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

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Introduction and Objectives

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).

Table 2. Assessment of methodological 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
Raessi [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

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

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).

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]	Palliative 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 ^a C: 0 ^b	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: 49.99 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 ^a C: 0 ^b	H: 1:1 glycerol/honey applied topically after meals, 3 times/day C: Anesthetic and antacid solution
Bardy [2012] [13]	Patients with oropharyngeal squamous cell carcinoma	H: 64 (82.8) C: 63 (73.0)	H: 59 (39.45)* C: 58 (38.43)*	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 (19.48)* 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 locked and tasted like honey
Jayachandran [2012] [16]	Patients with oral malignancy; no history of radiochemotherapy	H: 20 (55) D: 20 (75) B: 54.0 C: 52 (84)	H: 40.5 B: 54.0 C: 55.55	H: 0 ^a B: 0 ^b C: 0 ^c	H: 20 mL of natural honey rinse 15 min before and after radiotherapy and 6 h later H: 15 mL of 0.15% benzylamine 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 ± 14.08	H: 0 C: 0	H: 15 mL of natural honey rinse 15 min 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 liposaccharic gel
Khanjani pour-fard-pachekenari [2018] [19]	Adult patients with AML planned for 1+7 chemotherapy	H: 17 (70.6) O: 17 (68.7) C: 19 (63.2)	NA	H: 0 ^a O: 0 ^b C: 0 ^c	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]	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 mouthwashes
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					
Abdellahman [2012] [27]	ALL patients with grade 2 and 3 chemotherapy-related oral mucositis	H: 30 C: 30	6.9 ± 3.8	H: 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 HONEY/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: 2 ^a C: 2 ^b	H: 20 mL of natural honey rinse 15 min before and after radiotherapy and 6 h later for 7 weeks C: Saline rinse
Raessi [2014] [22]	Patients with chemotherapy-related oral mucositis; age 18-40 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: 2-3 ^a M: 2-3 ^b S: 2-3 ^c	H: 10 mL of 50% natural honey + 3.3% coffee rinse every 3 h × 1 week S: 10 mL of diluted benzocaine 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 15 min before and after radiotherapy and 6 h later, with routine salt soda + benzylamine every 3 h during radiotherapy and up to 3 m post-radiotherapy C: Control
Singh [2018] [26]	Children with grade 1-2 oral mucositis	H: 50 C: 50	H: NA C: NA	H: 1-2 ^a C: 1-2 ^b	H: 1-2 mL of natural honey 1 times/day with analgesic and antiseptic gel applied topically C: Control

Values are presented as the mean ± standard deviation, except for *median (range)
Benzylamine group, O oral care group, C control group, H honey group, HPOE 4:2:1 mixture of natural honey, olive oil, propolis extract, and beeswax, M mixed, M mixed, OM oral mucositis, S steroid group, AML acute myeloid leukemia, ALL acute lymphoblastic leukemia
^a Oral Mucositis Assessing Scale
^b WHO Oral Toxicity Scale
^c Common Toxicity Criteria for Adverse Events

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

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

Figure 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.

Test for subgroup differences: Chi² = 0.56, df = 1 (P = 0.45), I² = 0%

Conclusions

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