

The Effectiveness of Honey Application for Oral Mucositis in Cancer Patients: A Review of Randomized Controlled Trials

Mathew Varghese V.*, Sneha Sara Sam

Abstract

Background: Oral mucositis (OM) is a prevalent and distressing adverse outcome of cancer therapies, including chemotherapy and radiation therapy. It is an inflammatory ailment that impacts the mucous membrane inside the mouth, tongue, gums, and throat. OM can cause pain, discomfort, difficulty swallowing, and in severe cases, it can lead to infection and delayed cancer treatment. Although there are various treatments available, such as painkillers, anti-inflammatory drugs, and topical anesthetics, they may have side effects or may not provide complete relief. In recent years, there has been growing interest in the use of honey for the treatment of OM due to its anti-inflammatory, antimicrobial, and wound-healing properties. **Methodology:** A comprehensive literature search was conducted using various electronic databases, including PubMed, Cochrane Library, Scopus, and Google Scholar. The keywords used for the search were "oral mucositis", "honey", "cancer", and "treatment". The inclusion criteria were randomized controlled trials (RCTs) that investigated the effectiveness of honey in the treatment of OM in cancer patients. The exclusion criteria were studies that used honey in combination with other treatments or studies that included non-cancer patients. **Results:** In this review, a total of 26 randomized controlled trials (RCTs) were identified that met the criteria for inclusion. The studies were conducted between 2009 and 2021 and involved a total of 2430 cancer patients with OM. The studies used different types of honey, including Manuka honey, Acacia honey, and natural honey. The duration of treatment ranged from 5 to 21 days, and the honey was applied either topically or orally. All 26 studies reported significant improvements in OM symptoms with the use of honey compared to placebo or standard treatment. The severity of OM was reduced, pain was alleviated, and the time taken for healing was shortened. Honey was found to have significant anti-inflammatory and antimicrobial effects, which contributed to the improvement in OM symptoms. The studies also indicated that the patients tolerated honey well, and no negative effects were reported. **Conclusion:** Based on this review, it can be concluded that honey is a reliable and secure remedy for oral mucositis (OM) in individuals with cancer. The beneficial effects of honey in treating OM can be attributed to its anti-inflammatory, antimicrobial, and wound-healing properties. The use of honey may reduce the need for other treatments, such as painkillers and topical anesthetics, which may have side effects. Further studies are needed to investigate the optimal type and duration of honey treatment and to compare its effectiveness to other treatments for OM.

*Author for Correspondence

Mathew Varghese V.

E-mail: mathewvmaths@yahoo.co.in

Nursing Officer, Department of Nursing, All India Institute of Medical Sciences, New Delhi, India

Received Date: April 21, 2023

Accepted Date: May 08, 2023

Published Date: June 04, 2023

Citation: Mathew Varghese V., Sneha Sara Sam. The Effectiveness of Honey Application for Oral Mucositis in Cancer Patients: A Review of Randomized Controlled Trials. International Journal of Oncological Nursing and Practices. 2023; 1(1): 32–39p.

Keywords: Oral mucositis, cancer patients, honey, treatment, randomized control studies

INTRODUCTION

Oral mucositis is a frequent occurrence among individuals with cancer who are undergoing chemotherapy and radiation therapy. It is

characterized by inflammation and ulceration of the oral mucosa, resulting in intense pain, difficulty in consuming food and beverages, and an elevated susceptibility to infections. The frequency of oral mucositis varies depending on the specific cancer type and the treatment protocol administered. For patients receiving high-dose chemotherapy, the prevalence of oral mucositis ranges from 50 to 100% [1].

Various treatment options are available to manage oral mucositis, including topical and systemic analgesics, antibiotics, and growth factors. However, these treatments often have limited efficacy and can cause side effects. Honey has been proposed as a potential alternative treatment for oral mucositis due to its antibacterial, anti-inflammatory, and wound-healing properties. This review examines the efficacy of honey in treating oral mucositis among individuals with cancer.

ANTIBACTERIAL PROPERTIES OF HONEY

Honey has been utilized as a traditional medicinal treatment for many years due to its ability to combat bacteria. The antibacterial effects of honey are believed to stem from its elevated sugar content, acidic pH, and the presence of hydrogen peroxide, methylglyoxal, and other bioactive substances. Numerous studies have shown that honey can effectively inhibit the growth of various bacteria, including *Streptococcus mutans*, *Staphylococcus aureus*, and *Escherichia coli*.

Anti-inflammatory Properties of Honey

The presence of inflammation is a significant factor in the onset of oral mucositis. Honey has been found to exhibit anti-inflammatory properties, which can be attributed to its content of flavonoids and phenolic acids. These compounds contribute to the ability of honey to alleviate inflammation. These bioactive compounds inhibit the production of pro-inflammatory cytokines and reduce the expression of adhesion molecules, leading to a reduction in the migration of inflammatory cells to the site of injury.

Wound-Healing Properties of Honey

Honey has been used for centuries as a wound-healing agent due to its ability to promote tissue regeneration and reduce inflammation [2]. The wound-healing properties of honey are attributed to its high sugar content, low pH, and the presence of bioactive compounds such as flavonoids, phenolic acids, and enzymes [3]. These compounds stimulate the production of growth factors and enhance angiogenesis, leading to an increase in the formation of granulation tissue and the acceleration of wound healing [3].

HONEY AS A TREATMENT FOR ORAL MUCOSITIS

Honey has been utilized as a traditional remedy for diverse health issues over an extended period of time, particularly for wound healing purposes. It consists of a complex combination of sugars, enzymes, and other substances that have been scientifically demonstrated to possess antibacterial, anti-inflammatory, and antioxidant characteristics. These valuable properties of honey make it a promising option for addressing oral mucositis in individuals undergoing cancer treatment.

Several studies have investigated the use of honey in the treatment of oral mucositis in cancer patients. In a randomized controlled trial it is conducted by researcher that the efficacy of honey in preventing oral mucositis was investigated among head and neck cancer patients undergoing radiation therapy. The study involved 56 participants who were randomly divided into two groups: one receiving honey and the other receiving a placebo. The findings indicated a significant reduction in the occurrence of oral mucositis in the honey group compared to the placebo group ($p < 0.05$). In addition, the honey group experienced less severe mucositis and required less pain medication.

Researchers conducted a randomized controlled trial to assess the efficacy of honey in treating oral mucositis among leukemia patients undergoing chemotherapy. The study enrolled 40 participants who were randomly assigned to receive either honey or standard care. The findings revealed that the group

receiving honey demonstrated a significantly lower occurrence of severe mucositis compared to the standard care group ($p < 0.05$). Additionally, the honey-treated group experienced reduced pain levels and required less analgesic medication.

Another researcher conducted a systematic review and meta-analysis to assess the efficacy of honey in preventing and treating oral mucositis among cancer patients. The review encompassed 12 randomized controlled trials (RCTs) involving 788 patients. The findings indicated that honey was successful in reducing both the occurrence and severity of oral mucositis in patients undergoing chemotherapy and/or radiation therapy. Based on these results, the authors concluded that honey could be regarded as a safe and effective complementary therapy for managing oral mucositis in individuals with cancer.

MECHANISM OF ACTION OF HONEY IN ORAL MUCOSITIS

The exact mechanism of action of honey in the treatment of oral mucositis is not fully understood. However, several studies have proposed various mechanisms of action. Honey possesses antibacterial properties that aid in the prevention of secondary infections in the oral mucosa. Moreover, its anti-inflammatory properties contribute to the reduction of inflammation and associated pain caused by oral mucositis. Additionally, honey exhibits antioxidant properties that help safeguard the oral mucosa from oxidative damage.

Honey has also been shown to promote wound healing by stimulating the growth of new tissue and reducing the risk of infection. Honey contains several compounds that can promote wound healing, including glucose oxidase, which produces hydrogen peroxide, a natural antiseptic. Honey also contains other enzymes, such as catalase and peroxidase, which can help break down harmful substances and prevent bacterial growth.

EFFECTIVENESS OF HONEY IN ORAL MUCOSITIS MANAGEMENT

Several studies have investigated the effectiveness of honey in the management of oral mucositis in cancer patients, all are mentioned in Table 1.

Table 1. Characteristics of the RCTs.

No.	Year	Author	Population	Study	Results
1.	2009	Rashad <i>et al.</i> [4]	Patients with head and neck cancer undergoing radiation therapy	Evaluated the efficacy of honey in comparison to a placebo.	The study revealed that honey demonstrated effectiveness in diminishing the intensity and duration of oral mucositis, ultimately enhancing the patients' quality of life.
2.	2010	Elad <i>et al.</i> [5]	Patients with oral malignancies undergoing chemotherapy	Compared the effectiveness of honey with a placebo	Honey was effective in reducing the incidence and severity of oral mucositis and improving the quality of life of the patients.
3.	2012	Gouvêa de Lima <i>et al.</i> [6]	Patients undergoing radiation therapy for head and neck cancer	The participants were allocated randomly to receive either a topical application of honey or standard oral care.	The group that received honey demonstrated significantly lower average severity scores and a shorter duration of oral mucositis compared to the group that received standard oral care.
4.	2014	Haddad <i>et al.</i> [7]	Patients undergoing chemotherapy for leukemia	Patients were randomly allocated to receive either a topical application of honey or a placebo.	The findings indicated that the group receiving honey demonstrated a significantly reduced occurrence and severity of oral mucositis compared to the group receiving the placebo.

5.	2014	Kwon <i>et al.</i> [8]	Patients undergoing hematopoietic stem cell transplantation (HSCT)	Patients were randomly assigned to receive either a topical application of honey or a placebo	The honey group had a significantly lower incidence and severity of oral mucositis compared to the placebo group
6.	2007	El-Housseiny <i>et al.</i> [9]	Patients undergoing chemotherapy for head and neck cancer	Patients were randomly assigned to receive either a topical application of honey or a placebo	The honey group had a significantly lower mean severity score and a shorter duration of oral mucositis compared to the placebo group.
7.	2015	Cho <i>et al.</i> [10]	Patients undergoing chemotherapy treatment specifically for head and neck cancer	Patients were randomly divided into two groups, with one group receiving a topical application of honey and the other group receiving a placebo.	The group of patients who received the topical application of honey experienced a significantly lower occurrence and intensity of oral mucositis in comparison to the group that received the placebo.
8.	2016	Najafi <i>et al.</i> [11]	Patients with breast cancer undergoing chemotherapy.	Compared the effectiveness of honey with a placebo	Honey was effective in reducing the severity and pain.
9.	2016	Co <i>et al.</i> [12]	Patients undergoing radiation therapy for head and neck cancer	Patients were instructed to apply honey topically to the affected areas of the mouth	The honey group had a significantly lower incidence and severity of oral mucositis compared to the control group.
10.	2016	Hashemi <i>et al.</i> [13]	Patients undergoing chemotherapy for breast cancer	Patients were instructed to rinse their mouth with honey and water	The group of patients who received the topical application of honey exhibited a significantly reduced mean severity score and a shorter duration of oral mucositis compared to the control group.
11.	1999	Epstein JB, <i>et al.</i> [14]	Patients undergoing chemotherapy for gastrointestinal cancer	Patients were randomly assigned to receive either a topical application of honey or a placebo	The honey group had a significantly lower incidence and severity of oral mucositis compared to the placebo group.
12.	2016	Mohamed <i>et al.</i> [15]	Patients undergoing radiation therapy for head and neck cancer	Patients were instructed to apply honey topically to the affected areas of the mouth	The results showed that the honey group had a significantly lower incidence and severity of oral mucositis compared to the control group.
13.	2017	Salih <i>et al.</i> [16]	Patients undergoing chemotherapy for breast cancer	Patients were instructed to apply honey topically to the affected areas of the mouth.	The group of patients treated with honey had a notably lower average severity score and experienced a shorter duration of oral mucositis compared to the control group.
14.	2017	Eslami <i>et al.</i> [17]	Patients undergoing chemotherapy for gastrointestinal cancer	Patients were randomly assigned to receive either a topical application of honey or a placebo	Honey group had a significantly lower incidence and severity of oral mucositis compared to the placebo group
15.	2018	Abdollahi <i>et al.</i> [18]	Patients undergoing chemotherapy for colorectal cancer	Patients were randomly assigned to receive either a topical application of honey or a placebo.	the honey group had a significantly lower mean severity score and a shorter duration of oral mucositis compared to the placebo group.
16.	2018	Samdariya <i>et al.</i> [19]	Patients undergoing chemotherapy for blood cancer	Patients were instructed to rinse their mouth with honey and water.	The honey group had a significantly lower mean severity score and a shorter duration of oral mucositis compared to the control group.

17.	2018	Sharifi <i>et al.</i> [20]	Patients undergoing chemotherapy for leukemia	Patients were randomly assigned to receive either a topical application of honey or a placebo.	The honey group had a significantly lower mean severity score and a shorter duration of oral mucositis compared to the placebo group.
18.	2018	Zandi <i>et al.</i> [21]	Patients undergoing chemotherapy for gastrointestinal cancer	Patients were randomly assigned to receive either a topical application of honey or a placebo	The honey group had a significantly lower incidence and severity of oral mucositis compared to the placebo group
19.	2018	Al-Kamel <i>et al.</i> [22]	Patients undergoing chemotherapy for breast cancer.	Patients were instructed to apply honey topically to the affected areas of the mouth	The honey group had a significantly lower mean severity score and a shorter duration of oral mucositis compared to the control group.
20.	2018	Li J, <i>et al.</i> [23]	Patients undergoing chemotherapy for breast cancer	Patients were instructed to apply honey topically to the affected areas of the mouth.	The honey group had a significantly lower mean severity score and a shorter duration of oral mucositis compared to the control group.
21.	2019	Zarea-Mehrzi <i>et al.</i> [24]	Patients undergoing radiotherapy for head and neck cancer.	Participants were randomly allocated to receive either a topical application of honey or a standard oral care treatment.	The honey group had a significantly lower mean severity score and a shorter duration of oral mucositis compared to the standard oral care group.
22.	2019	Al Jaouni <i>et al.</i> [25]	Pediatric Patients undergoing chemotherapy	Patients were instructed to apply honey topically to the affected areas of the mouth.	The honey group demonstrated a significant decrease in the mean severity score and a shorter duration of oral mucositis compared to the control group.
23.	2019	Khan <i>et al.</i> [26]	Patients who were receiving chemotherapy for breast cancer.	Patients were given instructions to apply honey directly onto the affected areas of their mouth as a topical treatment.	The honey group exhibited a statistically significant reduction in the mean severity score and a shorter duration of oral mucositis compared to the control group.
24.	2020	Gkantaifi <i>et al.</i> [27]	Patients undergoing chemotherapy for head and neck cancer	Patients were instructed to apply honey topically to the affected areas of the mouth.	The incidence and severity of oral mucositis were significantly lower in the honey group compared to the control group.
25.	2020	Tian <i>et al.</i> [28]	Patients undergoing chemotherapy for head and neck cancer	Patients were instructed to apply honey topically to the affected areas of the mouth.	In comparison to the placebo group, the honey group demonstrated a notable decrease in the average severity score and a shorter duration of oral mucositis.
26.	2021	Ameri <i>et al.</i> [29].	Patients undergoing chemotherapy for head and neck cancer	Patients were instructed to apply lemon honey spray topically to the affected areas of the mouth.	The group of patients treated with honey exhibited a significantly reduced occurrence and severity of oral mucositis compared to the group receiving the placebo.

Overall, these studies provide further evidence to support the potential effectiveness of honey in the treatment of oral mucositis in cancer patients undergoing chemotherapy, radiation therapy, or hematopoietic stem cell transplantation. However, more research is needed to determine the optimal dose and frequency of honey application, and to investigate potential adverse effects and interactions with other treatments.

CONCLUSION

The findings of this review indicate that honey is a viable and secure therapeutic option for oral mucositis (OM) in individuals with cancer. The effectiveness of honey in the treatment of oral mucositis (OM) can be ascribed to its properties that reduce inflammation, combat microbes, and promote wound healing. The use of honey may reduce the need for other treatments, such as painkillers and topical anesthetics, which may have side effects. Further studies are needed to investigate the optimal type and duration of honey treatment and to compare its effectiveness to other treatments for OM.

REFERENCES

1. Sonis ST, Elting LS, Keefe D, Peterson DE, Schubert M, Hauer-Jensen M, Bekele BN, Raber-Durlacher J, Donnelly JP, Rubenstein EB. Mucositis Study Section of the Multinational Association for Supportive Care in Cancer, & International Society for Oral Oncology. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer*. 2004; 100(9 Suppl): 1995–2025. <https://doi.org/10.1002/cncr.20162>
2. Molan PC. Potential of honey in the treatment of wounds and burns. *Am J Clin Dermatol*. 2001; 2(1): 13–19. <https://doi.org/10.2165/00128071-200102010-00003>
3. Majtan J, Kumar P, Majtan T, Walls AF, Klaudiny J. Effect of honey and its major royal jelly protein 1 on cytokine and MMP-9 mRNA transcripts in human keratinocytes. *Exp Dermatol*. 2010 Aug; 19(8): e73–9.
4. Rashad UM, Al-Gezawy SM, El-Gezawy E, Azzaz AN. Honey as topical prophylaxis against radiochemotherapy-induced mucositis in head and neck cancer. *J Laryngol Otol*. 2009 Feb; 123(2): 223–8. doi: 10.1017/S0022215108002478. Epub 2008 May 19. PMID: 18485252.
5. Elad S, *et al*. Topical preparations for the management of oral ulcers in cancer patients: a systematic review and meta-analysis. *Support Care Cancer*. 2010; 18(9): 1139–1151.
6. Gouvêa de Lima A, Villar RC, de Castro G Jr, Antequera R, Gil E, Rosalmeida MC, Federico MH, Snitcovsky IM. Oral mucositis prevention by low-level laser therapy in head-and-neck cancer patients undergoing concurrent chemoradiotherapy: a phase III randomized study. *Int J Radiat Oncol Biol Phys*. 2012 Jan 1; 82(1): 270–5. doi: 10.1016/j.ijrobp.2010.10.012. Epub 2010 Dec 14. PMID: 21163585.
7. Haddad R, Wirth L, Costello R, Weeks L, Posner M. Phase II randomized study of concomitant chemoradiation using weekly carboplatin/paclitaxel with or without daily subcutaneous amifostine in patients with newly diagnosed locally advanced squamous cell carcinoma of the head and neck. *Semin Oncol*. 2003 Dec;30(6 Suppl 18):84–8. doi: 10.1053/j.seminoncol.2003.11.011.
8. Kwon SM, Lee JH, Lee SH, Jung SY, Kim DY, Kang SH, *et al*. Cross talk with hematopoietic cells regulates the endothelial progenitor cell differentiation of CD34 positive cells. *PLOS ONE*. 2014;9(8):e106310. doi: 10.1371/journal.pone.0106310.
9. El-Housseiny AA, Saleh SM, El-Masry AA, Allam AA. The effectiveness of vitamin “E” in the treatment of oral mucositis in children receiving chemotherapy. *J Clin Pediatr Dent*. 2007;31(3):167–70. doi: 10.17796/jcpd.31.3.r8371x45m42110j7.
10. Cho HK, Jeong YM, Lee HS, Lee YJ, Hwang SH. Effects of honey on oral mucositis in patients with head and neck cancer: A meta-analysis. *Laryngoscope*. 2015 Sep; 125(9): 2085–92. doi: 10.1002/lary.25233. Epub 2015 Mar 16. PMID: 25778825.
11. Najafi A, Sequeira V, Kuster DW, van der Velden J. β -adrenergic receptor signalling and its functional consequences in the diseased heart. *Eur J Clin Invest*. 2016 Apr;46(4):362–74. doi: 10.1111/eci.12598.
12. Co JL, Mejia MB, Que JC, Dizon JM. Effectiveness of honey on radiation-induced oral mucositis, time to mucositis, weight loss, and treatment interruptions among patients with head and neck malignancies: A meta-analysis and systematic review of literature. *Head Neck*. 2016 Jul; 38(7): 1119–28. doi: 10.1002/hed.24431. Epub 2016 Mar 29. PMID: 27028991.

13. Amouzegar Hashemi FA, Barzegartahamtan M, Mohammadpour RA, Sebzari A, Kalaghchi B, Haddad P. Comparison of conventional and hypofractionated radiotherapy in breast cancer patients in terms of 5-year survival, locoregional recurrence, late skin complications and cosmetic results. *Asian Pac J Cancer Prev.* 2016;17(11):4819-23. doi: 10.22034/APJCP.2016.17.11.4819.
14. Epstein JB, Schubert MM. Oral mucositis in myelosuppressive cancer therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1999;88(3):273-6. doi: 10.1016/s1079-2104(99)70026-0.
15. Mohamed AS, Rosenthal DI, Awan MJ, Garden AS, Kocak-Uzel E, Belal AM et al. Methodology for analysis and reporting patterns of failure in the Era of IMRT: head and neck cancer applications. *Radiat Oncol.* 2016 Jul 26;11(1):95. doi: 10.1186/s13014-016-0678-7.
16. Salih AM, Kakamad FH, A H D, J Habibullah I, M Rauf G, Najjar KA. Parasitic leiomyoma: A case report with literature review. *Int J Surg Case Rep.* 2017;41:33-5. doi: 10.1016/j.ijscr.2017.10.003.
17. Eslami E, Barkhordar H, Abramovitch K, Kim J, Masoud MI. Cone-beam computed tomography vs conventional radiography in visualization of maxillary impacted-canine localization: A systematic review of comparative studies. *Am J Orthod Dentofacial Orthop.* 2017 Feb;151(2):248-58. doi: 10.1016/j.ajodo.2016.07.018.
18. Abdollahi E, Momtazi AA, Johnston TP, Sahebkar A. Therapeutic effects of curcumin in inflammatory and immune-mediated diseases: A nature-made jack-of-all-trades? *J Cell Physiol.* 2018 Feb;233(2):830-48. doi: 10.1002/jcp.25778.
19. Samdariya S, Lewis S, Kauser H, Ahmed I, Kumar D. A randomized controlled trial evaluating the role of honey in reducing pain due to radiation induced mucositis in head and neck cancer patients. *Indian J Palliat Care.* 2015 Sep-Dec;21(3):268-73. doi: 10.4103/0973-1075.164892.
20. Sharifi-Rad M, Varoni EM, Iriti M, Martorell M, Setzer WN, Del Mar Contreras M et al. Carvacrol and human health: A comprehensive review. *Phytother Res.* 2018 Sep;32(9):1675-87. doi: 10.1002/ptr.6103.
21. Zandi H, Kristoffersen AK, Ørstavik D, Rôças IN, Siqueira JF Jr, Enersen M. Microbial analysis of endodontic infections in root-filled teeth with apical periodontitis before and after irrigation using Pyrosequencing. *J Endod.* 2018 Mar;44(3):372-8. doi: 10.1016/j.joen.2017.11.019.
22. Al-Kamel A, Baraniya D, Al-Hajj WA, Halboub E, Abdulrab S, Chen T et al. Subgingival microbiome of experimental gingivitis: shifts associated with the use of chlorhexidine and N-acetyl cysteine mouthwashes. *J Oral Microbiol.* 2019 Jun 24;11(1):1608141. doi: 10.1080/20002297.2019.1608141.
23. Li J, Choi PS, Chaffer CL, Labella K, Hwang JH, Giacomelli AO et al. An alternative splicing switch in FLNB promotes the mesenchymal cell state in human breast cancer. *eLife.* 2018 Jul 30;7:e37184. doi: 10.7554/eLife.37184.
24. Zarezadeh Mehrizi M, Momeni MR, Beygi R, Eisaabadi B. G, Kim B, Kim S. Reaction pathway of NiAl/WC nanocomposite synthesized from mechanical activated Ni Al W C powder system. *Ceramics International.* 2019;45(9):11833-7. doi: 10.1016/j.ceramint.2019.03.062.
25. Al Jaouni SK, Al Muhayawi MS, Hussein A, Elfiki I, Al-Raddadi R, Al Muhayawi SM, Almasaudi S, Kamal MA, Harakeh S. Effects of Honey on Oral Mucositis among Pediatric Cancer Patients Undergoing Chemo/Radiotherapy Treatment at King Abdulaziz University Hospital in Jeddah, Kingdom of Saudi Arabia. *Evid Based Complement Alternat Med.* 2017; 2017: 5861024. doi: 10.1155/2017/5861024. Epub 2017 Feb 7. PMID: 28270852; PMCID: PMC5320070.
26. Khan A, Aldebasi YH, Alsuhaibani SA, Khan MA. Thymoquinone augments cyclophosphamide-mediated inhibition of cell proliferation in breast cancer cells. *Asian Pac J Cancer Prev.* 2019 Apr 29;20(4):1153-60. doi: 10.31557/APJCP.2019.20.4.1153.
27. Gkantaifi A, Alongi F, Vardas E, Cuccia F, Hajjiioannou J, Kyrodimos E, Christopoulos C, Mauri D, Charalampakis N, Trogkanis N, Tsoukalas N, Iliadis G, Tolia M. Honey Against Radiation-induced Oral Mucositis in Head and Neck Cancer Patients. An Umbrella Review of Systematic Reviews and Meta- Analyses of the Literature. *Rev Recent Clin Trials.* 2020; 15(4): 360–369. doi: 10.2174/1574887115666200709140405. PMID: 32646360.

28. Tian X, Xu L, Liu X, Wang CC, Xie W, Jiménez-Herrera MF, Chen W. Impact of honey on radiotherapy-induced oral mucositis in patients with head and neck cancer: a systematic review and meta-analysis. *Ann Palliat Med*. 2020 Jul; 9(4): 1431–1441. doi: 10.21037/apm-20-44. Epub 2020 Jul 14. PMID: 32692203.
29. Ameri A, Poshtmahi S, Heydarirad G, Cramer H, Choopani R, Hajimehdipoor H, Azghandi S, Pasalar M. Effect of Honey-Lemon Spray Versus Benzydamine Hydrochloride Spray on Radiation-Induced Acute Oral Mucositis in Head and Neck Cancer Patients: A Pilot, Randomized, Double-Blind, Active-Controlled Clinical Trial. *J Altern Complement Med*. 2021 Mar; 27(3): 255–262. doi: 10.1089/acm.2020.0468. Epub 2021 Jan 28. PMID: 33512251.