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REVIEW ARTICLE

Prophylactic and therapeutic effects of honey on radiochemotherapy-induced mucositis: a meta-analysis of randomized controlled trials

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Abstract

Purpose Oral mucositis is a common side effect of radiochemotherapy and may adversely affect the patients' quality of life (QoL). Honey application may reduce the mucositis grade in patients. Here, we conducted a meta-analysis of randomized controlled trials (RCTs) to evaluate the prophylactic and therapeutic effects of honey on radiochemotherapy-induced oral mucositis.

Methods Publications on RCTs were extracted from the PubMed, Embase, CINAHL, and Cochrane Library databases. The primary outcomes were mucositis grades and pain scores. Secondary outcomes were the recovery time and QoL. The study was registered with PROSPERO (number CRD42018108486).

Results Nineteen RCTs, involving 1276 patients, were reviewed. Honey considerably mitigated oral mucositis in both prophylactic and therapeutic phases. In the prophylactic phase, intolerable mucositis development was significantly prevented in the honey-treated group (RR = 0.18, 95% confidence interval [CI] = 0.09 to 0.41). Patients treated with honey showed significant decrease in pain scores in the first month of treatment (weighted mean difference [WMD] = − 3.25, 95% CI = − 4.41 to − 2.09) and at the end of the treatment (WMD = − 2.32, 95% CI = − 4.47 to − 0.18).

Conclusion Honey, which is relatively cheap and easily available, prevented mucositis and effectively mitigate mucositis in patients after radiochemotherapy. Moreover, it significantly reduced the mucositis grade and engendered a fast and painless healing process. Therefore, honey use during and after radiochemotherapy is recommended for mucositis prevention and treatment.

Keywords Honey · Mucositis · Radiotherapy · Chemotherapy · Meta-analysis

Tzu-Ming Liu and Yu-Wei Luo contributed equally to this work.

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Introduction

Radiochemotherapy is the most common treatment modality for cancer. Although ionizing radiation and chemotherapeutic agents can damage cancer cells, they may also affect normal tissues, leading to adverse side effects in patients with cancer.

Oral mucositis is a common side effect in patients undergoing radiochemotherapy for head and neck cancer; oral mucositis results from oral mucosal atrophy and breakdown. Severe oral mucositis may affect oral function in patients. Moreover, even moderate oral mucositis can affect patients' quality of life (QoL), reducing their willingness to complete the radiochemotherapy regimen [1]. Although interventions can prevent or reduce oral mucositis severity in patients, the most beneficial intervention remains unknown [2].

Honey is a by-product of floral nectar, which is mainly composed of carbohydrates and water, along with some vitamins and enzymes. Recently, honey is being used in modern medicine, such as for treating burns and surgical site infections [3] because of its glucose-producing, hygroscopic, and antimicrobial properties [4]. A randomized controlled trial (RCT) by Biswal et al. revealed that topical application of honey decreased radiotherapy-induced oral microsites [5]. Since then, several related studies on the beneficial effects of honey on radiotherapy-induced oral mucositis have been published.

A recent meta-analysis reported that honey can decrease the incidence of radiochemotherapy-induced oral mucositis [6]. However, this meta-analysis considered the incidence of grade 3 and 4 oral mucositis alone. Moreover, some new RCTs have been conducted since the publication of the aforementioned meta-analysis. Therefore, a new meta-analysis combining the results of all relevant RCTs may strengthen the statistical power of these studies. Hence, we conducted the current systematic review and meta-analysis to investigate the prophylactic and therapeutic effects of honey on radiochemotherapy-induced oral mucositis.

Materials and methods

Inclusion criteria

In this review, we included RCTs comparing the outcomes of honey application between prophylactic or treatment groups and control groups of patients with radiochemotherapy-induced oral mucositis. We included only the studies that clearly reported the patient inclusion and exclusion criteria, honey ingredients or sources, mucositis grades, and treatment procedures for all groups. Mucositis grade was determined using the Radiation Therapy Oncology Group (RTOG) criteria, World Health Organization Oral Toxicity Scale (WHO-OTS), Oral Mucositis Assessment Scale (OMAS), or Common Terminology Criteria for Adverse Events (CTCAE).

Search strategy and study selection

Relevant studies published before October 2018 were extracted from the PubMed, Cochrane Library, Embase, and CINAHL databases. The following medical subject heading terms were used: *honey*, *mucositis*, and *radiotherapy* OR *chemotherapy*. All abstracts, studies, and citations retrieved were reviewed. In addition, we searched the reference sections of the selected papers for relevant studies. No language restrictions were applied. PROSPERO, an online international prospective register of systematic reviews, curated by the National Institute for Health Research, has accepted our systematic review (number CRD42018108486).

Data extraction

Baseline and outcome data were independently abstracted by two reviewers (Z.M.L. and Y.W.L.); these data included study designs, study population characteristics, inclusion and exclusion criteria, mucositis grade, intolerable mucositis (grades 3–4) incidence, and post-treatment pain. The reviewers' decisions were individually recorded and compared; any disagreements were resolved by consulting a third reviewer (T.W.H.). The authors of studies were contacted for additional information.

Methodological quality appraisal

The two reviewers (Z.M.L. and Y.W.L.) independently assessed the methodological quality of each study by using the revised risk-of-bias (version 2.0) method, recommended by the Cochrane Collaboration [7]. Several domains, including randomization adequacy, allocation concealment, blinding of patients and outcome assessors, follow-up duration, information provided to participants regarding study withdrawal, whether intention-to-treat analysis was performed, and freedom from other biases, were assessed.

Outcomes

Primary outcomes assessed in the prophylactic phase were the (1) incidence of intolerable oral mucositis and (2) number of lesions of oral mucositis or patients with intolerable grades of oral mucositis. Primary outcomes assessed in the treatment phase were the (1) oral mucositis grade after 1 week and (2) pain score for the oral cavity. The incidence of intolerable oral mucositis, the number of lesions of oral mucositis or patients with intolerable oral mucositis, and oral mucositis grade after 1 week were measured using the RTOG (grade 0–4), WHO-OTS (grade 0–4), and CTCAE, respectively. By contrast, the pain score of the oral cavity was assessed using Likert and visual analog scales (both of 0–10 points). Secondary outcomes included the recovery duration and QoL of the

treatment group. The QoL was measured using the global QoL score.

Statistical analyses

Data were entered and analyzed using Review Manager (version 5.3; Cochrane Collaboration, Oxford, UK). The meta-analysis was performed according to the PRISMA guidelines [8]. Continuous outcomes were analyzed using the weighted mean difference (WMD). The precision of effect sizes was reported as 95% confidence intervals (CIs). A pooled estimate of the WMD was computed using the DerSimonian and Laird random-effect model [9]. The Cochran Q test and I^2 statistics were used to evaluate statistical heterogeneity and inconsistency in prophylactic and therapeutic effects, respectively, across studies. Statistical significance was set at $P < 0.10$ for the Cochran Q test. Statistical heterogeneity across studies was assessed using the I^2 test, which quantifies the proportion of the total outcome variability across studies.

Results

Trial characteristics

Supplement 1 illustrates the flow of trial screening and selection. The initial search yielded 322 citations, of which 124 were ineligible due to replication and 161 were ineligible based on the criteria used for screening titles and abstracts. Therefore, 37 full texts were retrieved. However, of those, 1 used a different intervention in the experiment, 5 were meta-analysis related to honey and oral mucositis, and 12 were systematic reviews on the use of honey for treating oral mucositis. Finally, 19 RCT articles were eligible for this study (Table 1) [5, 10–27].

The 19 RCTs were published between 2003 and 2018, and their sample sizes ranged from 28 to 127, with a total of 1276 participants. Of the 19 RCTs, 14 included patients without oral mucositis before the RCTs in the prophylactic phase [5, 10–13, 15–21, 23, 24] and 5 included patients with oral mucositis before the RCTs in the treatment phase [14, 22, 25–27]. All the RCTs recruited patients with head and neck cancer, except 2 that recruited patients with acute lymphoblastic leukemia [20, 27] and one that recruited patients with acute myeloid leukemia [19]. Four studies recruited pediatric patients [10, 20, 26, 27]. Moreover, 11 RCTs measured the oral mucositis severity by using the RTOG criteria [5, 11, 13–15, 17, 18, 23–25, 27], 6 measured mucositis grade by using the WHO-OTS [10, 16, 19, 20, 22, 26], 1 measured mucositis grade by using the OMAS [21], and 1 measured mucositis grade by using the CTCAE [12]. Furthermore, 11 studies categorized patients into honey-treated and control groups; the control group followed the same protocol as the honey-treated group except that honey was not used [5, 10–12, 14, 17, 20, 21, 24–26]. Two studies used a placebo that looked and tasted like honey in the control group [13, 15]. Two studies compared the outcome of honey application with that of another intervention [18, 23]. Four studies categorized patients into three groups [16, 19, 22, 27]. Mouth was rinsed with honey in the honey-treated group all studies, except three studies in which honey was used topically [12, 26, 27] and one in which honey ice chips were used [20]. All the studies performed the intervention more than three times a day, except for one that performed the intervention only once a day [20]. All the studies used natural honey; of these, two studies particularly used Manuka honey [13, 15]. Eleven studies used a honey dosage of 10–20 mL [5, 11, 14, 16–18, 21, 22, 24–26], whereas two used that of 1–5 mL [15, 26]. However, one study used variable honey dosage depending on the patient body weight [27], and five did not mention the honey dosage used [10, 12, 19, 20, 23].

The methodological quality of the included RCTs is summarized in Table 2. Eleven studies reported acceptable randomization methods [12–19, 23, 25, 27], 15 did not describe patient blinding [5, 10–12, 14, 16–21, 23–25, 27], and 10 did not mention the blinding of outcome assessors [5, 10–12, 16, 17, 20, 21, 25, 27]. One study applied intention-to-treat analysis [15], whereas 2 reported > 20% loss to follow-up [15, 17].

Prophylactic phase

Incidence of intolerable mucositis

Eight studies measured the incidence of intolerable mucositis (grades 3 and 4 according to the RTOG, WHO-OTS, and CTCAE) [5, 10, 12, 13, 15, 18, 20, 23]. Al Jaouni et al. and Bansal et al. calculated the mucositis score by using the WHO-OTS and CTCAE, respectively; other studies used the RTOG to calculate the mucositis score. Four studies compared the outcomes of the honey-treated group with those of the control group, which followed the same protocol as the honey-treated group except for the absence of honey [5, 10, 12, 20]. However, Bardy et al. and Hawley et al. compared the outcomes of honey-treated group with those of the honey-like placebo group; moreover, Khanal et al. and Rao et al. compared the outcomes of the honey-treated group with those of the lidocaine-treated and betadine-treated groups, respectively. We pooled the data of all the eight RCTs for evaluation. The results revealed a RR of 0.48 (95% CI = 0.26–0.87). The result significantly favored the honey-treated group with regard to the decrease in intolerable mucositis incidence.

Moreover, Khanjani pour-fard-pachekenari et al. compared the honey mouthwash group with the control group. Although both the groups had only mild or moderate mucositis, the patients with honey mouthwash demonstrated decreased mucositis incidence and severity. Furthermore, Mishra and

Table 1 Characteristics of included studies

Author [year]	Inclusion criteria	No. of patients (male, %)	Age, mean ± SD	Baseline of oral mucositis grade	Intervention
Prophylactic					
Al Jaouni [2017] [10]	Pediatric cancer patients who received radiochemotherapy; age > 1 year	H: 20 (55) C: 20 (50)	H:7.9 ± 4.1 C: 8.1 ± 4.9	H: 0‡ C: 0‡	H: Natural honey rinse 4–6 times/day C: Control
Amanat [2017] [11]	Adult patient with head and neck cancer planned for radiotherapy	H: 41 (65.8) C: 41 (80)	H: 49.9* C: 50.17*	H: 0 C: 0	H: 20 mL of natural honey rinse, 15 min before and after radiotherapy and before sleeping C: Saline rinse
Bansal [2017] [12]	Patients with oral cavity and oropharyngeal cancers planned for radiochemotherapy	H: 50 (94) C: 50 (94)	H: 50.82 ± 9.7 C: 49.36 ± 10.95	H: 0¥ C: 0¥	H: 1:1 glycerine:honey applied topically after meals, 3 times/day C: Anesthetic and antacid solution
Bardy [2012] [13]	Patients with oropharynx squamous cell carcinoma	H: 64 (82.8) C: 63 (73.0)	H: 59 (39–85) * C: 58 (38–83) *	H: 0 C: 0	H: 20 mL of Manuka honey rinse, 4 times/day (during 4 weeks of radiotherapy + 2 weeks after radiotherapy) C: 20 mL of golden syrup
Biswal [2003] [5]	Adult patient with head and neck cancer planned for radiotherapy; no history of radiochemotherapy	H: 20 (75) C: 20 (40)	H: 63 (19–89) * C: 54 (14–78) *	H: 0 C: 0	H: 20 mL of natural honey rinse, before and after radiotherapy and 6 h after every radiotherapy C: control
Hawley [2014] [15]	Adult patient with head and neck cancer planned for radiotherapy	H: 54 (81) C: 52 (84)	H: 56.8 C: 59.5	H: 0 C: 0	H: 5 mL of Manuka honey gel rinse, 4 times/day throughout radiotherapy, plus 7 more days C: Sugar-free placebo gel looked and tasted like honey
Jayachandran [2012] [16]	Patients with oral malignancy; no history of radiochemotherapy	H: 20 (55) B: 20 (75) C: 20 (75)	H: 49.5 B: 54.0 C: 55.55	H: 0‡ B: 0‡ C: 0‡	H: 20 mL of natural honey rinse 15 min before and after radiotherapy and 6 h later B: 15 mL of 0.15% benzydamine hydrochloride rinse 15 min before and after radiotherapy and 6 h later C: 20 mL of 0.9% normal saline
Jayalekshmi [2016] [17]	Adult patient with head and neck cancer planned for radiotherapy	H: 14 C: 14	H: 59.71 ± 4.34 C: 52.28 ± 14.04	H: 0 C: 0	H: 15 mL of natural honey rinse 15 m before and after radiotherapy and 6 h later C: 15 mL of water
Khanal [2010] [18]	Adult patients with oral carcinoma planned for radiotherapy	H: 20 C: 20	Not provided	H: 0 C: 0	H: 20 mL of natural honey rinse 15 min before and after radiotherapy and before going to bed C: 20 mL of lignocaine gel
Khanjani pour-fard-pachekenari [2018] [19]	Adult patients with AML planned for 3 + 7 chemotherapy	H: 17 (70.6) O: 17 (64.7) C: 19 (63.2)	NA	H: 0‡ O: 0‡ C: 0‡	H: 5% natural honey rinsed 30 s after each meal and before going to bed O: Brush teeth twice/day, dental floss once/d, and 60 mL saline rinsed 3 times/day C: Control
Mishra [2017] [20]	Children patients planned for chemotherapy (5 Fluorouracil or methotrexate)	H: 20 C: 20	NA (5–19)*	H: 0‡ C: 0‡	H: Honey and Tulsi ice chips rinsed 5 min before chemotherapy and lasted 30 min C: Plain ice chips
Motallebnejad [2008] [21]	Adult patient with head and neck cancer; no history of radiochemotherapy	H: 20 C: 20	Not provided	H: 0† C: 0†	H: 20 mL of natural honey rinse 15 min before and after radiotherapy and 6 h later C: 20 mL of normal saline
Rao [2017] [23]	Adult patient with head and neck cancer planned for radiotherapy	H: 25 (50) C: 25 (50)	H: 54.1 ± 11.3 C: 55.8 ± 10.8	H: 0 C: 0	H: Natural honey rinse 1 h before radiotherapy and 2 h and 6 h after radiotherapy C: 1 mL of betadine and 100 mL of water mouthwash
Rashad [2009] [24]	Adult patient with head and neck cancer	H: 20 (80) C: 20 (75)	H: 47.7 ± 13.2 C: 48.2 ± 10.5	H: 0 C: 0	H: 20 mL of natural honey rinse, 15 min prior and after radiotherapy and 6 h later C: Control
Treatment					
Abdulrhman [2012] [27]		H: 30	6.9 ± 3.8	H: 2–3	

Table 1 (continued)

Author [year]	Inclusion criteria	No. of patients (male, %)	Age, mean ± SD	Baseline of oral mucositis grade	Intervention
	ALL patients with grade 2 and 3 chemotherapy-related oral mucositis	M: 30 C: 30		M: 2–3 C: 2–3	H: 0.5 g of natural honey/kg (max 15 g) applied topically 3 times/day M: 0.25 g of HOPE/kg (max 5 g) applied topically 3 times/day C: Benzocaine 7.5% gel applied topically 3 times/day
Charalambous [2018] [14]	Head and neck cancer patients with grade 1 or above oral mucositis; age > 18 y	H: 43 (50) C: 43 (50)	Not provided	H: ≥1 C: ≥1	H: 20 mL of natural honey rinse 15 min before and after radiotherapy and 6 h later for 7 weeks C: Saline rinse
Raeessi [2014] [22]	Patients with chemotherapy-related oral mucositis; age 15–80 y	H: 23 (50) M: 23 (42.9) S: 23 (52.4)	H: 54.9 ± 11.6 M: 54.7 ± 15.4 S: 55.9 ± 12.7	H: 2.5‡ M: 2.67‡ S: 2.52‡	H: 10 mL of 50% natural honey rinse every 3 h × 1 week M: 10 mL of 50% natural honey + 3.3% coffee rinse every 3 h × 1 week S: 10 mL of diluted betamethasone every 3 h × 1 week
Samdariya [2015] [25]	Patients with head and neck cancer planned for radiochemotherapy; age 18–70 y	H: 40 (50) C: 38 (42)	H: 52.58 ± 12.21 C: 54.15 ± 7.92	NA	H: 20 mL of natural honey rinse 15 min before and after radiotherapy and 6 h later, with routine salt-soda + benzydamine every 3 h during radiotherapy and up to 3 m postradiotherapy C: Control
Singh [2018] [26]	Children with grade 1–2 oral mucositis	H: 50 C: 50	H: NA C: NA	H: 1–2‡ C: 1–2‡	H: 1–2 mL of natural honey 4 times/day with analgesic and antiseptic gel applied topically C: Control

Values are presented as the mean ± standard deviation, except for *median (range)

B benzydamine group, *O* oral care group, *C* control group, *H* honey group, *HOPE* 4:2:1 mixture of natural honey, olive oil–propolis extract, and beeswax, *M* mixed, *OM* oral mucositis, *S* steroid group, *AML* acute myeloid leukemia, *ALL* acute lymphoblastic leukemia

†Oral Mucositis Assessing Scale

‡WHO Oral Toxicity Scale

¥ Common Toxicity Criteria for Adverse Events

Nayak showed that the patients with honey ice chips demonstrated decreased mucositis incidence and severity.

Number of mucositis lesions or patients with intolerable mucositis

Two studies used the RTOG to measure the mucositis grade weekly [5, 11]. In these studies, the numbers of lesions in each grade were obtained from weeks 1 to 6. Week 6 marked the end of the intervention; therefore, we pooled the data of week 6. The result showed an RR of 0.22 (95% CI = 0.06–0.84). The result significantly favored the honey-treated group with regard to preventing intolerable mucositis development (Fig. 1).

Three studies used the RTOG [17, 18, 24] and one used the CTCAE [12] to measure the mucositis grade. However, these studies counted the number of patients for each grade. Jayalekshmi et al. and Rashad et al. recorded the grade from week 1 to 6. However, Bansal and Khanal et al. recorded the grade for only week 4. Therefore, we pooled the data of week 4 to assess the effect of honey. The results showed an RR of 0.18 (95% CI = 0.09–0.41) and significantly favored the honey-treated group with regard to preventing intolerable mucositis development (Fig. 2).

Treatment phase

Mucositis grade after week 1

Two studies measured the mean mucositis grade after treatment [14, 22]. Charalambous et al. measured the mucositis grade at the end of week 1 to 7 by using the RTOG. Raeessi et al. measured the mucositis grade only at the end of week 1 by using the WHO-OTS. Therefore, measurements obtained at the end of week 1 in both the studies were pooled. The pooled mean difference in the mean mucositis grade (WMD = − 0.33; 95% CI = − 0.68 to 0.02) slightly favored the honey-treated group; however, the results were nonsignificant (Fig. 3).

Singh et al. determined the number of patients for each grade every 2 days after treatment to compare the effectiveness of honey in treating radiochemotherapy-induced mucositis. On day 1, grade 1 and 2 mucositis was noted respectively

Table 2 Assessment of methodological quality of included trials

RCT evaluated by RoB 2.0

Author [year]	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Others
Abdulrhman [2012] [27]	Low risk	Some concerns	Some concerns	Low risk	Low risk	None
Al Jaouni [2017] [10]	Some concerns	Some concerns	Some concerns	Low risk	Low risk	None
Amanat [2017] [11] [11]	Some concerns	Some concerns	Some concerns	Low risk	Low risk	None
Bansal [2017] [12]	Low risk	Some concerns	Some concerns	Low risk	Low risk	None
Bardy [2012] [13]	Low risk	Low risk	Low risk	Low risk	Low risk	None
Biswal [2003] [5]	Some concerns	Some concerns	Some concerns	Low risk	Low risk	None
Charalambous [2018] [14]	Low risk	Some concerns	Low risk	Low risk	Low risk	None
Hawley [2014] [15]	Low risk	Low risk	Low risk	High risk	Low risk	None
Jayachandran [2012] [16]	Low risk	Some concerns	Some concerns	Low risk	Low risk	None
Jayalekshimi [2016] [17]	Low risk	Some concerns	Some concerns	High risk	Low risk	None
Khanal [2010] [18]	Low risk	Some concerns	Low risk	Low risk	Low risk	None
Khanjani pour-fard-pachekenari [2018] [19]	Low risk	Some concern	Low risk	Low risk	Low risk	None
Mishra [2017] [20]	Some concern	Some concern	Some concern	Low risk	Low risk	None
Motallebnejad [2008] [21]	Some concerns	Some concerns	Some concerns	Low risk	Low risk	None
Raeessi [2014] [22]	Some concerns	Low risk	Low risk	Low risk	Low risk	None
Rao [2017] [23]	Low risk	Some concerns	Low risk	Low risk	Low risk	None
Rashad [2009] [24]	Some concerns	Some concerns	Low risk	Low risk	Low risk	None
Samdariya [2015] [25]	Low risk	Some concerns	Some concerns	Low risk	Low risk	None
Singh [2018] [26]	Some concerns	high	Low risk	Low risk	Low risk	None

in 4% and 96% of the patients in the honey-treated group and 22% and 78% of the patients in the control group. On day 7 (week 1), 82% of the patients recovered from mucositis in the honey-treated group; however, only 54% of the patients recovered from mucositis in the control group. On day 13 (week 2), all the patients of both the groups recovered from mucositis. Thus, honey is an effective intervention for treating radiochemotherapy-induced oral mucositis.

Pain score for the oral cavity

Two studies measured the pain score for the oral cavity [14, 25]. Charalambous et al. assessed the postintervention pain score at months 1 and 6 by using a Likert scale (score 1–10). Samdariya et al. evaluated the pain score every half a month until month 3 by using a visual analog scale (score 0–10). Measurements obtained at month 1 in the two studies were pooled; in addition, measurements obtained at month 6 were pooled along with those obtained at month 3. At month 1, the pooled mean difference showed a significant reduction in the pain score (WMD = − 3.25, 95% CI = − 4.41 to − 2.09; Fig. 4). At the end of the treatment, the pain score (WMD = − 2.32, 95% CI = − 4.47 to − 0.18) was also significantly lower in the honey-treated group (Fig. 4). The results suggested that honey significantly alleviates pain in the oral cavity.

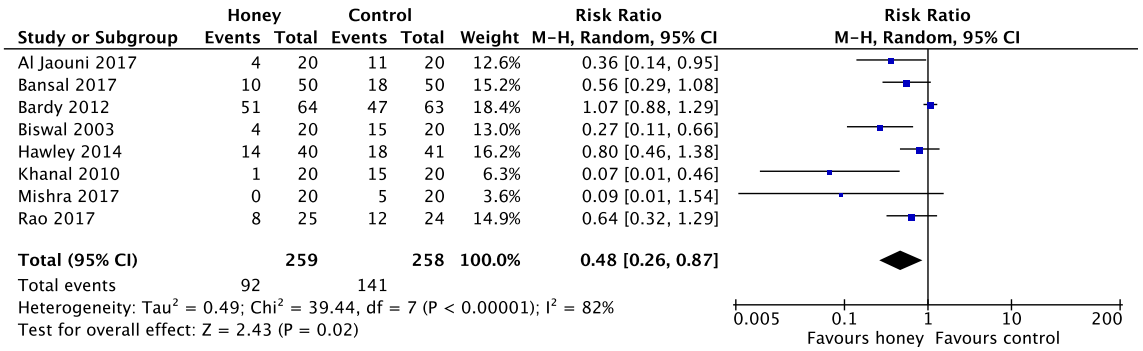

Fig. 1 Forest plot of honey-treated versus control group comparison in the prophylactic phase; outcome: incidence of intolerable mucositis

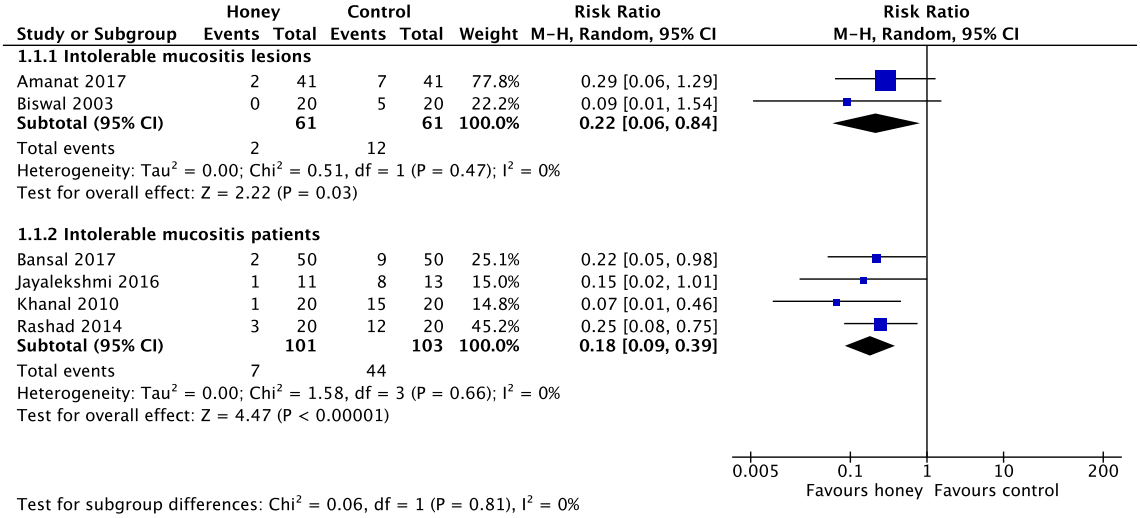

Fig. 2 Forest plot of honey-treated versus control group comparison in the therapeutic phase; outcome: number of intolerable mucositis lesions at weeks 6 and 4

Recovery time

Abdulrman et al. measured the recovery time of the honey-treated group, HOPE (4:2:1 mixture of natural honey:olive oil–propolis extract:beeswax) group, and control group, rather than their mucositis grade, because all the patients recovered from mucositis. However, the recovery time significantly differed among the groups. Among patients with grade 2 mucositis, the honey-treated group recovered in 3.6 ± 0.8 days, whereas the HOPE and control groups recovered in 4.2 ± 0.7 and 4.6 ± 0.9 days, respectively. The *p* value of only the honey-treated group versus the control group was significant, suggesting that honey was more effective in mucositis treatment compared with the control group. Among patients with grade 3 mucositis, the honey-treated group recovered in 5.4 ± 1.1 days, whereas the HOPE and control groups recovered in 5.8 ± 2.6 and 8.6 ± 1.0 days, respectively. The *p* values of the honey-treated versus control group and the HOPE versus control group was significant, suggesting that honey and HOPE both were more effective in treating mucositis compared with the control. Therefore, honey and HOPE were more effective in treating intolerable mucositis (grade 3) compared with the control; however, the beneficial effects of honey were not superior to those of HOPE because the result was nonsignificant. By contrast, in tolerable mucositis (grade 2), only honey demonstrated a more favorable effect compared with the control.

Quality of life

Charalambous et al. evaluated the QoL by using the global QoL score (the total score is 100); a higher score represents better QoL. At the end of the treatment, the score of the honey-treated group (48.61 ± 24.8) was significantly higher than that of the control group (34.72 ± 24.7). The authors also evaluated the score at months 1 and 6 after the treatment and reported that the QoL score significantly increased in the honey-treated group at both months 1 (57.64 ± 20.7) and 6 (78.91 ± 18.8). However, in the control group, the QoL score decreased at month 1 (24.31 ± 17.5) and increased again at month 6 (45.40 ± 19.1) after the treatment. Thus, honey could significantly improve the QoL of patients with radiochemotherapy-induced oral mucositis.

Discussion

Oral mucositis, a common side effect of radiochemotherapy, often affects the QoL of patients with cancer. The use of honey may reduce the severity of radiochemotherapy-induced oral mucositis. The results of this meta-analysis indicated that honey significantly decreased the mucositis grade and efficiently healed oral mucositis in patients who received radiochemotherapy.

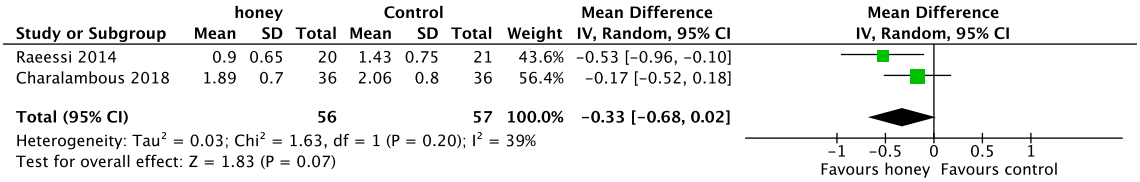

Fig. 3 Forest plot of honey-treated versus control group comparison in the therapeutic phase; outcome: mucositis grade after 1 week of treatment

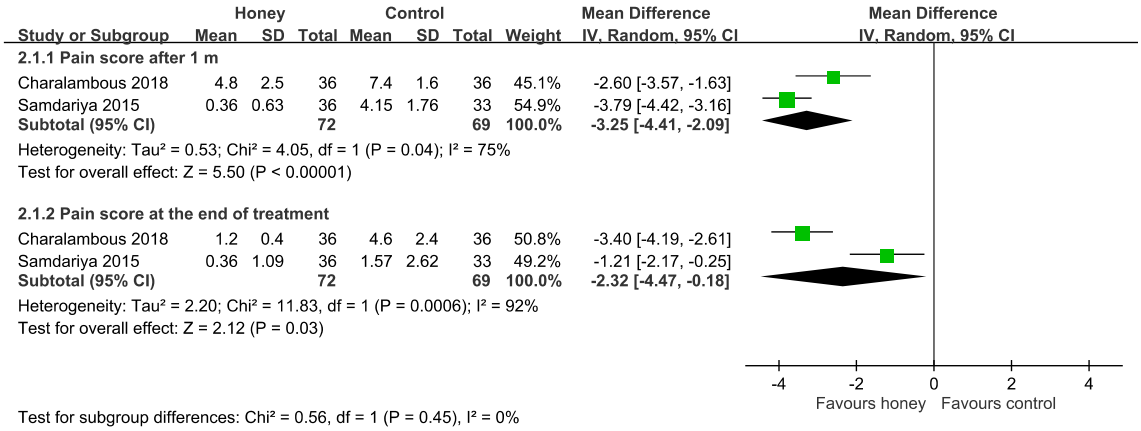

Fig. 4 Forest plot of honey-treated versus control group comparison in the therapeutic phase; outcome: pain score of the oral cavity at month 1 and the end of treatment

In the prophylactic phase, the incidence of intolerable mucositis was lower in the honey-treated group. Both the numbers of intolerable mucositis lesions at weeks 6 and 4 after treatment were lower in the honey-treated group.

In the treatment phase, the mucositis grade after week 1 was lower in the honey-treated group; however, the results were nonsignificant. One study reported that the recovery duration of the honey-treated group was significantly shorter than that of the control group after the treatment [27]. The results obtained for the mucositis grade after week 1 of treatment were nonsignificant because 1 week is inadequate for determining the differences between the honey-treated and control groups. Charalambous et al. measured the mucositis grade from weeks 1 to 7 and showed a significant effect of honey across the 7 weeks. The long-term honey use until the recovery of mucositis may indicate the real benefit of honey against radiochemotherapy-induced mucositis. Furthermore, oral cavity pain could be relieved after treatment with honey. In addition, because the QoL of patients improved after treatment with honey, honey may relieve radiochemotherapy-induced mucositis.

In this study, we included RCTs including patients who underwent radiotherapy or chemotherapy. However, only eight studies used chemotherapy. In 2018, a review showed that honey was effective in chemotherapy-induced mucositis in pediatric patients [28]; this finding supports our conclusion. We also included three studies that reported the effectiveness of honey in relieving mucositis in adult patients who underwent chemotherapy. Raeessi et al. showed that patients demonstrated a better healing effect after treatment with honey for 1 week; Mishra and Nayak and Rashad et al. reported that the use of honey during radiochemotherapy could reduce the mucositis grade in patients. Thus, honey can be used for treating chemotherapy-induced mucositis in adults; however, additional RCTs related to the use of honey in chemotherapy are required.

Different types of honey were used in different studies; Bardy et al. and Hawley et al. used Manuka honey in their trials. Unlike the honey available in the market, Manuka honey has proven healing properties [29]. However, both the studies reported that Manuka honey reduced mucositis severity, but not significantly. Moreover, because of the peculiar taste of Manuka honey, the trial conducted by Hawley et al. had a high dropout rate (57.4%). No study compared the effect of Manuka honey with that of regular honey. Therefore, future RCTs must evaluate the effect of Manuka honey on radiochemotherapy-induced mucositis.

To investigate the prophylactic and therapeutic effects of honey on radiotherapy- and chemotherapy-induced mucositis, we reviewed 14 and 5 RCTs, respectively; we considered honey significantly to have beneficial prophylactic and therapeutic applications. In 2017, a systematic review evaluated the relationship between honey and cancer therapy. A study inferred that honey has both prophylactic and therapeutic effects on mucositis induced by radiotherapy or chemotherapy [30], which supports our conclusion.

Body weight loss is a major issue in patients with cancer. Some studies have noted that using honey in radiotherapy- and chemotherapy-induced mucositis prevented body weight loss [5, 10, 12–15, 21, 23]. We believe that using honey reduced mucositis severity, which could have led to dysphagia and thus weight loss. Hence, a crucial relationship exists between arresting body weight loss and honey; additional RCTs are required to establish this.

The clinical use of honey in mucositis could provide patients with an alternative to ease their pain. Most studies we collected demonstrated good compliance and acceptable outcome. However, because of the bitter taste and lower water content of Manuka honey, the two studies using Manuka honey showed poor compliance [13, 15]. In future studies for using Manuka honey in mucositis, the use of a palatable formula, such as honey ice chips [20] and diluted honey, should be considered.

Considerable heterogeneity was observed across the studies because of various clinical factors. First, the applied

radiochemotherapy differed across the studies, with inconsistent dosage and treatment durations; moreover, some studies included only chemotherapy as the treatment modality. Second, some studies recruited children as participants [10, 20, 26, 27]. In addition, different control groups were compared with the honey-treated group across studies [13, 16, 18, 22, 23, 27]. Finally, the mucositis grade was measured using different scales. Such diversities among studies resulted in heterogeneity.

This study has several limitations. First, some included RCTs recruited a relatively small sample of patients in each group [5, 10, 14, 16–18, 21, 23, 24]. Second, several primary and secondary outcomes were reported inconsistently. In addition, the questionnaire used to evaluate QoL might have been subjective [14]. Moreover, patients in each study had different stages of head and neck cancer and received different dosages of radiotherapy or chemotherapy; thus, the risk of intolerable mucositis might have been higher in those with advanced stages of cancer. Finally, each study used different honey dosages and application frequencies, thereby potentially limiting our analysis outcome.

Conclusion

Our meta-analysis revealed that honey could prevent and rapidly heal mucositis in patients who undergo radiochemotherapy. In the prophylactic phase, honey can decrease the mucositis grade and deter its progress, which may increase the willingness of patients to continue their radiochemotherapy. Honey treatment engendered faster recovery, which could reduce hospitalization duration. Moreover, with a more painless healing process, patients could have a better food intake to maintain their health condition. Furthermore, honey is relatively cheap and easily available. Therefore, we recommend using honey during and after radiochemotherapy to prevent and treat mucositis.

In future studies, the flavor of honey should be adjusted to yield high compliance. Furthermore, the protocol should be unified to obtain more consistent results for determining the best clinical application.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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