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Effects of various treatments for preventing oral mucositis in cancer patients: A network meta-analysis

Tzu-Rong Peng, Fang-Pei Tsai, Ta-Wei Wu*

Department of Pharmacy, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei City, Taiwan

* p8561825@yahoo.com.tw

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Abstract

Background

Oral mucositis (OM) is a common side effect of chemotherapy and radiotherapy in patients with cancers. The prevention or treatment of OM in cancer patients is crucial in the treatment of cancer.

Methods

We searched PubMed, Embase, and Cochrane Library for the randomized control trials (RCTs) of interventions for preventing and treating OM. Network meta-analysis (NMA) was performed to estimate odds ratios (ORs) and 95% confidence intervals (CI) from both direct and indirect evidence. The prespecified primary efficacy outcome was the treatment effect of moderate to severe oral mucositis with 12 interventions. The outcome was moderate to a severe grade of OM.

Results

This study included 55 RCTs with 3,552 participants. The results showed that honey significantly lowered the risk of chemo/radiotherapy-induced moderate to severe oral mucositis than placebo (OR: 0.01, 95%CI 0.00 to 0.45), followed by lignocaine (OR: 0.07, 95%CI 0.00 to 0.95). The surface under cumulative ranking curve (SUCRA) values for honey were 0.95, followed by lignocaine (SUCRA, 0.81) and benzydamine (SUCRA, 0.78).

Conclusions

The honey is effective for patients with cancer undergoing chemotherapy or radiotherapy-induced oral mucositis.

Introduction

Chemotherapy and radiotherapy are the most methods for treating cancer, they can result in serious adverse reactions [1]. Oral mucositis (OM) is one of the main side effects of

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chemotherapy and radiotherapy, and the incidence rate is 40% to 100%. The incidence of OM is related to age, tumor type, treatment methods, nutritional status, and oral hygiene [2–4]. The symptom of OM is erythema, which can progress to painful ulcerations. Ulcerations in oral mucositis are painful and require local analgesics, which may cause the patient to have difficulty eating and cause malnutrition. Malnutrition status will affect the quality of life of patients and delay chemical therapy and radiotherapy.

The prevention and treatment of OM caused by chemotherapy or radiotherapy remain challenging. Several interventions have been investigated for the prevention and treatment of OM, such as chlorhexidine, benzydamine, sucralfate, povidone-iodine, glutamine, and honey, which have been found to prevent mucositis or reduce the severity of mucositis [5–8]. However, no approach has been completely successful for OM. Therefore, the prevention or treatment of OM remains to be resolved.

Although several meta-analyses have been conducted independently to assess the effects of the different interventions compared with placebo [8–11]. The evidence of meta-analysis was limited due to the lack of multiple comparisons. Network meta-analysis is a methodology for assessing multiple interventions through direct and indirect comparison [12]. Therefore, we performed a network meta-analysis to comprehensively compare and rank the efficacy of interventions used for preventing and treating OM in cancer patients receiving chemotherapy and radiotherapy.

Materials and methods

Systematic literature review

This network meta-analysis was performed by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions (PRISMA-NMA) [13]. We searched the PubMed, Embase, and Cochrane Library database up to 30th December 2021. Titles and abstracts were screened, and relevant articles were independently and fully reviewed by two reviewers (TW Wu and TR Peng). Disagreements were resolved by consensus. No language restrictions were imposed. In the event of duplicate publications, we selected the publication that reported the data of interest most completely. The references of included studies were additionally screened to identify relevant RCTs.

Study selection and outcome measures

This study was performed by Cochrane Collaboration guidelines [14]. The following information was extracted: author, year of publication, study design, number of enrolled patients, cancer types, prevent or treatment OM, chemotherapy- or radiation therapy-induced OM, and clinical efficacy (the incidence of moderate-severe OM). Trials that met the following criteria were included: (1) randomized control trial, (2) comparison of application between the prophylactic or treatment groups and control groups of patients with cancer with chemotherapy- or radiation therapy-induced OM, (3) included all cancer types, and (4) studies that mentioned patient inclusion and exclusion criteria, mucositis grades, and treatment procedures for all groups. In addition, OM grades were determined using the Radiation Therapy Oncology Group criteria [15], Organization WH. World Health Organization (WHO) handbook for the report [16], or Common Terminology Criteria for Adverse Events [17]. The outcome is presented as the overall odds ratios for the occurrence of moderate-severe OM induced by chemo/radiotherapy in patients with cancer. Severe OM is defined as grades 3–4, and moderate OM as grades 2.

Data extraction and quality assessment

The Cochrane Collaboration tool was used to assess the risk of bias [14], which covers the potential sources of bias including selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective reporting). Each study was categorized as having either low risk (green), unclear risk (yellow), or high risk (red) of bias. The risk of attrition bias was considered to be low if the dropout rate was lower than 20%.

Statistical methods and data synthesis. Network meta-analysis was performed using odds ratio (OR) for the incidence of oral mucositis with a 95% confidence interval (CI) for the indirect and mixed comparisons. We checked for similarity, transitivity, and consistency. Transitivity was judged clinically, whereas consistency was judged formally [18]. We tested for possible global and local inconsistency by performing a $\chi 2$ test and by side-splitting, respectively. We estimated the ranking probabilities of being at each possible rank for each intervention. Comparison-adjusted funnel plots were employed to assess publication bias. In addition, sensitivity analysis was performed to determine the effect of each study by excluding a study with a high risk of bias or studies which could cause global or local inconsistency. Statistical evaluation of inconsistency and the production of network graphs and figures were performed using the network and network graphs packages in STATA version 15 (STATA Corporation, College Station, TX, USA). The Begg's and Egger's tests were used to detect publication bias.

Results

Search results

We identified 3,045 records from PubMed, EMBASE, and Cochrane electronic databases. Three hundred seventy studies were removed due to duplication, 592 studies were removed due to non-RCTs, and 1,589 studies were removed due to not being the targets in this study. After the exclusion of these studies, we reviewed 194 studies based on title and abstract, and 139 studies were removed because of irrelevant records. Finally, 55 studies matched our inclusion criteria. The Systematic Reviews and Meta-Analyses (PRISMA) flowchart shows the detailed process of study selection (Fig 1).

Eligible studies and patient characteristics

The basic characteristics of the eligible studies are presented in the Table 1. All included studies were published in English and randomized control trials, between 1994 and 2019. Most of the included studies have two arms, and only 2 studies have three arms. The risk of bias assessment of the 55 included trials is summarized in S1 Fig. The included studies encompassed 3,552 participants mostly with head and neck cancer.

Network geometry and testing for inconsistency

The network constructions are presented in Fig 2. The p-value was higher than 0.05 ($p = 0.9555$) for the test of inconsistency at the overall level. No p-values were lower than 0.05 for the test of local inconsistency (S2 Fig). Significance was not found in any of the global or local tests, indicating that the consistency assumption was accepted.

Treatment effect of moderate to severe oral mucositis

Network meta-analysis showed that, in comparison with placebo, honey ranked the best for the incidence of moderate-severe oral mucositis prevention and treatment (OR: 0.01, 95%CI

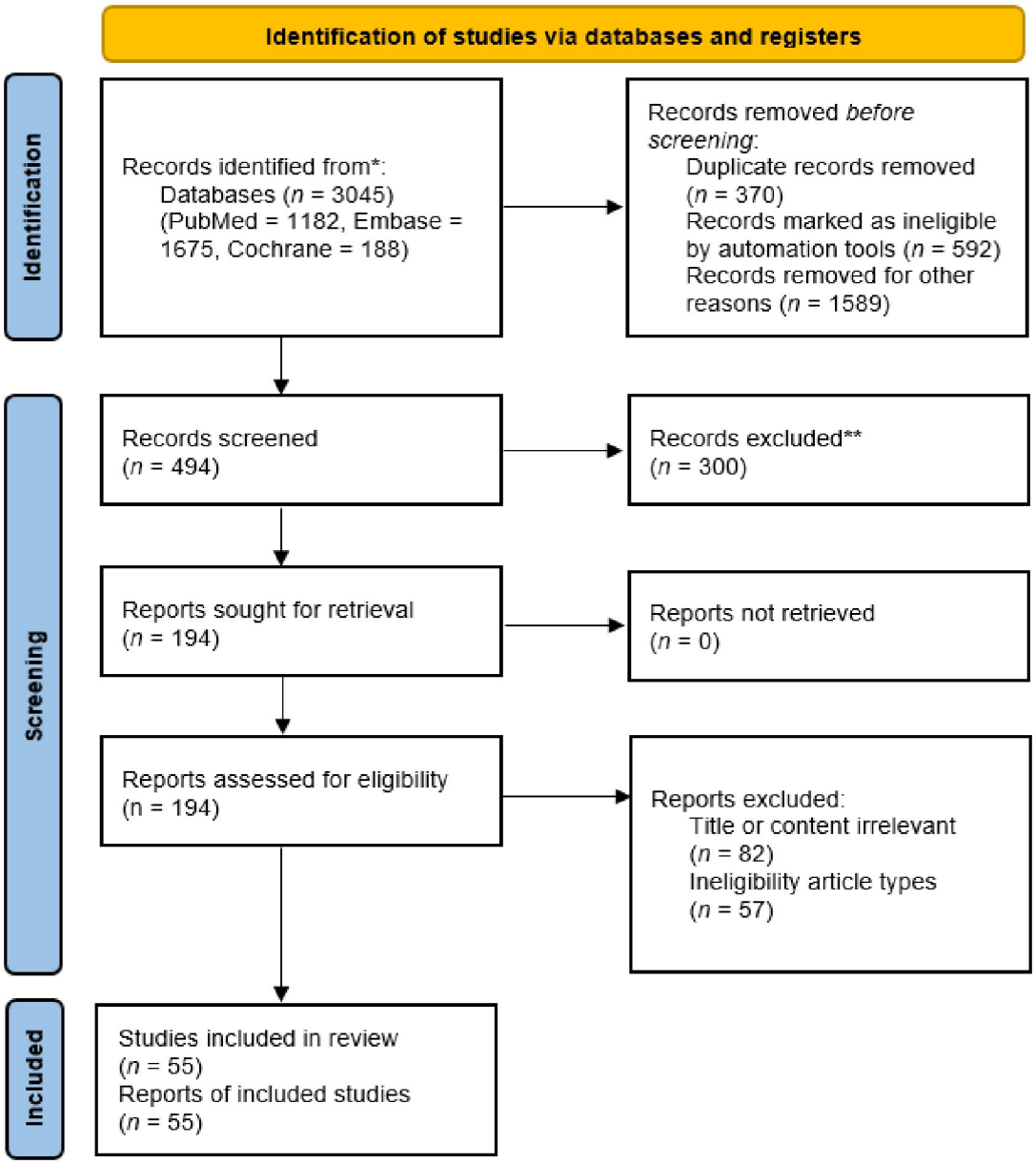

Fig 1. Flow diagram of the studies identified. *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

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0.00 to 0.45), followed by lignocaine (OR: 0.07, 95%CI 0.00 to 0.95), benzydamine (OR: 0.07, 95%CI 0.00 to 1.19), allopurinol (OR: 0.22, 95%CI 0.01 to 4.84), sucralfate (OR: 0.12, 95%CI 0.01 to 2.10), aloe (OR: 0.17, 95%CI 0.01 to 3.67), probiotics (OR: 0.13, 95%CI 0.01 to 2.80), povidone-iodine (OR: 0.16, 95%CI 0.01 to 3.02), all of which ranked higher than placebo (Fig 3, Tables 2 and 3). However, granulocyte-macrophage colony-stimulating factor (GM-CSF), curcumin chlorhexidine, and glutamine were ranked lower than placebo. However, this network meta-analysis suggested that honey with the highest probability of preventing moderate-severe OM induced by chemo/radiotherapy in patients with all cancers. The surface under

Table 1. Characteristics of included studies.

Study	Study design	Cancer type	Chemoradiation (C)/ Radiotherapy (R)	Number	Intervention	Events/Number (Grade 3 or 4 OM)
Lopez-Vaquero (2017) [19]	RCT	Head and neck	CR	25 24	Glutamine Placebo	1/25 2/24
Tanaka (2015) [20]	RCT	Esophageal	C	10 10	Glutamine Placebo	3/10 2/10
Tsujimoto (2015) [21]	RCT	Head and neck	C	20 20	Glutamine Placebo	18/20 20/20
Huang (2000) [22]	Randomized trial	Head and neck	R	8 9	Glutamine Placebo	0/8 4/9
Cerchietti (2006) [23]	RCT	Head and neck	C	14 15	Glutamine Placebo	0/14 5/15
Choi (2007) [24]	RCT	Advanced solid tumors	C	22 29	Glutamine Placebo	1/22 6/29
Peterson (2007) [25]	RCT	Breast	C	163 163	Glutamine Placebo	2/163 11/163
Okuno (1999) [26]	RCT	Undefined	C	66 68	Glutamine Placebo	4/66 5/68
Coghlin Dickson (2000) [27]	RCT	Hematologic (HSCT)	R	29 29	Glutamine Placebo	19/29 18/29
Jebb (1994) [28]	RCT	Advanced GI cancers	C	17 17	Glutamine Placebo	5/17 4/17
Skubitz (1996) [29]	RCT	Various	C	14 14	Glutamine Placebo	0/14 1/14
Nihei (2018) [30]	RCT	Colorectal or breast	C	34 33	Glutamine Placebo	11/34 19/33
Pathak (2019) [31]	RCT	Oropharynx and Larynx Carcinoma	CR	30 30	Glutamine Placebo	12/30 27/30
Huang (2019) [32]	RCT	Head and neck	R	31 33	Glutamine Placebo	17/31 26/33
Diwan (2018) [33]	RCT	Head and neck	R	30 30	Glutamine Placebo	4/30 7/30
Pattanayak (2016) [34]	RCT	Head and neck	CR	81 81	Glutamine Placebo	0/81 61/81
Amanat et al. (2017) [35]	RCT	Head and neck	R	41 41	Honey Placebo	2/41 7/41
Rao et al. (2017) [36]	RCT	Head and neck	R	25 25	Honey Povidone-iodine	8/25 12/24
Jayalekshmi et al. (2016) [37]	RCT	Head and neck	R	14 14	Honey Placebo	1/14 9/14
Eslami et al. (2016) [38]	Randomized trial	Acute lymphoblastic leukemia	C	24 24	Chlorhexidine Honey	9/24 1/24
Sahebjamee et al. (2015) [39]	RCT	Head and neck	R	13 13	Aloe Benzydamine	5/13 4/13
Hawley et al. (2014) [40]	RCT	Head and neck	R	40 41	Honey Placebo	14/40 18/41
Rao et al. (2014) [41]	RCT	Head and neck	R	39 40	Curcumin Povidone-iodine	14/39 34/40
Jayachandran and Balaji (2012) [42]	RCT	Head and neck	R	20 20 20	Honey Benzydamine Placebo	2/20 10/20 16/20

(*Continued*)

Table 1. (Continued)

Study	Study design	Cancer type	Chemoradiation (C)/ Radiotherapy (R)	Number	Intervention	Events/Number (Grade 3 or 4 OM)
Roopashri et al. (2011) [43]	RCT	Head and neck	R	25 25 25	Povidone-iodine Chlorhexidine Placebo	2/25 3/25 4/25
Panahi et al. (2010) [44]	RCT	malignant disorders	C	15 15	Allopurinol Placebo	13/15 15/15
Khanal et al. (2010) [45]	RCT	oral carcinoma	R	20 20	Honey Lignocaine	1/20 15/20
Sorensen et al. (2008) [46]	RCT	Gastrointestinal Malignancies	C	70 64	Chlorhexidine Placebo	20/70 31/64
Cheng et al. (2006) [47]	RCT	Head and neck	R	7 7	Chlorhexidine Benzydamine	3/7 2/7
Vokurka et al. (2005) [48]	RCT	Autologous transplantation	C	37 65	Povidone-iodine Placebo	32/37 29/65
Dazzi et al. (2003) [49]	RCT	Autologous transplantation	C	46 44	GM-CSF Placebo	15/46 17/44
Costa et al. (2003) [50]	RCT	Acute lymphoblastic leukemia	C	7 7	Chlorhexidine Placebo	1/7 5/7
Nottage et al. (2003) [51]	RCT	Gastrointestinal Malignancies	C	41 39	Sucralfate Placebo	3/41 0/39
Castagna et al. (2001) [52]	RCT	bone marrow transplantation	C	51 51	Sucralfate Placebo	15/51 24/51
Cengiz et al. (1999) [53]	RCT	Head and neck	R	18 10	Sucralfate Placebo	9/18 9/10
Adamietz et al. (1998) [54]	RCT	Head and neck	CR	20 20	Povidone-iodine Placebo	4/20 13/20
Foote et al. (1994) [55]	RCT	Head and neck	R	25 27	Chlorhexidine Placebo	22/25 21/27
Alvi et al. (2013) [56]	RCT	Head and neck	R	30 30	Honey Placebo	4/30 12/30
Biswal et al. (2003) [57]	RCT	Nasopharynx, larynx	R	20 20	Honey Placebo	0/20 5/20
Rashad et al. (2010) [58]	RCT	Head and neck	R	20 20	Honey Placebo	0/20 7/20
Bardy et al. (2012) [59]	RCT	Head and neck	C	64 63	Honey Placebo	51/64 47/63
Charalambous et al. (2018) [60]	RCT	Head and neck	C	36 36	Honey Placebo	1/36 19/36
Abbasi et al. (2007) [61]	RCT	Head and neck	CR	14 10	Allopurinol Placebo	5/14 10/10
Pitten et al. (2003) [62]	RCT	leukopenia	C	24 23	Chlorhexidine Placebo	9/24 2/23
Schneider et al. (1999) [63]	RCT	Head and neck	CR	8 6	G-CSF Placebo	1/8 3/6
Su et al. (2006) [64]	RCT	Head and neck	R	19 21	G-CSF Placebo	4/19 11/21
Rahn et al. (1997) [65]	RCT	Head and neck	R	20 20	Povidone-iodine Placebo	9/20 20/20
Sharma et al. (2011) [66]	RCT	Head and neck	CR	93 95	Probiotics Placebo	49/93 73/95

(*Continued*)

Table 1. (Continued)

Study	Study design	Cancer type	Chemoradiation (C)/ Radiotherapy (R)	Number	Intervention	Events/Number (Grade 3 or 4 OM)
Jiang et al. (2018) [67]	RCT	nasopharyngeal carcinoma	CR	58 35	Probiotics Placebo	9/58 16/35
De Sanctis et al. (2019) [68]	RCT	Head and neck	R	32 36	Probiotics Placebo	13/32 15/36
Mansourian et al. (2015) [69]	RCT	Head and neck	R	19 18	Curcumin Placebo	0/19 7/18
Delavarian et al. (2019) [70]	RCT	Head and neck	R	15 14	Curcumin Placebo	10/15 12/14
Arun et al. (2019) [71]	RCT	Head and neck	C	30 31	Curcumin Placebo	0/30 4/31
Su et al. (2004) [72]	RCT	Head and neck	R	28 30	Aloe Placebo	23/28 28/30
Puataweepong et al. (2009) [73]	RCT	Head and neck	R	30 31	Aloe Placebo	16/30 27/31

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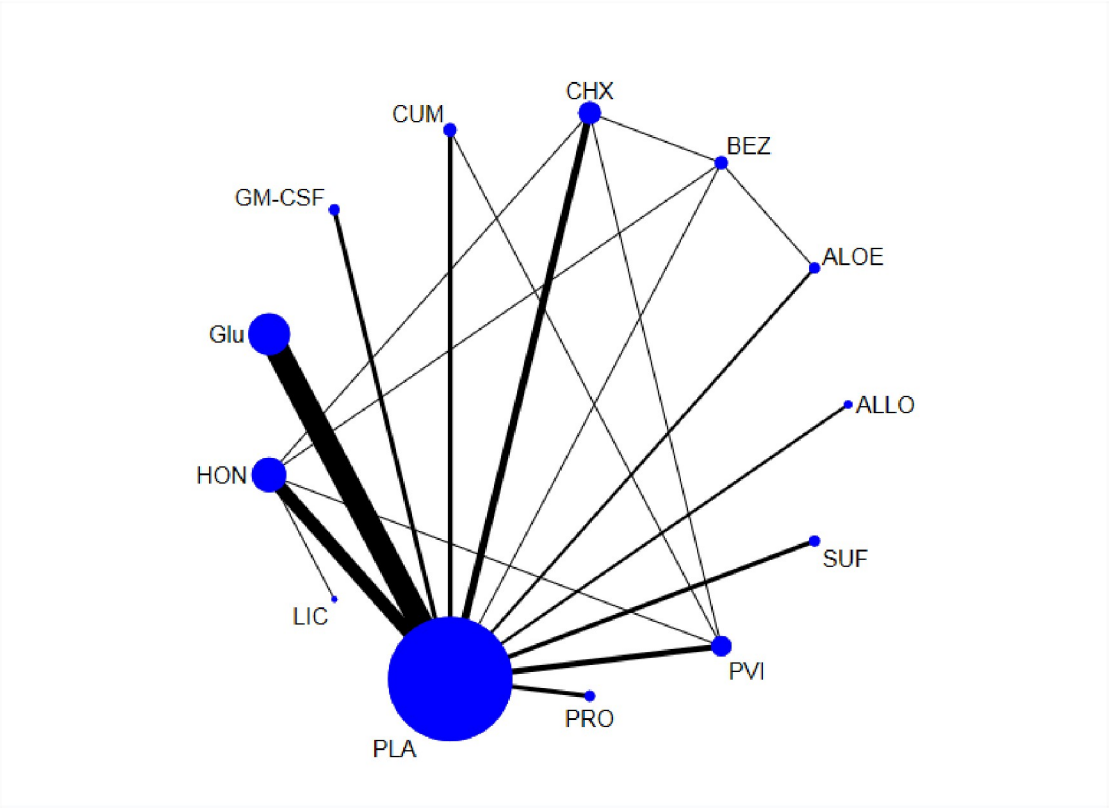

Fig 2. Evidence network of the RCTs in the network meta-analysis. Abbreviation: ALOE, aloe; ALLO, allopurinol; BEZ, benzydamine; CHX, chlorhexidine; CUM, Curcumin; Glu, glutamine; GM-CSF, granulocyte-macrophage colony-stimulating factor; HON, honey; LIC, lignocaine; PLA, placebo; PRO, probiotics; PVI, povidone-iodine; SUF, sucralfate.

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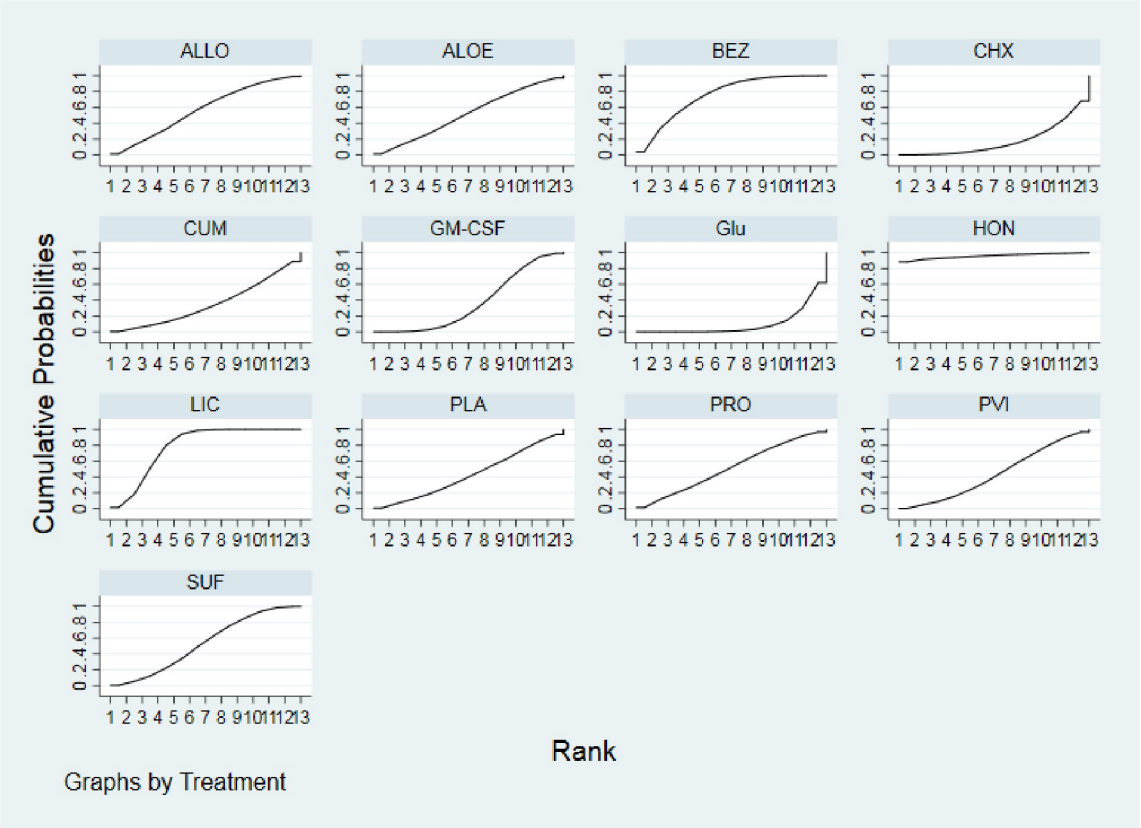

Fig 3. Rankograms for the network shows the probability of the incidence of moderate-severe oral mucositis of each treatment in patients with cancer. Abbreviation: ALOE, aloe; ALLO, allopurinol; BEZ, benzydamine; CHX, chlorhexidine; CUM, Curcumin; Glu, glutamine; GM-CSF, granulocyte-macrophage colony-stimulating factor; HON, honey; LIC, lignocaine; PLA, placebo; PRO, probiotics; PVI, povidone-iodine; SUF, sucralfate.

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Table 2. Rank probability to be the best treatment (PrBest) by the moderate-severe oral mucositis of each treatment of patients with cancer.

Treatment	Pbest
Honey	85.6%
Benzydamine	5.1%
Probiotics	2.7%
Lignocaine	2.1%
Sucralfate	1.2%
Aloe	1.1%
Curcumin	0.09%
Povidone-iodine	0.07%
Allopurinol	0.04%
Placebo	0.02%
GM-CSF	0%
Glutamine	0%
Chlorhexidine	0%

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Table 3. Results of the incidence of moderate-severe oral mucositis; results presented as constant odds ratios between all competing interventions with 95% confidence intervals. *Comparisons of treatments should be read from left to right. The rate ratio lower than 1 favors the top left treatment. The treatments have been sorted from left to right according to treatment ranking. Statistically significant differences between regimens are shown in bold with green background.

HON												
0.11 (0.00,2.60)	**LIC**											
0.10 (0.00,2.90)	0.98 (0.34,2.78)	**BEZ**										
0.03 (0.00,1.14)	0.31 (0.06,1.51)	0.31 (0.05,2.00)	**ALLO**									
0.06 (0.00,1.68)	0.57 (0.19,1.72)	0.58 (0.14,2.44)	1.85 (0.27,12.78)	**SUF**								
0.04 (0.00,1.47)	0.41 (0.08,2.03)	0.42 (0.07,2.39)	1.33 (0.21,8.55)	0.72 (0.11,4.90)	**ALOE**							
0.06 (0.00,2.09)	0.54 (0.11,2.77)	0.55 (0.08,3.86)	1.76 (0.18,17.32)	0.95 (0.13,6.94)	1.33 (0.13,13.20)	**PRO**						
0.05 (0.00,1.44)	0.43 (0.11,1.60)	0.44 (0.08,2.35)	1.40 (0.18,11.06)	0.76 (0.14,4.24)	1.06 (0.13,8.44)	0.79 (0.10,6.48)	**PVI**					
0.01 (0.00,0.45)	**0.07 (0.00,0.95)**	0.07 (0.00,1.19)	0.22 (0.01,4.84)	0.12 (0.01,2.10)	0.17 (0.01,3.67)	0.13 (0.01,2.80)	0.16 (0.01,3.02)	**PLA**				
0.03 (0.00,0.83)	**0.30 (0.15,0.61)**	0.31 (0.09,1.08)	0.97 (0.17,5.59)	0.53 (0.14,1.96)	0.73 (0.13,4.26)	0.55 (0.09,3.30)	0.70 (0.16,3.11)	4.39 (0.29,67.34)	**GM-CSF**			
0.04 (0.00,1.32)	0.36 (0.08,1.65)	0.37 (0.06,2.34)	1.18 (0.13,10.69)	0.64 (0.10,4.18)	0.89 (0.10,8.14)	0.67 (0.07,6.27)	0.85 (0.11,6.30)	5.33 (0.25,111.69)	1.22 (0.23,6.48)	**CUM**		
0.01 (0.00,0.35)	**0.10 (0.02,0.45)**	**0.10 (0.02,0.61)**	0.31 (0.03,2.86)	**0.17 (0.03,0.86)**	0.24 (0.03,2.16)	0.18 (0.02,1.68)	0.22 (0.03,1.69)	1.41 (0.07,29.84)	0.32 (0.06,1.75)	0.26 (0.03,2.29)	**CHX**	
0.02 (0.00,0.38)	**0.17 (0.07,0.39)**	**0.17 (0.05,0.60)**	0.54 (0.09,3.20)	0.29 (0.08,1.04)	0.41 (0.07,2.27)	0.31 (0.05,1.96)	0.39 (0.08,1.86)	2.44 (0.15,39.02)	0.56 (0.19,1.67)	0.46 (0.08,2.59)	1.74 (0.31,9.73)	**Glu**

Abbreviation: ALOE, aloe; ALLO, allopurinol; BEZ, benzydamine; CHX, chlorhexidine; CUM, Curcumin; Glu, glutamine; GM-CSF, granulocyte-macrophage colony-stimulating factor; HON, honey; LIC, lignocaine; PLA, placebo; PRO, probiotics; PVI, povidone-iodine; SUF, sucralfate.

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cumulative ranking curve (SUCRA) values for honey were 0.95, followed by lignocaine (SUCRA, 0.81) and benzydamine (SUCRA, 0.78).

Subgroup by head and neck cancer

The network meta-analysis for the incidence of moderate-severe oral mucositis of each treatment in patients with head and neck cancer was based on 39 trials. Results from network meta-analysis that honey is the best intervention to prevent or treat moderate-severe grade oral mucositis than placebo (OR: 0.00, 95%CI 0.00 to 0.36) with the highest probability of ranking the best (85.5%; S3 Fig, S1 and S3 Tables). However, the honey with the highest probability of preventing moderate-severe OM induced by chemo/radiotherapy in patients with head and neck cancer (SUCRA, 0.96), followed by lignocaine (SUCRA, 0.83), benzydamine (SUCRA, 0.79), and povidone-iodine. (SUCRA, 0.59).

Subgroup by radiotherapy

The network meta-analysis for radiotherapy-induced moderate-severe oral mucositis of each treatment in patients with cancer was based on 26 trials. Results from network meta-analysis that honey is the best intervention for preventing or treatment of moderate-severe grade oral mucositis than placebo (OR: 0.03, 95%CI 0.00 to 0.67) with the highest probability of ranking the best (85.9%; S4 Fig, S2 and S4 Tables). However, the honey with the highest probability of

preventing moderate-severe OM induced by radiotherapy in patients with cancers (SUCRA, 0.97), followed by lignocaine (SUCRA, 0.79), benzydamine (SUCRA, 0.77), and GM-CSF (SUCRA, 0.54).

Adverse events

Most of the included studies did not describe the occurrence of adverse events to therapy with these agents. Few studies reported the adverse events of the interventions.

Glutamine. Ten studies did not assess the safety issues [20–22, 24, 26–29, 32, 33]. Six studies found that patients in the glutamine group experienced no side effects or significant differences between the glutamine group and the control group [19, 23, 25, 30, 31, 34].

Honey. All of the studies did not examine the safety of honey [35–37, 40, 42, 56–60]. Two studies compared to honey and lignocaine or chlorhexidine and also did not evaluate the safety outcome [38, 45].

Aloe. All of the studies did not examine the safety of aloe [39, 72, 73].

Curcumin. Three studies examined the safety of curcumin. Two studies found that patients in the curcumin group experienced no side effects or discomfort caused by curcumin [70, 71]. In one study, two patients experienced nausea after the administration of curcumin gel [69]. One study does not assess the safety issue [41].

Probiotics. Only one study examined the safety of probiotics. The study found that patients in the probiotics group experienced no side effects caused by probiotics [66]. Two studies did not assess the safety issues [67, 68].

Publication bias, and sensitivity analysis

The comparison-adjusted funnel plots did not reveal any evidence of apparent asymmetry (Fig 4). No significant publication bias was observed. We also do sensitivity analysis. We excluded two studies with a high risk of bias one by one [43, 50], which resulted in similar results of the incidence of moderate-severe oral mucositis in comparison with our basic analysis (S5 Table).

Discussion

Several interventions are effective in preventing and treating OM. However, current evidence is based on a direct meta-analysis. Network meta-analysis is a technique for comparing multiple treatments simultaneously in a single analysis by combining direct and indirect results. This network meta-analysis investigated available evidence on the efficacy of preventing the risk of chemotherapy- or radiation therapy-induced moderate-severe oral mucositis of various interventions for patients with cancer. The results of this network meta-analysis showed that honey and lignocaine were more effective than placebo.

A previous network meta-analysis conducted by Yu et al. This network meta-analysis was compared nine oral care solutions (allopurinol, aloe, benzydamine, chlorhexidine, curcumin, granulocyte-macrophage colony-stimulating factor, honey, povidone-iodine, and sucralfate), including 28 RCTs with 1,861 patients. The results of network meta-analysis showed that chlorhexidine, benzydamine, honey, and curcumin were more effective than placebo ($p < 0.05$) [74]. Another meta-analysis demonstrated that honey significantly reduced the severity of grade 3 and 4 OM [75]. This result was similar to our study [76]. Some network meta-analyses are comparing the prevention or treatment of OM in cancer patients, but the research directions are slightly different. There is a study of OM in patients with head and neck cancer who received radiotherapy, and in addition to standard oral care, they also added low-level laser [77]. However, our study only analyzed methods that are easily accessible to

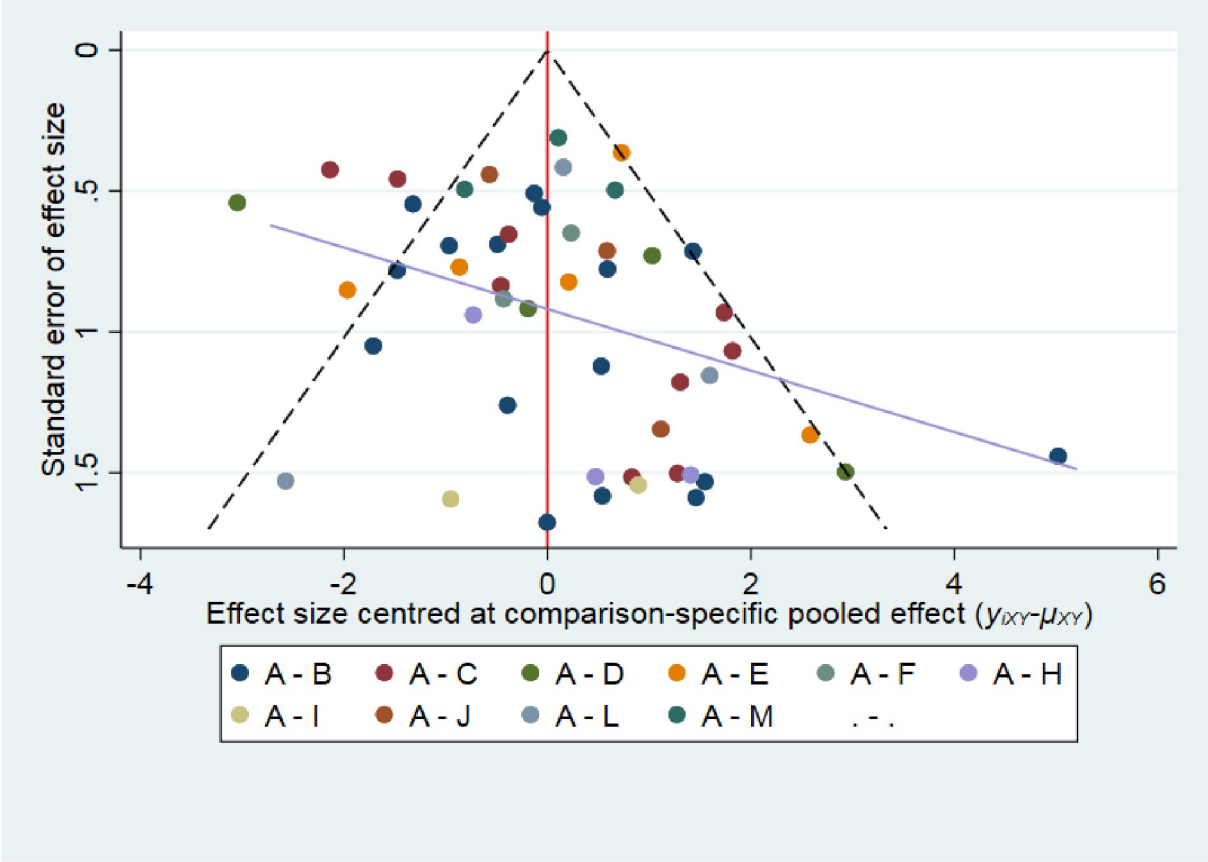

Fig 4. Comparison-adjusted funnel plot for the selected studies with the incidence of moderate-severe oral mucositis. Abbreviation: A, placebo; B, glutamine; C, honey; D, povidone-iodine; E, chlorhexidine; F, aloe; G, benzydamine; H, Curcumin; I, allopurinol; J, granulocyte-macrophage colony-stimulating factor; K, lignocaine; L, sucralfate; M, probiotics. Note: Comparisons including only one study (when present) have been excluded.

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patients and do not require special interventions such as low-level laser or cryotherapy [77, 78].

Honey has been proven to have anti-inflammatory, antioxidant, antimicrobial, and rapid tissue-healing properties [79, 80]. The mechanism of honey that can prevent OM is attributed to its antimicrobial property. This property with high osmolality is sufficient to inhibit microbial growth and its production of hydrogen peroxide [81]. Honey has been demonstrated to improve the epithelization of tissue when used for wound dressing to improve wound healing. Benzydamine mouthwash, an anti-inflammatory agent, significantly reduces erythema and ulceration. Lignocaine application is an anesthetic agent but has no anti-inflammatory properties. These agents may reduce erythema, ulceration, and pain of the OM.

Almost all patients with head and neck cancer who receive radiation therapy occur in OM [82]. We have also conducted subgroups by chemotherapy and radiation therapy-induced OM in head and neck cancer patients, and radiation therapy-induced OM in cancer patients. Honey still has the highest probability of preventing moderate-severe OM in the subgroup analysis.

Among the adverse events of treatment, few studies reported adverse events of interventions. In some sporadic reports of curcumin used in OM, only one study reported nausea in

two patients. Glutamine or probiotics had no side effects or significant differences between the glutamine or probiotics group and the control group. While this study was the most effective honey, none of the studies examined the safety of honey.

This study has several limitations. First, this study was not assessing the side effects of different interventions. Because these data on side effects in different interventions were not available. Second, some of the treatments, including lignocaine and allopurinol, were covered in 1 and 2 studies with a small number of patients. Third, regarding the quality of evidence (GRADE), several comparisons were assessed with low quality which may restrict the interpretation of these results.

Conclusions

This network meta-analysis results indicate that honey and lignocaine may be the preferred choices for patients with cancers to prevent or treat OM. Further large randomized controlled trials providing a higher level of evidence should be conducted to confirm our findings.

Supporting information

S1 Fig. The risk of bias summary.
(TIF)

S2 Fig. Side-splitting results of the selected studies with the incidence of moderate-severe oral mucositis for evaluating local inconsistency. (**Abbreviation**: A, placebo; B, glutamine; C, honey; D, povidone-iodine; E, chlorhexidine; F, aloe; G, benzydamine; H, Curcumin; I, allopurinol; J, granulocyte-macrophage colony-stimulating factor; K, lignocaine; L, sucralfate; M, probiotics.).
(TIF)

S3 Fig. Rankograms for the network showing the probability for the incidence of moderate-severe oral mucositis of each treatment in patients with head and neck cancer. (**Abbreviation**: ALOE, aloe; ALLO, allopurinol; BEZ, benzydamine; CHX, chlorhexidine; CUM, Curcumin; Glu, glutamine; GM-CSF, granulocyte-macrophage colony-stimulating factor; HON, honey; LIC, lignocaine; PLA, placebo; PRO, probiotics; PVI, povidone-iodine; SUF, sucralfate.).
(TIF)

S4 Fig. Rankograms for the network showing the probability for the incidence of radiotherapy-induced moderate-severe oral mucositis of each treatment in patients with cancer. (**Abbreviation**: ALOE, aloe; ALLO, allopurinol; BEZ, benzydamine; CHX, chlorhexidine; CUM, Curcumin; Glu, glutamine; GM-CSF, granulocyte-macrophage colony-stimulating factor; HON, honey; LIC, lignocaine; PLA, placebo; PRO, probiotics; PVI, povidone-iodine; SUF, sucralfate.).
(TIF)

S1 Checklist. PRISMA 2009 checklist.
(DOC)

S1 Table. Rank probability to be the best treatment (PrBest) by the incidence of moderate-severe oral mucositis of each treatment in patients with head and neck cancer.
(DOCX)

S2 Table. Rank probability to be the best treatment (PrBest) by the incidence of radiotherapy-induced moderate-severe oral mucositis of each treatment in patients with cancer.
(DOCX)

S3 Table. Results of the incidence of moderate-severe oral mucositis in patients with head and neck cancer.
(DOCX)

S4 Table. Results of the incidence of radiotherapy-induced moderate-severe oral mucositis in patients with cancer.
(DOCX)

S5 Table. Results of the incidence of moderate-severe oral mucositis. a. Excluding the study performed by Roopashri et al. b. Excluding the study performed by Roopashri and Costa et al.
(DOCX)

Author Contributions

Conceptualization: Tzu-Rong Peng, Fang-Pei Tsai, Ta-Wei Wu.

Data curation: Tzu-Rong Peng, Fang-Pei Tsai.

Formal analysis: Tzu-Rong Peng, Ta-Wei Wu.

Software: Tzu-Rong Peng.

Writing – original draft: Tzu-Rong Peng, Fang-Pei Tsai.

Writing – review & editing: Ta-Wei Wu.

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