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Topical application of honey in the management of chemo/radiotherapy-induced oral mucositis: A systematic review and network meta-analysis

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ABSTRACT

Background: Mucositis is an inflammatory response of mucosal epithelial cells to the cytotoxic effects of chemotherapy and radiation therapy. To assess the comparative efficacy of honey for patients with cancer undergoing chemo/radiotherapy-induced oral mucositis through a systematic review and network meta-analysis.
Methods: A network meta-analysis was used to identify evidence from relevant randomized controlled trials (RCTs). We searched PubMed, Embase, and the Cochrane Library for publications up to November 2017. The prespecified primary efficacy outcome was the treatment effect of moderate-severe oral mucositis with honey. We performed subgroup analyses and meta-regressions according to the age group, cancer type, mucositis cause, honey type, control arm and type of assessment scale. Moreover, secondary efficacy outcomes were treatment completed, onset time of mucositis, swallowing diary, fungal colonization, bacterial colonisation and analgesic use. And, we did standardize meta-analyses using the random-effects model, later completing the random-effects network meta-analyses by different treatment/control arms.
Results: A total of 17 RCTs were eligible (22 analyses), involving 1265 patients and 13 arms. Honey treatment arm significantly increased the therapeutic effect of chemo/radiotherapy-induced moderate-severe oral mucositis (0.25, 0.14–0.46); significant efficacy was observed in a large proportion of subgroups. The meta-regression may have identified the causes of heterogeneity as the honey type ($P = 0.038$). Therefore, we need to perform further comparisons of difference in honey types and controls by network meta-analysis, and the results from network meta-analysis revealed that pure natural honey was superior in therapeutic effect (0.05, 0.01–0.46). For secondary outcomes, significant effect was found in decreasing onset time of mucositis (0.41, 0.08–0.73), while no increase in adverse effects was observed. The study is registered with PROSPERO (CRD42017070873).
Conclusions: The adjuvant treatment honey is effective and safe for patients with cancer undergoing chemo/radiotherapy-induced oral mucositis, especially applied pure natural local honey can be invoked as a first-line adjuvant therapy agent.

What is already known about the topic?

- The main symptom of oral mucositis is severely debilitating oral pain and be more susceptible to infection which may result in the demise of the patient due to infections and compromising the cancer treatment.
- Several treatments have been used to prevent or reduce the moderate-severity of oral mucositis but outcomes are inconsistent.

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- We aimed to compare and rank honey treatment arms and no-honey control arms for patients with cancer undergoing chemo/radiotherapy-induced oral mucositis.

What this paper adds

- Treatment with honey for moderate-severe chemo/radiotherapy-induced oral mucositis is effective with large therapeutic effect.
- The adjuvant treatment honey is effective and safe for patients with cancer undergoing chemo/radiotherapy-induced oral mucositis.
- Positive outcomes were obtained more frequently in pure natural honey, which is probably the best options to consider in the application of adjuvant therapy agent.

1. Introduction

Cancer is a major public health problem worldwide and is the second leading cause of death in the United States (Siegel et al., 2017). Radiotherapyand chemotherapy are still important means of treating cancer, although it may cause serious adverse reactions (Miller et al., 2016; Miao et al., 2017; Zhang et al., 2018). Mucositis is an inflammatory response of mucosal epithelial cells to the cytotoxic effects of chemotherapy and radiation therapy, which is a result of imbalance between cell loss and cell proliferation. The main symptom of oral mucositis is severely debilitating oral pain and be more susceptible to infection which may result in the demise of the patient due to infections and compromising the cancer treatment (for example, neck and head cancer, leukemia). Therefore, oral mucositis is one of the most unpleasant side effects of chemo/radiotherapy in patients with cancer. However, about 40%–76% patients with cancer undergoing chemo/radiotherapy develop mucositis which manifests itself as intense erythema in the treated areas and patients suffer from difficulties with swallowing (Araújo et al., 2015; Sonis, 2004). What's more, the incidence of moderate to severe (grades ≥ 3) mucositis is typically 30%–40% for conventional radiotherapy over 6–7 weeks, but double this when chemotherapy is added or an accelerated fractionation is used (Biswal et al., 2003; Köstler et al., 2001). As a result, effective management of this complication is therefore very important. Several treatments have been used to prevent or reduce the moderate-severity of oral mucositis but outcomes are inconsistent (Le et al., 2017).

Currently, researches are trying to reach newer agents that are effective, safe, easy to use and inexpensive. Honey is a natural substance made, by-product of flower nectar and secretion of the upper digestive tract of the honey-bee, which is then concentrated through a dehydration process inside the bee hive, and kept in the honeycomb by honey bees. Its main components are the sugars glucose and fructose; its third greatest component is water. Although honey is an age-old remedy, it has got a place in modern medicine recently. It has found a place in the treatment of burns, infected wounds and skin ulcers (van der Weyden, 2003; Molan and Moore, 2001; Vardi et al., 1998). In treatment for cancers, honey may be used for chemo/radiation-induced oral mucositis (Bardy et al., 2008; Wardill et al., 2014). Honey has antibacterial properties and enhances epithelization, thereby improving wound healing (Al-Waili and Saloom, 1999). The impaired mucosal barrier often permits the development of superadded bacterial and fungal infections (Nicolatou-Galitis et al., 2001; Dale et al., 2018). Therefore, honey is an agent which holds promise.

Oral mucositis has also a major impact on the quality of life and nutritional status, prolonged hospital stays, and severe infections in patients with cancer. Cancer treatment will be much more effective if it is not associated with short/long term adverse effects as those associated with oral mucositis. Due to the numerous classifications of honey and the small sample sizes, the efficacy and safety of honey are still inconsistent. To further explore these issues, we performed a network meta-analysis of all available randomized controlled trial of chemo/radiotherapy-induced oral mucositis in cancer patients. No previous reviews have provided a comprehensive overview with meta-regressions and network meta-analyses (Cho et al., 2015; Co et al., 2016; Xu et al., 2016).

2. Methods

2.1. Search strategy and selection criteria

This systematic review was performed with an a priori established protocol (PROSPERO CRD42017070873 (PROSPERO, 2009), and the meta-analysis was performed following the PRISMA (Preferred Reporting Items for the Systematic Reviews and Meta-analyses) statement, the PRISMA network statement, and the Cochrane Collaboration recommendations (Higgins and Green, 2011; Maddocks-Jennings et al., 2009; Moher et al., 2009).

We considered large-scale RCTs of patients with chemo/radiotherapy-induced oral mucositis, searched PubMed, EMBase, and the Cochrane Library for eligible trials form the very beginning of the databases to November 2017, comparing any of the following treatments: treatment of chemo/radiotherapy-induced oral mucositis in cancer patients with any type of honey (see details in Table S1).

The inclusion criteria consisted of: RCTs of patents with any type of cancer (such as head and neck cancer, nasopharyngeal cancer, etc.); patients of any age, gender, tumor stage, and histological grade; either smoking or not; and either using pure natural honey, manuka honey or local honey for treatment. We also excluded trials published only as abstract (with no additional data available from other sources). No language restrictions were applied. We then screened reference lists of all obtained articles to avoid missing relevant trials.

2.2. Data abstraction and assessment of risk of bias

Two investigators (YC and ZYS) independently abstracted data on study, patients, and treatment related characteristics onto a standardized form; discrepancies were resolved by consensus, referring back to the original study, or in consultation with a third reviewer (SB or PXZ). Data on efficacy and safety were abstracted from original studies. We extracted trial design, trial size, details of treatment arms including honey type and instructions, period and duration of follow-up, type of outcome (efficacy and safety), and type of assessment scale. We extracted results from intention-to-treat analyses whenever possible.

The risk of bias of the randomized controlled trials was assessed using the Cochrane risk of bias tool (Higgins et al., 2011).We assessed the following 7 items of risk of bias: random sequence (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. Low risk, high risk, and unclear risk were classified in all studies. Otherwise, the quality of controlled clinical trials was assessed using the Newcastle-Ottawa Scale (NOS) (Stang, 2010). NOS was used as suggested by the Cochrane Non-Randomized Studies Methods Working Group. NOS utilized the following criteria labels, "yes" or "no", for the following questions: Is the case defnition adequate? Representativeness of the cases? Selection of Controls? Defnition of Controls? Comparability of cases and controls? (0–2) Ascertainment of exposure? (0–2) Same method of ascertainment for cases and controls? And nonresponse rate? We excluded some studies which scores less than 5. Any discrepancies were resolved by consensus and arbitration by a panel of investigators within the review team (GGZ and JES).

2.3. Outcomes

The primary efficacy outcome was chemo/radiotherapy-induced moderate-severe oral mucositis. Oral mucositis was measured by the RTOG scale, WHO scale and NCI-CTC scale, etc (see details in Table S2).

Subgroup analyses and a meta-regression were performed according to age of patients (teenager and adult), cancer type (head and neck cancer and other cancer), mucositis cause(chemo/radiotherapy-induced, radiation-induced and chemotherapy-induced), honey type(pure natural honey, manuka honey and local honey), control arm(placebo and usual care) and type of assessment scale (RTOG scale, WHO scale and NCI-CTC scale). And then we performed a network meta-analysis according to the treatment and control arms(bee glue; benzocaine; benzydamine; caramel dye; chamomile; dabur honey; golden syrup; kanuka honey; lidocaine; local honey; manuka honey; pure natural honey; and usual care).

The secondary efficacy outcomes were treatment completed, onset time of mucositis, swallowing diary, fungal colonization, bacterial colonisation and analgesic use.

2.4. Data synthesis and statistical analysis

Studies that reported multiple comparisons were categorized as substudies (marked as a/b) to avoid double counting and mistreating data. First, a standardized meta-analysis was performed using a random effects model because it is likely the most appropriate and conservative methodology to account for between-trial heterogeneity within each comparison (Dias et al., 2013; Mills et al., 2013). To estimate pooled odds ratios (OR) and 95% confidence intervals (95%CI) incorporating heterogeneity within and between studies, STATA v14.0 was used. Statistical heterogeneity was assessed with a P value and I^2 statistic, with values over 50% indicating substantial heterogeneity (Higgins et al., 2003). The Begg's and Egger's tests were used to detect publication bias (The Cochrane Collaboration, 2011).

To further investigate the heterogeneity, a meta-regression and subgroup analysis were performed to assess the primary outcome data and whether associations by age group (teenager and adult), cancer type (head and neck cancer and other cancer), mucositis cause (chemo/radiotherapy-induced, radiation-induced and chemotherapy-induced), honey type (pure natural honey, manuka honey and local honey), control arm (placebo and usual care) and type of assessment scale (RTOG scale, WHO scale and NCI-CTC scale). The P values in the meta-regression revealed the overall significance of the influence factors. Additionally, the P values were inversely proportional to the size of heterogeneity; P values less than 0.05 indicate factors that could present an important source of heterogeneity.

Second, a random-effects network meta-analysis was conducted using STATA v14.0. The results of the network meta-analysis were summarized using OR and their credible intervals (CrI) (Salanti et al., 2008). A common heterogeneity parameter was assumed for all comparisons, and the global heterogeneity was assessed using the P value and the I^2 statistic.

Each therapy efficacy of treatment/control arm resulted from the combination of the direct and the indirect evidence derived from the network meta-analysis, which was assumed to be coherent (Dias et al., 2013). Inconsistencies between direct and indirect sources of evidence were statistically assessed globally (by comparison of the fit and parsimony of consistency and inconsistency models) and locally (by calculating the difference between the direct and indirect estimates in all closed loops in the network) (Chaimani et al., 2013). When a direct connection between two treatment arms was not available, the results were based on indirect evidence.

We estimated the ranking probabilities for all treatments of being at each possible rank for each treatment arm. The treatment hierarchy was summarized and reported as surface under the cumulative ranking curve (SUCRA) (Salanti et al., 2011), ranging from 1, indicating that the treatment has a high likelihood of being best, to 0, indicating that the treatment has a high likelihood of being worst. A high SUCRA score corresponds to a higher ranking of treatment method from moderate-severe mucositis compared with other treatments.

2.5. Quality of evidence

In addition, the quality of evidence for the primary outcomes was assessed based on the GRADE system using GRADEpro GDT (Balshem et al., 2011; Guyatt et al., 2008). The GRADE system assesses risk of bias (study limitations), imprecision, inconsistency, indirectness of study results, and publication bias (classifying each as high, moderate, low, or very low) across the body of evidence to derive an overall summary of the quality of evidence.

3. Results

3.1. Description of the network and patients

In total, 112 citations were retrieved from the databases; after removing duplicates, 77 citations were screened on title and abstract; 46 were excluded from further analysis. A total of 31 citations were included for full-text analysis. The network consists of 17 trials and 1269 patients, which were included in the standard meta-analysis (Abdulrhman et al., 2012; Al Jaouni et al., 2017; Bahramnezhad et al., 2015; Bardy et al., 2012; Biswal et al., 2003, Bulut and Tüfekci, 2016, Fogh et al., 2017; Hawley et al., 2014, Jayachandran and Balaji, 2012, Khanal et al., 2010; Lai et al., 2016; Maddocks-Jennings et al., 2009; Maiti et al., 2012; Motallebnejad et al., 2008; Rashad et al., 2009; Samdariya et al., 2015; Tomaževič and Jazbec, 2013). Because of a factorial design in five trials, these 17 trials were split into 22 analyses. There were thirteen different treatments: bee glue; benzocaine; benzydamine; caramel dye; chamomile; dabur honey; golden syrup; kanuka honey; lidocaine; local honey; manuka honey; pure natural honey; and usual care. Fig. S1 shows the screening flowchart.

Table 1 summarizes the differences in the fundamental characteristics between the honey treatment arm and the control arm (see the full list of characteristics in Table S3). These statistics revealed that the two arms were similar in age, gender, tumor stage and smoking rate. In the baseline characteristics analysis, we did not group trials by cancer type, mucositis cause, honey type, control arm or type of assessment scale; the baseline characteristics were balanced between the honey treatment arm and the control arm. Quality assessments of this study are presented in Fig. S2 and Table S4; the quality assessment indicated that all included trials were of acceptable quality.

3.2. Primary efficacy outcome - treatment effect of moderate to severe oral mucositis

3.2.1. Standardized meta-analysis

Fig. 1 and Table 2 summarize the results of chemo/radiotherapy-induced moderate-severe oral mucositis stratified by age of patients (teenager and adult), cancer type (head and neck cancer and other cancer), mucositis cause(chemo/radiotherapy-induced, radiation-induced and chemotherapy-induced), honey type (pure natural honey, manuka honey and local honey), control arm (placebo and usual care) and type of assessment scale (RTOG scale, WHO scale and NCI-CTC scale). Sixteen trials (21 analyses, 1200 patients) investigated cancer

Table 1
Characteristics of baseline in patients associated with honey treatment arm vs control arm.

	Treatment vs control (OR, 95%CI)	Heterogeneity
Age (year)	−0.07 (−0.36, 0.21)[a]	P = 0.975, I^2 = 0.0%
Male	1.13 (0.85, 1.51)	P = 0.815, I^2 = 0.0%
Tumor stage (I–II/ III–IV)	1.31 (0.68, 2.54)	P = 0.832, I^2 = 0.0%
Smoking	1.03 (0.59, 1.81)	P = 0.356, I^2 = 3.3%

[a] Standardized mean difference.

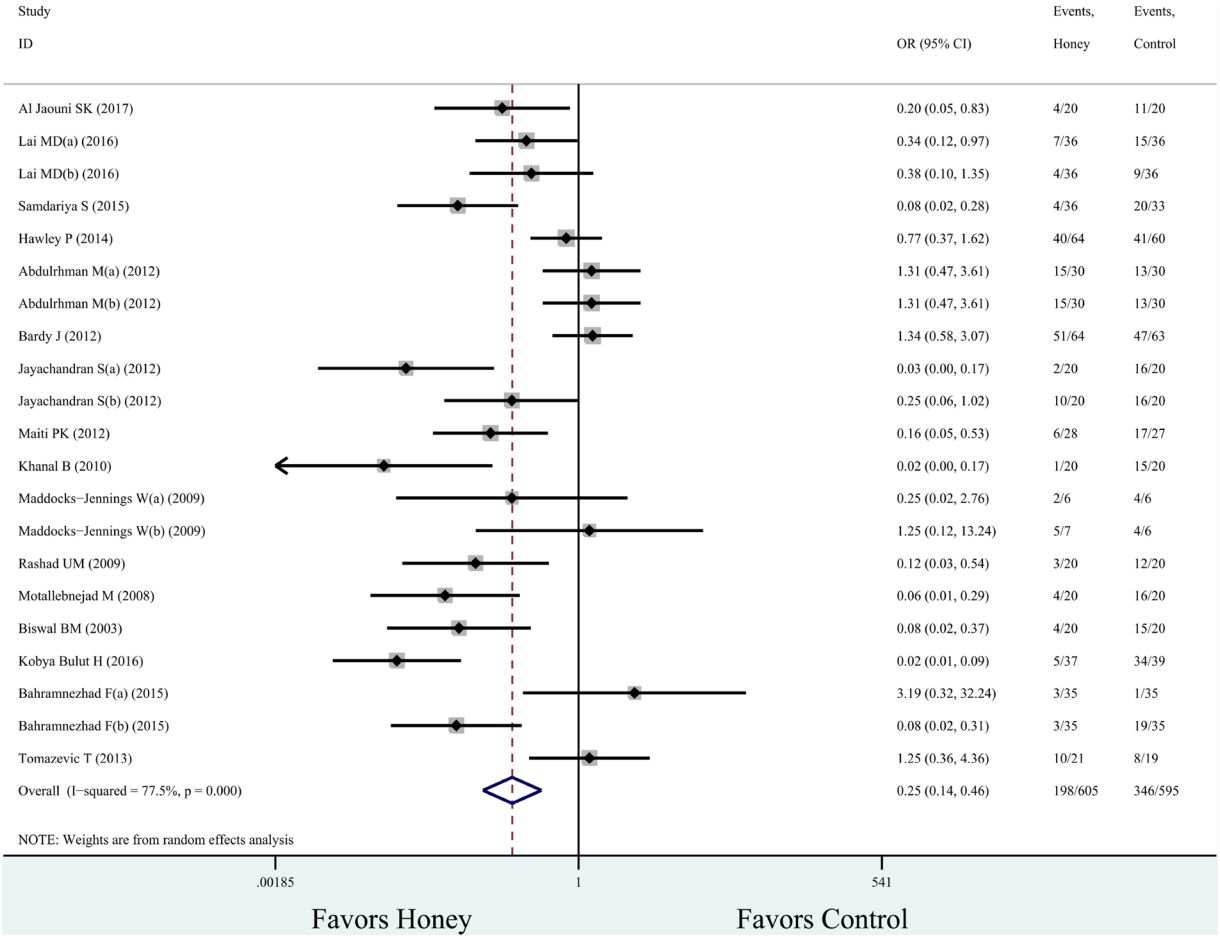

Fig. 1. Overall incidence of honey treatment arm versus control arm on chemo/radiotherapy-induced moderate-severe oral mucositis.

patients with chemo/radiotherapy-induced moderate-severe oral mucositis (odds ratios: 0.25, 95% confidence intervals: 0.14 to 0.46). Although the overall sample and subgroups showed a significant effect favors for honey treatment arm, there was still substantial heterogeneity ($P = 0.00$, $I^2 = 77.5\%$; Fig. 1, Table 2). Moderate evidence of bias could be found in Begg's test ($P = 0.121$) and Egger's test ($P = 0.014$), with moderate evidence according to the GRADE assessment.

Subgroup analyses and meta-regressions were used to explore the source of heterogeneity between the honey treatment arm and control arm in treatment efficacy of chemo/radiotherapy-induced moderate-severe oral mucositis (Table 2). The meta-regression results for the treatment of moderate-severe oral mucositis showed that the different mucositis causes and honey types might have had large influences on the final results. Significant efficacy could also be found in adults group (OR = 0.21, 95%CI: 0.11–0.41; $P = 0.000$, $I^2 = 72.3\%$), head and neck cancer group (OR = 0.21, 95%CI: 0.09–0.46; $P = 0.000$, $I^2 = 75.0\%$), other type of cancer group (OR = 0.30, 95%CI: 0.10–0.87; $P = 0.000$, $I^2 = 82.6\%$) chemo/radiotherapy-induced group (OR = 0.16, 95%CI: 0.06–0.44; $P = 0.600$, $I^2 = 0.0\%$), radiation-induced group (OR = 0.22, 95%CI: 0.11–0.44; $P = 0.000$, $I^2 = 73.4\%$), pure natural honey group (OR = 0.11, 95%CI: 0.06–0.22; $P = 0.025$, $I^2 = 52.7\%$), usual care group (OR = 0.18, 95%CI: 0.09–0.35; $P = 0.001$, $I^2 = 66.4\%$) and WHO scale group (OR = 0.12, 95%CI: 0.05–0.29; $P = 0.011$, $I^2 = 61.8\%$). Little evidence of bias could be found in Begg's and Egger's tests, with low to moderate quality evidence according to the GRADE assessment. In general, influence of mucositis cause might have caused less than the effects of difference in honey types because of the difference in sample size between subgroups was too large (15/2/4). Therefore, we need to perform further comparisons of difference in honey types and control types of network meta-analysis.

3.2.2. Network meta-analysis

Fig. 2 displays the network weight of eligible comparisons for treatment efficacy, also displaying the available, direct comparisons and network of the trials. There were thirteen different treatment and control arms: bee glue; benzocaine; benzydamine; caramel dye; chamomile; dabur honey; golden syrup; kanuka honey; lidocaine; local honey; manuka honey; pure natural honey; and usual care. The comparison-adjusted funnel plot for incidence of moderate-severe oral mucositis was not suggestive of any publication bias (Fig. S3).

Network meta-analysis suggested that, in comparison with usual care, chamomile ranked the best for the efficacy of moderate-severe oral mucositis treatment (OR:0.05, 95%credible intervals: 0.01–0.46), followed by pure nature honey ranked the best for the efficacy of all types of honey in moderate-severe oral mucositis treatment (0.05, 0.01–0.46), benzocaine (0.12, 0.02–0.71), dabur honey (0.12, 0.04–0.37), local honey (0.12, 0.04–0.37), caramel dye (0.23, 0.01–6.62), golden syrup (0.46, 0.10–2.19), manuka honey (0.54, 0.22–1.36), benzydamine (0.70, 0.19–2.58), and lidocaine (2.56, 0.09–73.42), all of which ranked higher than usual care. Bee glue was ranked as the least effective among honey treatment (0.39, 0.01–11.11), followed by kanuka honey (0.54, 0.07–4.35), these two were ranked lower than usual care.

When we assessed the comparative efficacy of the treatment/control arms, treatment/control arms were comparable with one another in improving efficacy, with a significant difference found in the pure natural honey v.s. bee glue, kanuka honey, lidocaine, benzydamine and

Table 2
Meta-analysis, meta-regression and quality of evidence for the moderate-severe oral mucositis between honey treatment arm vs. control arm.

Outcomes and subgroups	Participants (T/C)	OR (95%CI)	Heterogeneity (P, I^2)	Meta-regression (P)	Quality of evidence	Publication bias	
						Begg's (P)	Egger's (P)
Total (n = 21)	605/595	0.25 (0.14, 0.46)[a]	P = 0.000, I^2 = 77.5%[b]		Moderate	P = 0.121	P = 0.014[d]
Age group							
Teenager (n = 5)	138/138	0.41 (0.09, 1.83)	P = 0.000, I^2 = 87.3%[b]	P = 0.414	Moderate	P = 0.086	P = 0.169
Adult (n = 16)	467/457	0.21 (0.11,0.41)[a]	P = 0.000, I^2 = 72.3%[b]		Moderate	P = 0.207	P = 0.046[d]
Cancer type							
Head and neck cancer (n = 13)	375/365	0.22 (0.10, 0.47)[a]	P = 0.000, I^2 = 74.9%[b]	P = 0.633	Moderate	P = 0.625	P = 0.128
Other cancer (n = 8)	230/230	0.30 (0.10, 0.87)[a]	P = 0.000, I^2 = 82.6%[b]		Moderate	P = 0.019[d]	P = 0.057[d]
Mucositis cause							
Chemo/radiotherapy-induced (n = 2)	40/40	0.16 (0.06, 0.44)[a]	P = 0.600, I^2 = 0.0%	P = 0.364	Moderate	P = 0.317	P = 1.000
Radiation-induced (n = 15)	447/437	0.22 (0.11, 0.44)[a]	P = 0.000, I^2 = 73.4%[b]		Moderate	P = 0.216	P = 0.062
Chemotherapy-induced (n = 4)	118/118	0.49 (0.08, 2.91)	P = 0.000, I^2 = 89.8%[b]		Moderate	P = 0.090	P = 0.260
Honey type							
Pure natural honey (n = 10)	255/256	0.11 (0.06, 0.22)[a]	P = 0.025, I^2 = 52.7%[b]	P = 0.038[c]	Moderate	P = 0.929	P = 0.328
Manuka honey (n = 4)	170/165	0.70 (0.36, 1.35)	P = 0.184, I^2 = 38.0%		Moderate	P = 0.497	P = 0.394
Local honey (n = 7)	180/174	0.44 (0.15, 1.30)	P = 0.000, I^2 = 77.3%[b]		Low	P = 0.133	P = 0.268
Control arm							
Placebo (n = 9)	276/270	0.39 (0.14, 1.08)	P = 0.000, I^2 = 82.0%[b]	P = 0.219	Moderate	P = 0.048	P = 0.099
Usual care (n = 12)	329/325	0.18 (0.09, 0.35)[a]	P = 0.001, I^2 = 66.4%[b]		Moderate	P = 0.411	P = 0.155
Type of assessment scale							
RTOG scale (n = 6)	181/175	0.33 (0.10, 1.08)	P = 0.001, I^2 = 76.7%[b]	P = 0.586	Moderate	P = 0.348	P = 0.175
WHO scale (n = 8)	215/216	0.12 (0.05, 0.29)[a]	P = 0.011, I^2 = 61.8%[b]		Moderate	P = 0.458	P = 0.349
NCI-CTC scale (n = 4)	132/132	0.71 (0.34, 1.50)	P = 0.133, I^2 = 46.4%		Moderate	P = 0.308	P = 0.370

T, treatment group; C, control group.
[a] Results with significant differences.
[b] Substantial heterogeneity.
[c] Factors could be an important source of heterogeneity.
[d] Publication bias.

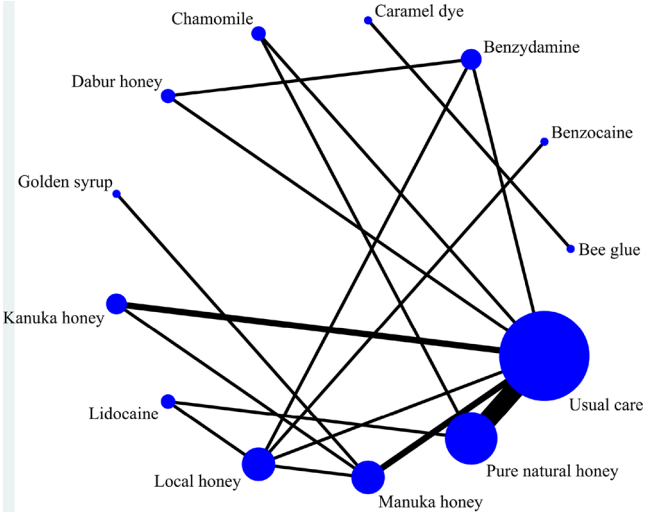

Fig. 2. Network of eligible comparisons for incidence of moderate-severe oral mucositis.
The size of the nodes and the thickness of the edges are weighted according to the number of studies evaluating each treatment and direct comparison, respectively. The size of each circle is proportional to the number of randomly assigned patients and represents the sample size. The width of the lines corresponds to the number of studies.

manuka honey group; chamomile v.s. lidocaine and benzydamine group; benzocaine v.s. kanuka honey and lidocaine group; dabur honey v.s. kanuka honey, lidocaine, benzydamine, manuka honey and local honey; local honey v.s. bee glue, lidocaine, manuka honey; caramel dye v.s. bee glue (Fig. 3).

Therefore, honey can improve the therapy efficacy of moderate-severe oral mucositis caused by chemo/radiotherapy, especially the use of pure natural honey. Similar results are illustrated in Table 2 with the highest OR values in subgroup analysis.

3.3. Secondary efficacy outcomes

Table 3 summarizes results of the secondary efficacy outcomes toxicity associated with the honey treatment arm versus the control arm. We found that honey not only did not increase the risk of adverse effects but also reduced the onset time of oral mucositis (0.41, 0.08–0.73). Moreover, the use of honey was effective and safe, with mostly moderate to high quality evidence according to GRADE assessment.

4. Discussion

The network meta-analysis represents the most comprehensive synthesis of data for currently available data for the treatment for chemo/radiotherapy-induced oral moderate-severe mucositis with honey. We combined direct and indirect evidence from 17 randomized controlled trials (22 analyses) comparing thirteen different interventions on over one thousand cancer patients undergoing chemo/radiotherapy-induced oral moderate-severe mucositis to make several key observations regarding the potential efficacy and safety of honey. Firstly, honey treatment arm was superior to non-honey control arm in overall treatment efficacy accompanied by substantial heterogeneity (Fig. 2). Furthermore, a majority of subgroups associations reached statistical significance(such as head and neck cancer group,chemo/radiotherapy-induced group and pure natural honey group), and heterogeneity also existed in most of the outcomes, with low to moderate confidence in estimates (Table 2). Besides, due to the large differences in treatment arms (by meta-regression), according to network meta-analysis of therapy efficacy by treatment method, pure natural honey

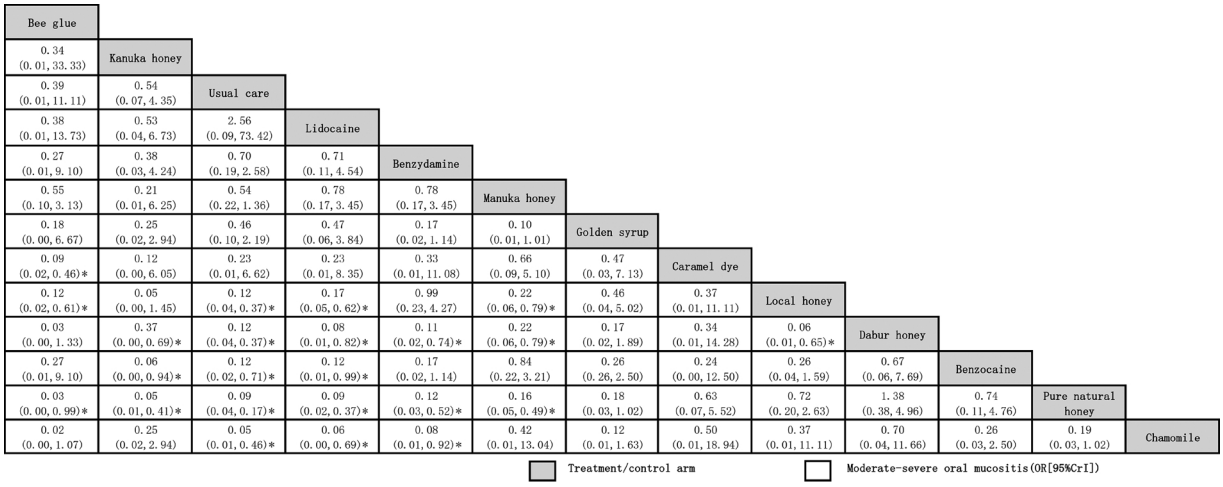

Fig. 3. Summary ORs and CrIs from network meta-analysis.
Treatment are reported in order of incidence of moderate-severe oral mucositis ranking according to SUCRA. Comparisons between treatments should be read from left to right. For incidence of moderate-severe oral mucositis, OR < 1 suggests favors for the honey treatment arm than with the control arm.

Table 3
Secondary efficacy outcomes between honey treatment arm vs. control arm.

Outcomes	Patients (T/C)	OR (95%CI)	Heterogeneity (P, I^2)	Quality of evidence
Treatment completed	5 (189/187)	0.91 (0.57,1.45)	P = 0.370, I^2 = 6.4%	High
Onset time of mucositis	3 (76/76)	0.41 (0.08,0.73)[a]	P = 0.363, I^2 = 1.3%	Moderate
Swallowing diary	3 (171/169)	0.98 (0.63,1.51)	P = 0.571, I^2 = 0.0%	High
Fungal colonization	3 (104/103)	0.39 (0.11,1.35)	P = 0.059, I^2 = 64.7%[b]	Moderate
Bacterial colonisation	2 (84/83)	0.35 (0.03.3.69)	P = 0.006, I^2 = 86.8%[b]	Low
Antalgesic use	3 (171/169)	1.02 (0.64,1.65)	P = 0.909, I^2 = 0.0%	High

T, treatment group; C, control group.
[a] Result with significant differences.
[b] Substantial heterogeneity.

had superior efficacy in terms of treatment arms (Fig. 3). Finally, honey not only did not increase the risk of adverse effects but also reduced the onset time of oral mucositis (Table 3). Overall, compared with non-honey control arm, honey was found to be both safe and efficacious in treatment for chemo/radiotherapy-induced oral moderate-severe mucositis.

This review followed the guidelines for conducting rigorous systematic reviews and network meta-analyses (Higgins and Green, 2011; Maddocks-Jennings et al., 2009; Moher et al. 2009). To identify as many relevant reports as possible and to decrease the risk of bias, a comprehensive search strategy was designed. Based on these considerations, we observed moderate evidence of publication bias by statistical assessment. The treatment by honey signifcantly increased the treatment efficacy in cancer patients suffer from chemo/radiotherapy-induced oral moderate-severe mucositis. Subgroup analyses and network meta-analysis revealed that pure natural honey ranked best with significantly increased treatment efficacy. A meta-regression was used to assess the heterogeneity. Over all, mucositis cause and honey type were the main factors affecting heterogeneity. In our meta-analysis, based on the subgroup analyses, we found positive results in favor of eight subgroups: adults group, head and neck cancer group, other type of cancer group, chemo/radiotherapy-induced group, radiation-induced group, pure natural honey group, usual care group and WHO scale group. The results overlapped in two ways and might have helped identify the most effective treatment method. When the studies were grouped by control arm, positive results appeared in placebo and also in the usual care group for chemo/radiotherapy-induced oral moderate-severe mucositis. This result might indicate that honey had an effect regardless of whether the control group participated in an activity, similar results were also confirmed by the results of the network meta-analysis.

Although our group is very meticulous and detailed, but pure natural honey is intersecting, so the best choice is to use pure natural honey for treatment. Our results could be confirmed in many publication articles, Song's researched made a conclusion that overall relative risk of developing mucositis was almost 80% lower in the honey treatment group than in the control group (Song et al., 2012). And, Raeessi MA considered honey plus coffee regimen was the most effective modality for the treatment of oral mucositis, the results need further identification (Raeessi et al., 2014).

The network meta-analysis had some limitations that merit further discussion. First, in the GRADE framework, several comparisons were determined to be moderate or low-quality, which largely restricts the interpretation of the results. In addition, the network analysis contained some inconsistencies, which were mainly determined by the loop (Table 3). Moreover, thirteen arms in sixteen analyses were measured due to the small sample size. Furthermore, positive results are likely to be published, while negative results are not likely to be shared (Feng et al., 2018; Zhang et al., 2017). An additional limitation of the standardized outcomes was the extensive heterogeneity (Fig. 1, Tables 2), which indicated a substantial variability in the outcomes of the included studies, which indicated substantial variability in the outcomes of the included studies, because there was no presence of heterogeneity in the baseline outcomes (Table 1).

This study extends the findings from primary randomized controlled trial and previous meta-analyses by systematically synthesizing the efficacy data. The meta-analysis differs from those in earlier studies in several ways. First, the main objective of the study was to determine the

efficacy and safety of honey in patients with cancer undergoing chemo/radiotherapy-induced moderate-severe oral mucositis, whereas the previous pairwise studies included only patients with head and neck cancer (Cho et al., 2015; Co et al., 2016). Secondly, subgroup analyses and meta-regressions were used to identify the differences between the different cancer type (head and neck cancer and other cancer), mucositis cause (chemo/radiotherapy-induced, radiation-induced and chemotherapy-induced), honey type(pure natural honey, manuka honey and local honey), control arm(placebo and usual care) and type of assessment scale (RTOG scale, WHO scale and NCI-CTC scale) to determine the most suitable treatment type of honey and the most suitable cancer and cause types, whereas the other meta-analyses have not been so detailed and so meticulous (Xu et al., 2016). Finally, a network meta-analysis was used to directly and indirectly compare the different treatment arms and the therapeutic effect, to determine the most appropriate type of honey.

Honey is safe and efficacious adjuvant therapy agent. Additional RCTs of honey should include larger samples and be robust and randomized to confirm the effects and toxicity of honey on patient-relevant or disease-specific outcomes, particularly in cancer patients undergoing chemo/radiotherapy-induced moderate-severe oral mucositis. Future studies should ensure that appropriate methods are used for randomization, blinding and intent to-treat. Furthermore, trials should assess outcomes using standardized or prescribed measures at similar time points. Analyses of individual data will be valuable for further exploration. More normative studies should be utilized in future network meta-analyses.

The suggested mechanism of action of honey in chemo/radiotherapy-induced oral mucositis may be through its positive effect on cell epithelialization and regrowth, thereby encouraging rapid recovery of cell loss (Dörr et al., 2001). Although the mechanism of action of honey is not clear, it is likely that factors like osmolality, phenol content, flavanoid levels, acidity, and the release of hydrogen peroxide are thought to be the most important factors for its activity (Almasaudi et al., 2016). Moreover, honey, because of their high permeability, honey may stimulate saliva production. Therefore, its effectiveness may be related to its high permeability, anti-foaming properties and antioxidant properties (Ghashm et al., 2010; Yarom et al., 2013). Besides, honey is known for its antioxidant and anti-inflammatory activity and increased nitric oxide(NO) in the lesion (Almasaudi et al., 2016; Raeessi et al., 2014). In summary, honey can accelerate the repair and healing of chemo/radiotherapy-induced oral mucosal damage and reduce the related stimulation.

The finding of this comprehensive network meta-analysis provides some evidence that honey might improve the therapy efficacy in patients with cancer undergoing chemo/radiotherapy-induced moderate-severe oral mucositis without increasing side effects. On a local scale, patients with cancer undergoing chemo/radiotherapy-induced moderate-severe oral mucositis could be encouraged to accept honey for adjuvant therapy, especially applied pure natural local honey. In the clinical therapy of patients with cancer undergoing chemo/radiotherapy-induced moderate-severe oral mucositis, honey can be invoked as a first-line adjuvant therapy agent.

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

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Ethical approval

The systematic review was not subject to ethical review.

Appendix A. Supplementary data

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