

## Nursing Intervention to Manage Oral Mucositis in Children Chemotherapy: A Systematic Review

Abbas Heydari<sup>1</sup>, Zahra Sadat Manzari<sup>1</sup>, Elahe Ghayebie<sup>2\*</sup>

1. Nursing and Midwifery Care Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

2. Student Research Committee, School of Nursing and Midwifery, Mashhad University of Medical Sciences, Mashhad, Iran

\*Corresponding author: Dr Elahe Ghayebie, Nursing and Midwifery Care Research Center, Mashhad University of Medical Sciences, Mashhad, Iran. Email: Ghaebime981@mums.ac.ir. ORCID ID: 0000-0001-8913-2218

Received: 15 June 2021

Accepted: 15 July 2022

### Abstract

**Background:** In 40-80% of children undergoing chemotherapy, oral mucositis is an acute complication which imposes significant financial and physical burdens on patients. In this article, a systematic review of published studies is conducted to investigate the role of nursing intervention in reducing oral mucositis.

**Materials and methods:** This systematic review investigated, critically appraised, and rated the evidence on nursing intervention to manage oral mucositis (OM) in children undergoing chemotherapy. The review was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist in 2018. A search was conducted through the literature using international databases (e.g., PubMed, Scopus, the Cochrane Database of Systematic Reviews and the Web of Science). Only English-language trials published from January 2007 to December 2019 were selected to consider. There were eleven studies relevant enough to review.

**Results:** A total of 127 articles were extracted in an electronic search. The excluded studies were combined research works on adults and children, descriptive studies, observational studies, and those about adults' endurance of chemotherapy, mucositis produced by other cancer treatments, and cohorts. Finally, eleven studies were deemed eligible for inclusion in this review. Based on them, honey, olive oil, ice chips and chewing gum have been used to prevent, reduce and treat chemotherapy-induced mucositis.

**Conclusion:** This review made a comprehensive examination of the available treatment options for nursing. Nurses can use one of the treatments depending on the child's conditions.

**Keywords:** Chemotherapy, Children, Nursing, Oral mucositis

### Introduction

Sickle cell anemia (SCA) is one of the Based on the type of drug that they take, 40-80% of children under chemotherapy have oral mucositis as an acute complication (1). Oral mucositis is mainly affected by factors such as the medication used during chemotherapy, drug dosage, underlying diseases, type of cancer, neutrophil count, age, nutritional status, and oral hygiene (2-4). It occurs about 3 to 10 days after the start of chemotherapy and can last up to 3 weeks, but the peak comes from 7 to 14 days of chemotherapy. The complication disappears if no secondary infection is added (5).

Oral mucositis is more common in children than in adults that use chemotherapy (3, 6). This may be due to

the faster and greater proliferation of cells in children and the different immunological status of children. The highest rate of cancer-related oral mucositis is induced by leukemia, as the most common cancer in children.

Oral mucositis is a painful side effect graded from mild to severe. To prevent the development of severe mucositis, the therapeutic dose of the chemical drug is reduced or the treatment is delayed (6). Severe mucositis can also increase the mortality of the treated children by up to 40% (2). Painful swallowing following mucositis leads the child to malnutrition and dehydration, which sometimes requires readmission or prolonged hospitalization (6, 7). The chance of septicemia is four times higher in patients

with oral mucositis than in those without oral mucositis (3). It can also disturb children's sleep and finally affect the quality of their life (8). Therefore, controlling infections and maintaining oral mucosal tissue integrity are essential tasks to ensure the quality of treatment with less pain and optimal nutrition in patients who are potentially disabled (9).

Oncology nurses who care children with oral mucositis are faced with a challenge regarding the use of chemotherapy drugs. This is because they try to provide appropriate care for the treatment or reduction of the symptoms and severity of mucositis in each child depending on his or her conditions and the medication received. There are many ways available to prevent oral mucositis as a complication, including the use of oral hygiene protocols, antimicrobial agents, anti-inflammatory agents, and physical therapies (10).

However, a search through domestic and foreign empirical and review studies on oral mucositis in children chemotherapy shows a wide range of interventions. Therefore, it is necessary to identify the various interventions offered by nurses as well as their contents and different forms. The purpose of this study is to identify and introduce the interventions provided by nurses to children with oral mucositis. This expands nurses' knowledge of the effective interventions that they can provide directly to children and shows ways to improve the quality of care. Moreover, knowing the consequences of any kind of nursing intervention makes it possible to select and offer appropriate intervention by considering resources, conditions and goals for each patient. This helps to save time and money according to the client's conditions.

## Materials and Methods

Regarding the search strategy, this study was organized based on the PRISMA (Preferred Items for Systematic Reviews and Meta-Analysis) statement (11). In

order to find the relevant articles, some research questions were drawn up based on patient, intervention, comparison, outcome (PICO). They would deal with nursing interventions for the prevention and treatment of oral mucositis caused by chemotherapy in children, preparation and other key issues. Then a comprehensive search was performed on MEDLINE via PubMed, Scopus, the Cochrane Database of Systematic Reviews, and the Web of Science. In order to avoid a search bias, only the articles written in English were selected without a time limit. The keywords of cancer, child, mucositis, and nursing intervention were the search entries. These keywords were combined using such operators as AND, OR and NOT. Referrals and references for original articles and related reviews were also searched. The World Health Clinical Trial Record site, conferences and congresses were reviewed too. Unpublished and hardly accessible dissertations as well as the articles published in low-credit sources were not reviewed. Duplicate studies and reports were also eliminated through screening the titles.

The selection criteria included the originality of clinical trials, English language of the texts, accessibility of the full texts of papers, performance on children up to 18 years of age with any type of cancer, and child treatment or prevention of oral mucositis. The exclusion criterion was animal studies. An article related to this review was found in the search for conferences, but there was no access to its full text. Similarly, the full text of an article was not received after it was sent by the author in charge.

As for data collection, to ensure the consensus among the evaluators, two pilot studies were conducted. In the next step, the authors' names, article titles, and journal names were covered to avoid bias by the evaluators. The articles were categorized according to the inclusion and exclusion criteria that were marked with yes/ no responses. Two authors

independently judged the articles and determined the bias risk using the modified Jadad guidelines (12, 13). These guidelines were used to evaluate the quality of the reported trials for a) more credibility in identifying the quality of the methods used in those studies and b) the ease of scoring and shortening. After the quality of the studies was evaluated, a Kappa coefficient of more than 80 was considered favorable, and a coefficient value of 60-80 suggested the evaluators' agreement with the discussion. If no consensus was reached, a third person would judge whether the paper had to be reviewed.

### **Ethical consideration**

The current study was approved by the Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.REC.1399.295).

### **Results**

A total of 127 articles were extracted through a series of electronic search (Figure 1). There were 100 articles left after the duplicate ones were excluded. Also, after the titles and abstracts were read, 30 articles were selected to be evaluated in full files in terms of the inclusion criteria. The excluded studies were descriptive and observational ones as well as those on adults enduring chemotherapy, a combination of adults and children, mucositis produced by other cancer treatments, and cohorts. Finally, 11 studies were considered proper enough for inclusion in this review.

A complete description of the reviewed studies is presented in Table I. It includes authors, years of publication, study locations, sample sizes, types and details of nursing intervention, and duration and severity of mucositis. The articles were published from 2007 to 2019. The purpose of this review is to identify the nursing interventions for the management of oral mucositis in children experiencing chemotherapy. Six articles discuss the outcome of using honey, 3 were on

chewing gum, 1 on olive oil, and 1 article on ice therapy. These studies have compared different treatments. In some of the studies, the method has been compared to the standard care (oral health protocol) so as to achieve the best care. The scale mostly used to assess mucositis severity in these studies is the WHO Oral Toxicity Scale. Of the eleven articles reviewed, eight were clinical trials, and three were quasi-experiments. The quality of the studies was assessed using the modified Jadad tool. The evaluation included randomization, proper randomization, blind research and proper blinding as well as references to trial interruptions and failures, inclusion and exclusion criteria, unwanted side effects, and statistical analyses. According to the evaluation, one study had a poor quality, seven had a moderate quality, and three were of a high quality (Table II). The reviewed studies cover all the continents, which can be helpful in terms of the diversity of intervention settings and the generalization of results. In addition, the variety of the interventions offered by nurses in these studies can help to select the kind of intervention according to the child's abilities and circumstances.

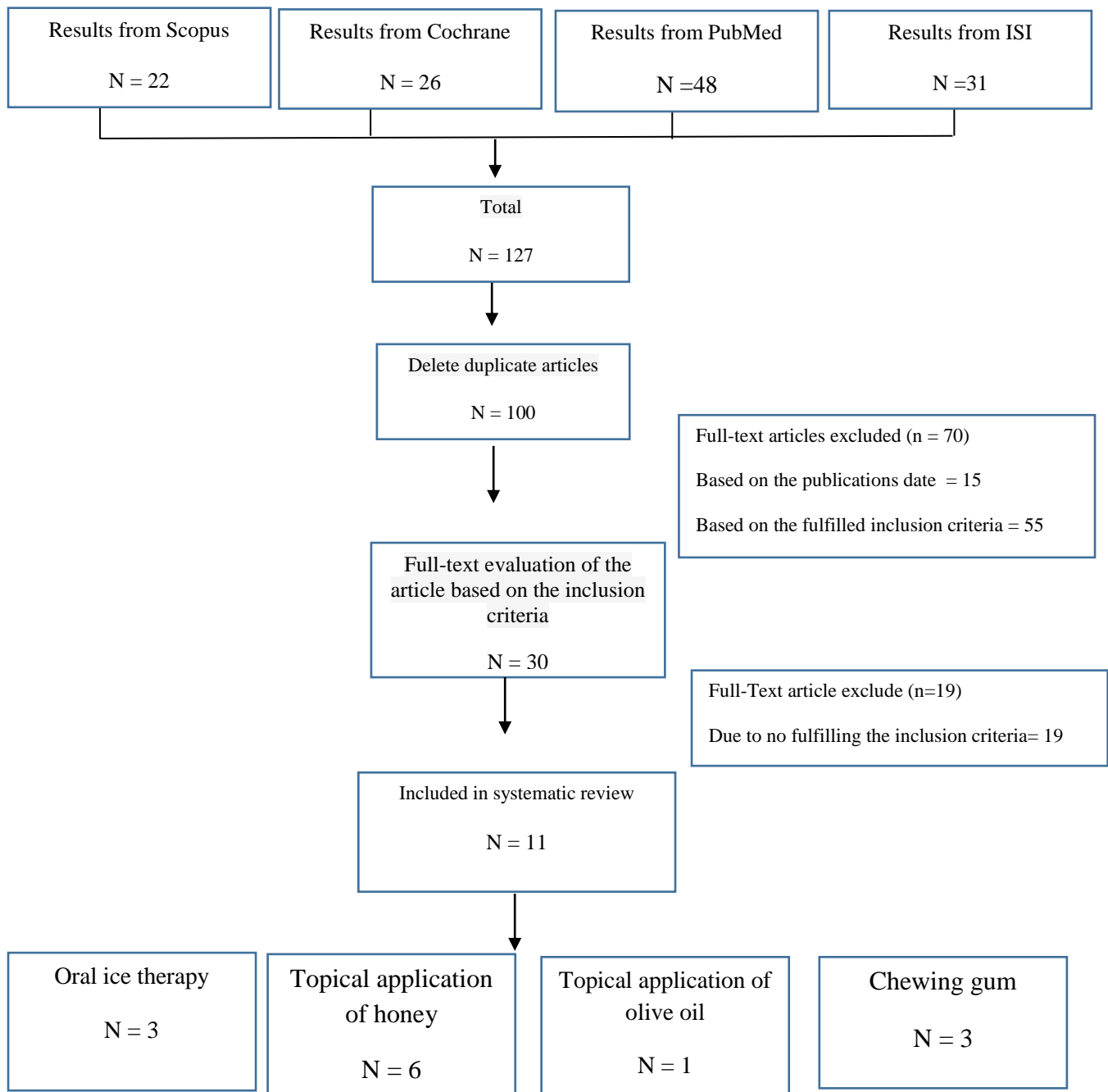


Figure 1. Selection diagram for the systematic review of studies

Table I: Summary of Reviewed Studies

Author / Year / Place of Study	Type of study	Purpose of study	Study tool	Number/ Characteristics of sample	Interventions in groups			Results
					Intervention	Intervention 2	control	
<b>Abdulrhman, (2012), Egypt(17)</b>	RCT	Treatment of oral mucositis	WHO	90 children	Use topical honey three times per day for 10 days	Use HOPE three times a day for up to 10 days	Benzocaine 5.7% three times a day	The recovery time in grade-2 mucositis was significantly decreased in the honey group. In grade 3, the recovery time was not significantly different for the intervention groups.
<b>Soad K. Al Jaouni (2017) Kingdom of Saudi Arabi(18)</b>	RCT	Treatment and prevention	WHO	40 children	In addition to routine treatment, topical use of pure honey		routine treatment	Decrease in the number of days of hospitalization in intervention group
<b>Geetarani Nayak (2017) India(20)</b>	RCT	Treatment and prevention	WHO	40 children	five minutes before chemotherapy, they used ice chips made of pure honey for 30 minutes		ice chips	The severity of mucositis was significantly decreased in the honey freeze group.
<b>Tomaževic (2013) Slovenia(22)</b>	RCT	Treatment	Modified OAG	40 Children	Topical use of 0.38gr propolis		Get placebo	The difference was not significant.
<b>Iraj Sedighi(2013) Iran(21)</b>	RCT	Treatment and prevention	WHO	48 children	In addition to oral hygiene and gargle normal saline and gargle 60 cc honey for 30 seconds.	In addition to oral hygiene, gargle 60 cc normal saline	Oral hygiene protocol	The incidence of mucositis was lower in the interventions group but it was not significant between the two groups
<b>Bulut(2016) Turkey(16)</b>	semi experimental	Prevention and treatment	WHO	83 children	Oral care protocol and 1g / kg honey 4 times daily for 3 weeks		Oral care protocol	Incidence and severity of mucositis was lower in the intervention group.
<b>Virginie Gandemer (2007) Multicenter (7)</b>	RCT	Prevention and reduction	WHO	145 children	From day one to three days after the end of the child chewing gum 5–6 pieces of sugar-free daily.		routine care	Chewing gum was effective
<b>Eghbali (2016) Iran (25)</b>	RCT	Prevention and reduction	WHO	130 children at 5-15 years of	For 15 days, six pieces of sugar-free gum were chewed.		The standard mouthwash	There was no significant difference in grade-3 mucositis, but there was in

<b>Ayverdi Didem (2014)</b>		Prevention and reduction	WHO	60 children at 6-18 years of age	Chewing gum 3 times a day	Any intervention	grades 1 and 2. The difference in the severity of mucositis was significant.
<b>Turkey (23)</b>							
<b>Alkhouli (2019), Syria (29)</b>	RCT	Prevention and reduction	WHO	24 children at 4-6 years of age with ALL	5 cc of olive oil	Twice a day 5% sodium bicarbonate.	The incidence of mucositis was significantly lower in the olive oil group from the second to the eighth weeks.
<b>Hanan Mohamed Rashad (2014), Egypt (28)</b>	semi experimental	Prevention and reduction of severity	OAG scale	60 Child with bone cancer	Keeping a piece of ice in mouth for 5 minutes before and 30 minutes after the drug is finished	Any intervention.	The severity of mucositis was less in the treatment group.

Table II: Evaluation of the quality studies based on the modified Jadad scale

Study	Randomization		Random allocation		Blindness		Appropriate randomization blindness			Description of dropouts		Description of the inclusion and exclusion criteria		References to side effects		Description of statistical analysis		Result
	Yes	No	Yes	No	Yes	No	Yes	No	Not mentioned	Yes	No	Yes	No	Yes	No	Yes	No	
<b>Bulut (16)</b>		*		*		*			*		*		*		*		*	3
<b>Alkhouli (29)</b>	*		*		*				*		*		*		*		*	7
<b>Abdulrhman (17)</b>	*		*			*			*		*		*		*		*	5
<b>Al Jaouni (18)</b>	*			*	*		*				*		*		*		*	5/5
<b>Nayak (20)</b>	*			*		*			*		*		*		*		*	4
<b>Tomazevic (22)</b>	*			*	*		*			*		*		*		*	*	7
<b>Sedighi (21)</b>	*		*		*		*			*		*		*		*	*	7
<b>Gandemer (7)</b>	*			*		*			*		*		*		*		*	4
<b>Eghbali (25)</b>	*			*		*			*		*		*		*		*	4
<b>Didem (23)</b>	*			*		*			*		*		*		*		*	4
<b>Rashad (28)</b>	*			*		*			*		*		*		*		*	4

## **Discussion**

The results of eleven reviews can be discussed in terms of a) the impact of nursing intervention on prevention, b) the reduction of mucositis severity, and c) the medication for oral mucositis (Table III).

Honey is a natural substance that can improve the oral mucosal healing process by decreasing prostaglandin concentrations, increasing nitric oxide and stimulating salivary production (14, 15). Three studies (16-18) have shown that the use of honey reduces the healing time of mucositis. According to the study by Jaouni et al. (18), honey can reduce the number of days a child is hospitalized. The results of a systematic review and a meta-analysis that have evaluated the topical use of honey to improve adult oral mucositis are consistent with the findings of this study; all have identified honey as an adjuvant treatment for mucositis (19). An important reason for the similarity of results in adults and children is the water solubility of honey; it dissolves in saliva and contacts the affected parts of the oral cavity. In a study by Abdulrahman et al. (17), purified honey was compared with HOPE (4:2:1: honey, olive oil and beeswax), which was found to be of less healing effect because of its insolubility in water. The results of such studies (16-18, 20, 21) support the use of honey to reduce the severity of mucositis. In this context, Tomažević et al. (22) showed that bee propolis could not affect the rate of grade-3 or 4 mucositis. Propolis is a paste-like, viscous, waxy substance that is composed of bee saliva and the powder of plants and has the properties of honey. It is not effective as a treatment due to its bad taste for children; it cannot be tolerated by the patient and leads to nausea. To use propolis in this study, it was dissolved in alcohol. This led to the irritation of the oral mucosa, and the positive effect of honey lamb wax was covered with this solvent. Jaouni (18) and Bulut (16) showed that honey, owing to its high viscosity and acidic properties (acidic pH), and

hydrogen peroxide can prevent the growth of bacteria and fungi, reduce the number of *Candida* and Aerobic bacteria, and, thus, reduce the use of antibiotics. As suggested, honey should be used in children over one year of age.

Saliva plays an important role in the health of the oral cavity owing to its antimicrobial materials such as lactoferrin, lactoperoxidase and lysozyme and mucosal protective compounds such as glycoproteins, immunoglobulin A and a growth factor. The treatment occurs with a decrease in the volume and acidity of saliva (23). Chewing gum increases the salivary gland activity and, thus, the salivary flow and gastrointestinal stimulation. This, in turn, increases the pH of saliva and its volume up to 10-folds (24). Three studies (7, 23, 25) confirmed the role of gum to prevent mucositis or reduce its severity. There was only the study by Eghbali et al. (25) which found no effect of chewing gum on the severity of grade-3 and 4 mucositis, possibly due to the poor oral health by the studied; there has been evidence for the inverse association of mucositis severity and poor health of the mouth in children (2, 26). It is remarkable that sugar-free chewing gum was used to protect the children's oral health and prevent tooth decay.

Oral ice therapy using ice, cold water, and ice cream has been systematically reviewed as an appropriate method of preventing and reducing mucositis severity in adults (27), but there was only one study to advise the use of ice as a method of preventing or treating mucositis in children (28). Oral ice therapy with oral vasoconstriction reduces the exposure of oral mucus to toxic agents and the penetration of oral agents into oral mucosa, which seems suitable for the prevention of oral mucositis following short half-life medications (23).

Olive oil contains unsaturated fatty acids such as oleic acid, palmitic acid and a phenolic compound called oleocanthal (29). Fatty acids inhibit inflammatory

reactions, oleic acid inhibits inflammatory cytokines, and oil phenolic compounds have antioxidant properties (30). Of the articles reviewed, only one supports the efficacy of the topical administration of olive oil in improving oral mucositis in children, which is like the results of the studies on adults (31).

This systematic review regards nursing interventions for children under chemotherapy. Due to the rejection of intrusive treatment by children and the increased willingness of patients to use non-chemical therapies, safe and low-cost interventions such as ice therapy and sweet and simple treatments such as using honey and ice cream seem to suit children's tastes better. Therefore, nurses, as the primary caregivers of children in the hospital, should be familiar with these treatments and assist in proper interventions during the nursing process.

Naturally, this review has some limitations. The researcher had no access to gray papers; there were only published English articles to review. There was also no access to the full texts of some articles after correspondence with the authors. Only the available databases were searched through the account of Mashhad University of Medical Sciences.

Finally, some research is recommended to compare standard treatment methods with the nursing interventions discussed in this study so as to identify the best care methods.

### Acknowledgments

We would like to thank all the authors of the articles cited in this review study. We also thank the central library officials at Mashhad University of Medical Sciences for providing access to the corresponding studies from various databases.

### Conflict of interests

There is no conflict to declare.

### References

1. Araújo SNM, Luz MHBA, Silva GRFd, Andrade EMLR, Nunes LCC, Moura RO. Cancer patients with oral mucositis: challenges for nursing care. *Rev Latino Am* 2015; 23(2):267-274.
2. Miller MM, Donald DV, Hagemann TM. Prevention and treatment of oral mucositis in children with cancer. *J Pediatr Pharmacol Ther* 2012;17(4):340-350.
3. McGuire DB, Fulton JS, Park J, Brown CG, Correa ME, Eilers J, et al. Systematic review of basic oral care for the management of oral mucositis in cancer patients. *Support Care Cancer* 2013; 21(11):3165-3177.
4. Friend A, Rubagumya F, Cartledge P. Global Health Journal Club: is honey effective as a treatment for chemotherapy-induced mucositis in paediatric oncology patients? *J Trop Pediatr* 2018; 64(2):162-168.
5. Mazhari F, Shirazi AS, Shabzندهdar M. Management of oral mucositis in pediatric patients receiving cancer therapy: A systematic review and meta-analysis. *Pediatr Blood Cancer* 2019; 66(3):e27403-e27413.
6. Cheng KK, Lee V, Li CH, Goggins W, Thompson DR, Yuen HL, Epstein JB. Incidence and risk factors of oral mucositis in paediatric and adolescent patients undergoing chemotherapy. *Oral oncology* 2011;47(3):153-62.
7. Gandemer V, Dollfus C, Auvrignon A, Bonnaure-Mallet M, Duval M, De Lumley L, et al. Multicenter randomized trial of chewing gum for preventing oral mucositis in children receiving chemotherapy. *J Pediatr Hematol Oncol* 2007; 29(2):86-94.
8. Hendrawati S, Nurhidayah I, Mediani HS, Mardhiyah A, Maryam NNA. Mucositis Effect on Quality of Life of Hospitalized Children with Cancer Who Received Chemotherapy. *JKP* 2019;7(1):29-37.



9. Razmara F, Khayamzadeh M. An investigation into the prevalence and treatment of oral mucositis after cancer treatment. *Int J Cancer Manag* 2019;12(11):e88405-e88416.
10. Chaveli-López B, Bagán-Sebastián JV. Treatment of oral mucositis due to chemotherapy. *J Clin Exp Dent* 2016;8(2):e201-e209.
11. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *Bmj* 2015; 4:349-358.
12. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17(1):1-12.
13. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010;8(5):336-41.
14. Almasaudi SB, El-Shitany NA, Abbas AT, Abdel-dayem UA, Ali SS, Al Jaouni SK, et al. Antioxidant, anti-inflammatory, and antiulcer potential of manuka honey against gastric ulcer in rats. *Oxid Med Cell* 2016;2016: 1-10.
15. Yarom N, Ariyawardana A, Hovan A, Barasch A, Jarvis V, Jensen SB, et al. Systematic review of natural agents for the management of oral mucositis in cancer patients. *Support Care Cancer* 2013; 21:3209-3221.
16. Bulut HK, Tüfekci FG. Honey prevents oral mucositis in children undergoing chemotherapy: A quasi-experimental study with a control group. *Complement Ther Med* 2016; 29:132-140.
17. Abdulrhman M, Barbary NSE, Amin DA, Ebrahim RS. Honey and a Mixture of Honey, Beeswax, and Olive Oil-Propolis Extract in Treatment of Chemotherapy-Induced Oral Mucositis: A Randomized Controlled Pilot Study. *J Pediatr Hematol Oncol* 2012; 29(3): 258-292.
18. Jaouni SA, Muhayawi MA, Hussein A, Elfiki I, Al-Raddadi R, Muhayawi SA, et al. 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: 5861024-58610249.
19. Yang C, Gong G, Jin E, Han X, Zhuo Y, Yang S, et al. Topical application of honey in the management of chemo/radiotherapy-induced oral mucositis: A systematic review and network meta-analysis. *Int J Nurs Stud* 2019;89:80-87.
20. Mishra L, Nayak G. Effect of Flavored (Honey and Tulsi) Ice Chips on Reduction of Oral Mucositis among Children Receiving Chemo Therapy. *Int J Pharm Sci Rev Res* 2017;43(1):25-28.
21. Sedighi I, Molaee S, Amanati A, Khoeinipourfar H, Nouri S. Antimicrobial Activity of Natural Honey: Topical Application of Pure Natural Honey in Prevention of Chemotherapy Induced Oral Mucositis. *J Compr Ped* 2013; 4(3):138-142.
22. Tomažević T, Jazbec J. A double blind randomised placebo controlled study of propolis (bee glue) effectiveness in the treatment of severe oral mucositis in chemotherapy treated children. *Complement Ther Med* 2013; 21(4):306-312.
23. Didem A, Ayfer E, Ferda OA. The Effect of Chewing Gum on Oral Mucositis in Children Receiving Chemotherapy. *Health Sci J* 2014;8(3):373-382.
24. Utami KC, Hayati H. Chewing gum is more effective than saline-solution gargling for reducing oral mucositis. *Enfermería clínica* 2018; 28:5-8.
25. Eghbali A, BTaherkhanchi, Bagheri B, Sedeh BS. Effect of Chewing Gum on Oral Mucositis in Children Undergoing Chemotherapy: A

Randomized Controlled Study. *Iran J Ped Hematol Oncol* 2016;6(1):9-14.

26. Peterson D, Bensadoun R, Roila F. Management of oral and gastrointestinal mucositis: ESMO clinical recommendations. *Ann Oncol* 2008;19:122-125.

27. Worthington HV, Clarkson JE. Prevention of Oral Mucositis and Oral Candidacies for Patients with Cancer Treated with Chemotherapy: Cochrane Systemic Review. *J Dent Educ* 2010;66(8):903-911.

28. Rashad HM, Darwish MM, Khaled WZ. Effect of Cryotherapy on the Occurrence of Stomatitis Induced by Chemotherapy among Children with Bone Tumors in Egypt. *JBAH* 2014;4(18):49-58.

29. Alkhoul M, Laflouf M, Alhaddad M. Evaluation of the effectiveness of olive oil to prevent chemotherapy induced oral mucositis: A randomized controlled clinical trial. *Pediatr Dent J* 2019; 29(3):123-131.

30. Montaña A, Hernández M, Garrido I, Llerena JL, Espinosa F. Fatty acid and phenolic compound concentrations in eight different monovarietal virgin olive oils from extremadura and the relationship with oxidative stability. *Int J Mol Sci* 2016;17(11):1960-1980.

31. Ahmed K. The effect of olive leaf extract in decreasing the expression of two pro-inflammatory cytokines in patients receiving chemotherapy for cancer: A randomized clinical trial. *Saudi Dent J* 2013; 25(4):141-147.