck cancer.

Results: Studies using manuka honey found little rationale for the medicinal use of honey (n = 4) in this field, whereas trials using conventional honey presented data on its usefulness (n = 13). Thus, the type of honey may explain the divergent results of trials in this area.

Conclusion: Conventional honey is likely to be effective in the prophylaxis and treatment of radiation- and chemoradiation-induced oral mucositis.

1. Introduction

Beside surgery, radiation therapy in combination with chemotherapy, especially cisplatinum, is the most common form of treatment for head and neck cancer and represents the gold standard [1]. However, this combination frequently leads to oral mucositis involving dose-limiting inflammation, ulceration of the oral cavity, pain, odynodysphagia, dysgeusia, dehydration, malnutrition, systemic infection and reduced quality of life and survival secondary to dose reduction or therapy discontinuation [2]. The pathogenesis of mucositis is related to ionizing radiation and chemotherapeutic agents through direct mechanisms (susceptibility of mucosal tissues to apoptosis from cytotoxic therapy) and indirect mechanisms (release of proinflammatory mediators such as tumour necrosis factor, interleukin-1 beta and interleukin-6 with a concomitant decrease in the anti-inflammatory cytokines interleukin-10 and transforming growth factor-β) [2]. Nodal status, smoking history, single dose parapharyngeal irradiation, and pre-treatment platelet count were found to be independent risk factors for an acute radiation-induced oral mucosal reaction [3]. However, there seems to be genetic susceptibility for the development of oral mucositis due to cancer therapy as well [4]. The German S3-guideline (guideline following a systematic development) for supportive care recommends standardized oral care consisting of regular application of mouth rinses, dental hygiene (use of a soft toothbrush, use of dental floss), avoidance of noxious substances (alcohol, tobacco, spicy and hot dishes, acidic food), continuous control for lesions and pain, prophylactic measures by dentists, fluoridation for dental protection, and clinical control and counselling during therapy [5]. Additionally, benzydamine and oral zinc supplementation are also suggested as possible means of prevention or treatment of oral mucositis. The committee voted against the use of antibiotic or antimycotic mouthwashes, sucralfate, misoprostol mouthwash, cryotherapy, palifermin and honey [6]. The votes against honey relate to good-quality trials showing a poorer outcome in the honey group and to work by Yarom et al. and Lalla et al. [7,8]. Other panels of specialists issued guidelines for the treatment of oral mucositis and associated pain and their recommendations do not substantially differ from the German S3-guideline [9,10]. However, more recent reviews suggest mouthwashes containing Matricaria recutita, Aloe vera, Glycyrrhiza glabra, indigo wood root, a Dead Sea product, and intramuscular application of an extract of human placenta [11]. Recent trials suggest that rebamipide gargle, amifostine, low-level laser therapy, black mulberry molasses or melatonin could help to improve

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Table 1
Systematic reviews and meta-analyses on honey for radiotherapy-induced oral mucositis.

	Number of studies included	Number of studies missed or excluded	Number of studies published later	Conclusion regarding honey	Needs
Xu et al., 2016	6	7	4	Effective reduction of incidence of oral mucositis	Further multi-centre randomized controlled trials
Co et al., 2016	5	7	4	Reasonable treatment for oral mucositis	More randomized clinical trials
Cho et al., 2015	9	3	5	Could prevent moderate to severe mucositis and associated weight loss	Further trials are required to confirm these results.

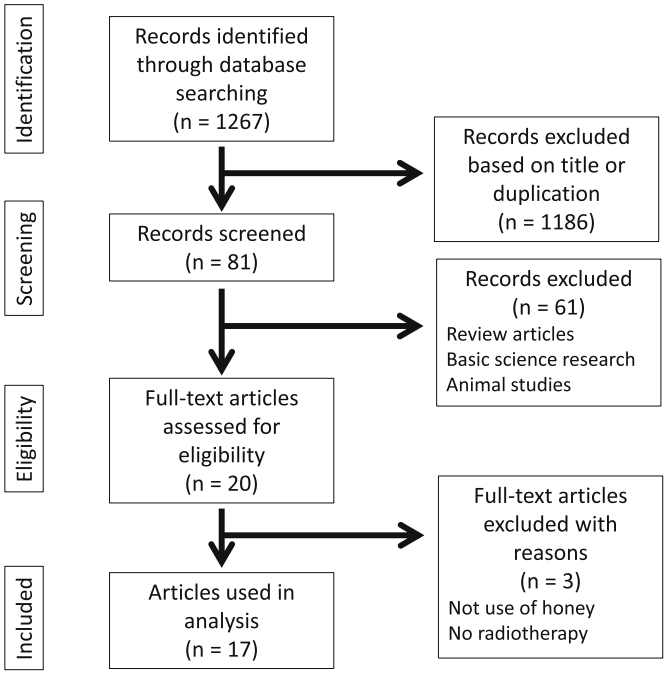

Fig. 1. Search strategy for this systematic review.

patients' symptoms during radiotherapy [12–16].

Looking at the plethora of studies on the subject, the question arises why honey was not considered as a reasonable option for the prophylaxis and treatment of radiotherapy-induced oral mucositis. Several systematic reviews and meta-analyses consider honey as a reasonable option [17–20]. It could be an inexpensive means of limiting oral mucositis and might find high acceptance by patients and their caregivers. A closer look at the systematic reviews and meta-analyses shows that more recently further trials on the topic have been published and others have been missed or been excluded from the systematic reviews and meta-analyses (Table 1). Therefore we did a new systematic review in order to find out whether the new and the unconsidered evidence allows a more convincing decision regarding the use of honey and if the type of honey could have had an influence on the outcome of the trials. Here it must be noted that honey is not a uniform product but greatly varies with its plant sources (floral nectar) or other insects secretions (aphid honeydew) which, however, has been used in medicine since ancient times [21].

2. Methods

The systematic review was carried out according to the recommendations of the PRISMA.

Literature search: A systematic search of the scientific literature concerning the effectiveness of honey in the treatment of oral mucositis was performed. All studies published between January 2000 and June 2018 were considered. The electronic retrieval systems and data bases PubMed (Medline), Cochrane Database, ScienceDirect and Google Scholar were searched for relevant articles. To search PubMed, the following descriptors in English according to the MeSH (Medical Subject Headings) were used: "honey" AND "oral mucositis" in June 2018.

The search string was based on the keywords "honey" and "oral mucositis". In the next step, studies on radiotherapy or radiotherapy in combination with chemotherapy were selected. Papers related to mucositis and chemotherapy without radiotherapy were excluded.

In a second step, the references of the retrieved studies were analysed for further studies which might not have been identified in the primary search. This was also true for meta-analyses and systematic

Table 2
Trials and publications included in the systematic review.

First author/year	Jadad Score (max. 5)	Design	Sample; intervention and control group	Oncological treatment	Endpoints (**OM** = oral mucositis)	**Main** results (only significant results are reported)
Charalambous 2018	3	Randomized controlled trial	86 patients Group 1: 43 patients with diluted thyme honey (20 ml of thyme honey in 100 ml water making gargles in the oral cavity - 15 min before and after radiotherapy and 6 h later) Group 2: 43 patients with saline 0.9%	Radiotherapy	• OM grade (Radiation Therapy Oral Mucositis Grading) • Weight loss • Oral problems (i.e. swallowing, drinking, eating, mouth and throat pain) • Quality of life	• Lower grades of oral mucositis ($p < 0.001$) • Better maintenance of body weight ($p < 0.001$) • Improvement in global health ($p < 0.001$) • Better quality of life ($p < 0.001$) in the honey group • No report of study discontinuation because of honey
Rao 2017	2	Randomized controlled trial	50 patients Group 1: 25 patients with polyfloral honey (exact quantity not given - 1 h prior to radiation, and 2 and 6 h after radiation) Group 2: 25 patients with povidone-iodine	Radiotherapy, most patients in combination with chemotherapy	• OM grade (Radiation Therapy Oral Mucositis Grading) • Treatment interruptions • Tumour response	• Lower grades of oral mucositis ($p < 0.001$) • Better maintenance of body weight ($p < 0.001$) • Fewer treatment interruptions ($p = 0.027$) in the honey group • Honey has no effect on tumour response • No report of study discontinuation because of honey
Amanat 2017	3	Randomized controlled trial	82 patients Group 1: 41 patients with ziziphus honey (20 ml - 15 min before and after the radiotherapy) Group 2: 25 patients with saline 0.9%	Radiotherapy	• OM grade (Radiation Therapy Oral Mucositis Grading)	• Lower grades of oral mucositis in the honey group ($p = 0.032$) • No report of study discontinuation because of honey
Fogh 2017	3	Randomized controlled trial	163 patients Group 1: 53 patients with supportive care Group 2: 54 patients with manuka honey (10 ml - lozenges 4 times per day, over a period of 12 h daily) Group 3: 56 patients with lozenge manuka honey (2 lozenges 4 times per day, over a period of 12 h daily)	Radiotherapy in combination with chemotherapy	• Pain on swallowing • Quality of life Secondary endpoints • Pain over time • Opioid use • Clinically graded and patient-reported adverse events • Weight loss • Dysphagia • Nutritional status, • Quality of life.	• No significant difference in the primary endpoint • No differences in any of the secondary endpoints except for opioid use • More patients on the supportive care arm took opioids ($p = 0.03$)
Jayalekshmi 2016	3	Randomized controlled trial	28 patients Group 1: 14 patients with polyfloral honey (15 ml - 15 min before and after radiotherapy and 6 h later) Group 2: 14 patients with water	Radiotherapy, most patients in combination with chemotherapy	• OM grade (Radiation Therapy Oral Mucositis Grading)	• Lower grades of oral mucositis in the honey group (0.003) • No report of study discontinuation because of honey
Bahramnezhad 2015	0	Non-randomized controlled trial	105 patients Group 1: 35 patients with diluted polyfloral honey (50 ml honey and 25 ml water – administration schedule not given) Group 2: 35 patients with water Group 3: 35 patients with water chamomile	Radiotherapy	• OM grade (WHO mucositis grading system)	• Lowest grades of oral mucositis in the honey group ($p < 0.001$) • No report of study discontinuation because of honey
Samdariya 2015	3	Randomized controlled trial	78 patients Group 1: 40 patients with polyfloral honey (20 ml - 15 min before and after radiotherapy and 6 h later) and salt-soda and benzydamine gargle Group 2: 38 patients with salt-soda and benzydamine gargle	Radiotherapy in combination with chemotherapy	• Pain (VAS scale)	• Less pain ($p < 0.001$) in the honey group • No report of study discontinuation because of honey
Hawley 2014	5	Randomized double blinded placebo controlled trial	106 patients Group 1: 54 patients with manuka honey (5-ml -four times a day after radiotherapy and after meals) Group 2: 52 patients with placebo gel	Radiotherapy, mainly in combination with chemotherapy	• OM grade (Radiation Therapy Oral Mucositis Grading)	• No significant difference in the primary endpoint • High dropout rates 57% in honey group vs. 52% in control group n.s.
Alvi 2013	2	Randomized controlled trial	60 patients Group 1: 30 patients with polyfloral honey (20 ml -	Radiotherapy	• OM grade (WHO mucositis grading system) • Weight loss	• Lower grades of oral mucositis ($p = 0.039$) • Better maintenance of body weight ($p = 0.002$)

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Table 2 (*continued*)

First author/year	Jadad Score (max. 5)	Design	Sample; intervention and control group	Oncological treatment	Endpoints (**OM** = oral mucositis)	**Main** results (only significant results are reported)
			15 min before and after radiotherapy and 6 h later) Group 2: 30 patients with saline 0.9%		• Treatment discontinuation	• No report of study discontinuation because of honey in the honey group • No discontinuation of radiotherapy in honey group (0 vs. 3 in control group)
Maiti 2012	1	Randomized controlled trial	55 patients Group 1: 28 patients with polyfloral honey (20 ml - 15 min before and after radiotherapy and 6 h later) Group 2: 27 patients no additional treatment	Radiotherapy in combination with chemotherapy	• OM grade (WHO mucositis grading system) • Weight loss	• Lower grades of oral mucositis, • Better maintenance of body weight in the honey group • No report of study discontinuation because of honey
Jayachandran 2012	2	Randomized controlled trial	60 patients Group 1: 20 patients with polyfloral honey (20 ml - 15 min before and after radiotherapy and 6 h later) Group 2: 20 patients with benzydamine hydrochloride Group 3: 20 patients with saline 0.9%	Radiotherapy	• OM grade (WHO mucositis grading system) • Onset of OM • Recovery after end of therapy	• Later onset of oral mucositis ($p < 0.001$ • Lower grades of oral mucositis during radiotherapy • Faster recovery from oral mucositis after the end of radiotherapy in the honey group • No report of study discontinuation because of honey
Bardy 2012	5	Randomized double-blinded placebo controlled trial	131 patients Group 1: 67 patients with manuka honey (20 ml - 4 times a day) Group 2: 64 patients with golden syrup	Radiotherapy in combination with chemotherapy	• OM grade (Radiation Therapy Oral Mucositis Grading) • OM duration Secondary aims • assessment of microbiological flora in the mouth, • requirements for antimicrobial drugs and analgesia • Weight loss • Need for tube feeding	• No significant differences in the primary and secondary endpoints • No differences in patients' compliance
Parsons 2012	1	Randomized controlled trial	28 patients Group 1: 6 patients with manuka honey (20 ml - 15 min before and after radiotherapy and 6 h later) Group 2: 12 patients with diluted manuka honey (10 ml in 30 ml of water - 15 min before and after radiotherapy and 6 h later) Group 3: 10 patients receiving standard care	Radiotherapy, mainly in combination with chemotherapy	• OM grade (mucositis score by Epstein 2001) • Weight loss • Quality of life (EORTC - QLQ-30)	• No significant difference regarding OM grade • Better maintenance of body weight in the honey group ($p < 0.05$) • Diluted manuka honey increased overall QoL in the radiotherapy group but not in group of radiotherapy in combination with chemotherapy ($p < 0.05$) • 6/6 patients in the honey group, 2/12 in the diluted honey group and 2/10in the control group withdrew from the study because of pain and nausea
Khanal 2010	2	Randomized controlled trial	40 patients Group 1: 20 patients with polyfloral honey (20 ml - 15 min before and after radiotherapy and before going to bed) Group 2: 20 patients with lignocaine gel	Radiotherapy	• OM grade (Radiation Therapy Oral Mucositis Grading) • Pain associated with OM	• Lower grades of oral mucositis ($p < 0.0001$) • Less pain in the honey group • No report of study discontinuation because of honey
Rashad 2009	2	Randomized controlled trial	40 patients Group 1: 20 patients with clover honey (20 ml - 15 min before and after radiotherapy and 6 h later) Group 2: 20 patients receiving standard care	Radiotherapy in combination with chemotherapy	• OM grade (WHO mucositis grading system) • assessment of microbiological flora in the mouth	• Lower grades of oral mucositis • Lower rates of pathogenic bacteria and fungi ($p = 0.007$)in the honey group
Motallebnejad 2008	2	Randomized controlled trial	40 patients Group 1: 20 patients with thyme and astragal honey (20 ml - 15 min before and after radiotherapy and 6 h later) Group 2: 20 patients with saline 0.9%	Radiotherapy	• OM grade (Oral Mucositis Assessing Scale (OMAS) • Weight loss	• Lower grades of oral mucositis ($p < 0.001$) • Better maintenance of body weight ($p < 0.001$) in the honey group • 4 patients in honey group with Grade 0 oral mucositis discontinued treatment
Biswal 2003	2	Randomized controlled trial	40 patients Group 1: 20 patients with tea plant honey (20 ml -	Radiotherapy	• OM grade (Radiation Therapy Oral Mucositis Grading)	• Lower percentage of patients with grade 3/4 mucositis ($p = 0.001$.)

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Table 2 (*continued*)

First author/year	Jadad Score (max. 5)	Design	Sample; intervention and control group	Oncological treatment	Endpoints (**OM** = oral mucositis)	**Main** results (only significant results are reported)
			15 min before and after radiotherapy and 6 h later) Group 2: 20 patients with saline 0.9%		• Weight loss • Treatment discontinuation • Duration of mucositis	• Better maintenance of body weight ($p < 0.05$)in the honey group • No discontinuation of radiotherapy in the honey group (0% vs. 20% in the control group) • Duration of mucositis = n.s. • No report of study discontinuation because of honey

reviews on the topic.

Eligibility criteria: Eligible studies were controlled randomized and non-randomized trials, including case-control studies. Studies were eligible only if they were published as full papers in the English language. Grey literature as well as animal studies were excluded. The publication date range included in the search was 01/01/2000 to 30/06/2018. The target population consisted of head and neck cancer patients of all ages and oncological treatment with radiotherapy and/or chemotherapy medication. The study by Fogh et al. [22] was included in the review because it focused on honey and esophagitis due to chemoradiation therapy, which is similar to oral mucositis.

Study selection: The full titles and abstracts of the articles retrieved in the initial search were assessed by two study authors (KM, JH) for adherence to the eligibility criteria. Articles not meeting the eligibility criteria, as well as duplicate articles, were removed. The full texts of the remaining articles were assessed for eligibility.

Data collection: Relevant data (title of the paper, author's information, country in which the study was conducted, condition treated, study design, primary and secondary endpoints, instruments, results from primary assessment to last follow-up and treatment discontinuation due to honey) from all retrieved studies were extracted using a standardized data extraction form. Methodological quality of a clinical trial was assessed using the Jadad scale [23]. In order to determine the Jadad score five questions had to be answered. For every answer with yes, the score went up one point. The questions were:

1. Was the study was described as randomized?
2. Was the randomization appropriate?
3. Was the study was described as double blind?
4. Was the blinding appropriate?
5. Was there a description of withdrawals and dropouts?

3. Results

The initial computerized search strategy and associated hand search yielded 1267 titles: PubMed (Medline) (n = 33), Cochrane Database (n = 1), ScienceDirect (n = 93) and Google Scholar (n = 1140). As shown in Fig. 1, most of the articles were discarded because they did not meet the eligibility criteria. All 20 articles that fulfilled the eligibility criteria were read in full. Among these, only 17 met the inclusion criteria. Key data from these studies are summarized in Table 2.

3.1. Overall analyses of the trials

The results of the studies on honey and radiotherapy/radiochemotherapy are summarized in Table 1. The primary endpoints of the studies varied, as did the methods and instruments used.

Most studies found lower grades for oral mucositis when honey was used [24–35]. The trials reported by Hawley et al. Bardy et al., and Parsons et al. showed no positive results in this respect [36–38]. The study by Samdariya et al. only assessed oral mucositis-associated pain and found positive effects of honey [39].

Another important issue is weight loss. In this regard, the most trials showed positive results for honey [24,29,30,34,35,38], leaving only one trial with no advantage of honey [37]. Less pain and better quality of life were also reported in the majority of trials [24,32,38,39], whereas only Fogh et al. reported no improvement with honey [22]. Moreover, treatment interruptions and pathogens in the oral flora were found to be less frequently associated with honey [25,33,39].

The majority of studies showed positive results for oral mucositis, whereas studies with higher Jadad Scores revealed negative results. However, it is unclear whether a higher study quality or a certain characteristic of manuka honey may have influenced the results.

Table 3
Comparison of results by type of honey.

	Trials using conventional honey	Trials using manuka honey
Trials with significant reduction of oral mucositis	• Charalambous et al., 2018 • Rao et al., 2017 • Amanat et al., 2017 • Jayalekshmi et al., 2016 • Bahramnezhad et al., 2015 • Samdariya et al., 2015[a] • Alvi et al., 2013 • Maiti et al., 2012 • Jayachandran et al., 2012 • Khanal et al., 2010 • Rashad et al., 2009 • Motollebnejad 2008 • Biswal et al., 2003	none
Trials with no significant reduction of oral mucositis	none	• Hawley et al., 2014 • Bardy et al., 2012 • Parsons et al., 2012 • (Fogh et al., 2017)[b]

[a] Oral mucositis-associated pain.
[b] Study on esophagitis.

3.2. Manuka honey and other types of honey

As there is a decisive difference between manuka honey and honey from other plants due to its content of methylglyoxal, we compared publications of trials using manuka honey or other honey and those supporting the use of honey for oral mucositis or not in the form of a crosstabulation (Table 3). All trials using manuka honey found no significant advantage regarding major endpoints, whereas all studies using conventional honey were in favour of honey. Only Fogh et al. and Parsons et al. provided some information on the methylglyoxal content of the honey used [22,38]. Fogh et al. used honey with a Unique Manuka Factor (UMF) of 16 (methylglyoxal > 514 mg/kg) and Parsons et al. used honey with UMF of 10 (methylglyoxal > 263 mg/kg) [22,38]. Thus, it was not possible to correlate methylglyoxal content with results, for example treatment discontinuation.

4. Discussion

This analysis shows that honey represents the superior alternative in about 76% of all trials on the subject of radiotherapy and radiochemotherapy-induced oral mucositis and the use of manuka honey may explain why honey failed in some trials. This overall positive assessment is supported by the most recent meta-analyses on the basis of 7 trials by Xu et al. and 5 trials by Co et al. which concluded that honey can effectively reduce the incidence of radio/chemotherapy-induced oral mucositis [19,20]. However, there is a significant flaw in the analysis by Xu et al. since it included a trial which studied the essential oils of manuka (*Leptospermum scoparium*) and kanuka (*Kunzea ericoides*) in water but not of manuka or kanuka honey [19].

Apart from discussions on the quality of trials and the possible risks of bias, one important question was not addressed so far in the literature – the type of honey. As mentioned, manuka honey contains many fold higher amounts of methylglyoxal than other honeys [40]. Methylglyoxal represents a cytotoxic substance which must be reduced to its non-toxic components [41,42]. If this reduction is impaired, methylglyoxal may lead to increased protein and DNA modification, contributing to cell and tissue dysfunction, which results in aging and disease [43]. Higher concentrations of methylglyoxal in animal trials delayed wound healing [44]. In a similar setting, even the facial nerve was affected by manuka honey treatment of a wound near the ear of an animal [45]. Therefore, the difference between ordinary honey and manuka honey could be the underlying reason for the failure of honey in the studies by Bardy et al. Parsons et al., Hawley et al. and Fogh et al. [22,36–38]. The only support for manuka honey comes from a case series of 9 patients which does not seem sufficient with respect to sample size and study design [46]. In order to test the hypothesis that methylglyoxal is the compound which determines whether the use of honey is reasonable for oral mucositis under chemoradiation or radiotherapy, a trial comparing manuka honey and conventional honey would be interesting. Until such a trial has been conducted, it is important that future meta-analyses acknowledge the difference between conventional honey and manuka honey and assess their effects differently.

Studies on chemotherapy-induced oral mucositis and the treatment of burns support this hypothesis. Epithelial healing in burns works with mechanisms comparable to the healing of oral mucositis. Regarding honey and chemotherapy, a review revealed Grade C evidence that honey is effective as a preventative and therapeutic measure for oral mucositis in paediatric oncology patients [47]. A very recent trial, not included in the review, also supports the use of honey [48]. For burns a systematic review showed that honey dressings promote better wound healing than silver sulfadiazine [49]. Interestingly, no trial has yet analysed the efficacy of manuka honey for burns, so all trials in the named analysis favour honey [49]. Finally, trials which have investigated the use of honey in the treatment of radiation induced epitheliolyis in breast cancer patients also found good results for honey [50,51].

In summary, this analysis of 17 trials on honey and radiotherapy or radiochemotherapy-induced oral mucositis shows that conventional honey, but not manuka honey, may be a very good means of improving the symptoms of patients undergoing such therapy. The limitations of this study are due to the fact that the risks of bias, especially regarding random sequence generation and adequate allocation concealment hypothesis, could not be estimated in many of the included studies. High-quality studies considering the CONSORT statements on reporting on phytotherapy investigating a direct comparison of conventional honey and manuka honey could thus verify our hypothesis [52]. Another limitation may be that we have missed some studies due to the fact that we limited the search to only four databases.

5. Conclusion

Conventional honey seems to be a very interesting option for the prophylaxis and treatment of radiotherapy-induced oral mucositis. In the future it would be important to identify the substances in honey which are likely to be responsible for its positive effect (e.g. flavonoids and phenolic acids). Until then future guidelines on oral mucositis should acknowledge the differences between manuka honey and other

types of honey and not discourage the use of honey in general but the use of manuka honey only. Future trials should be carried out to determine whether honey should be used as an alternative or adjunctive to other standard treatments like mucoadhesive hydrogels, antiseptic mouth rinses, low-level laser therapy, glutamine or amifostine in order to reduce the side effects of radiotherapy or chemoradiation for head and neck cancers [16,53,54].

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There was no funding. There are no conflicts of interest, except that KM is a hobby beekeeper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctcp.2018.11.016.

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