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REVIEW

The Effect of Oral Care Intervention in Mucositis Management Among Pediatric Cancer Patients: An Updated Systematic Review

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Background: Chemotherapy-induced mucositis is inflammation that develops in the oral mucosal due to anticancer treatment. Mucositis has negative consequences that may lead to distress in pediatric patients, resulting in escalated expenses, diminished quality of life, hindrance in cancer therapy, and decreased survival rates. However, despite the numerous methods, oral care protocols are suggested for implementation in the pediatric population despite a lack of high-level evidence studies, particularly regarding which appropriate oral care agents should be administered.

Purpose: This systematic review aimed to identify the effect of oral care intervention in mucositis management among pediatric cancer patients.

Methods: Studies were published between 2014 and 2023 from five databases: PubMed, Embase, Medline, ScienceDirect, and Scopus. They were identified using a search strategy to identify relevant studies that identify oral care interventions for managing mucositis in children with cancer. This study used the Joanna Briggs Institute (JBI) critical appraisal tools to assess the quality of the studies and followed the recommended reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.

Results: Eight studies met the inclusion criteria, including seven RCTs and one quasi-experimental study. Oral care interventions involving tooth brushing, mouthwash, and lip care are performed entirely or partially. The frequency of oral care ranges from two to six times daily, and the duration of intervention is from 5 days to six weeks. Oral care interventions using honey, olive oil, Aloe Vera, Andiroba, and salivary enzyme toothpaste are beneficial to lower the severity of mucositis, reduce pain, minimize mucositis duration, and reduce the use of analgesics, but not significantly improve the child's quality of life. However, Caphosol mouthwash did not significantly reduce mucositis.

Conclusion: Our study highlights that oral care intervention using effective agents integratively, including honey, olive oil, Aloe vera, Andiroba, and salivary enzyme toothpaste, is essential to manage chemotherapy-induced mucositis among children.

Systematic Review Registration: PROSPERO registration number was CRD42023456278.

Keywords: children, cancer, chemotherapy, oral care, mucositis

Introduction

Cancer is a lethal chronic disease that endangers the health of both adults and children worldwide. World Health Organization estimates that the cancer prevalence in children is around 4%.[1] Cancer affects up to 80% of children in developing or low-income countries, and it is estimated that 90,000 children and adolescents die from it each year.[2] World Health Organization emphasizes the need to improve effective treatment policies for all children with cancer to increase survival rates, particularly in developing countries.[1,3]

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Children's cancer treatment is intensive to control the number of cancer cells. Surgery, chemotherapy, and radiotherapy are the three main treatments used. Chemotherapy is the most commonly used treatment for children with cancer because it is highly effective.[4] Chemotherapy is performed by administering cytotoxic drugs, which destroy and inhibit the growth of rapidly dividing cells that cannot distinguish between cancerous and normal cells. Chemotherapy is beneficial for systemic cancers that cannot be treated with surgery or radiation. Multiagent chemotherapy has many successes and saves many children from cancer.[5]

Aside from the numerous benefits of chemotherapy treatment for childhood cancer, there are countless side effects. According to Harris et al, the most common chemotherapy side effects experienced by cancer patients (69.6%) are oral and gastrointestinal. Other chemotherapy-related side effects include fatigue, bone marrow depression, hair loss, and skin problems.[3,6] The most common side effect of chemotherapy is oral mucositis (OM), which affects approximately 75% of high-risk patients and 52–80% of children.[7] Mucositis symptoms range from mild to severe and may necessitate hospitalization. These symptoms include pain, erythema, edema, ulceration, bleeding, dry mouth, burning sensation, difficulty swallowing and speaking, and can impact all aspects of a child's life.[8]

Mucositis-related ulceration and pain can make eating and drinking difficult due to impaired chewing, swallowing, tasting food, and bad breath.[9] It can lead to decreased appetite and limited food and drink intake, putting children at risk of dehydration, weight loss, and nutritional changes.[10] Severe dietary changes can increase a child's enteral and parenteral nutrition needs.[11] Significant dietary changes have several unintended consequences, including worsening clinical conditions and increasing the risk of infection. It exacerbates the child's condition and can result in reduced chemotherapy doses, schedule delays, or even treatment discontinuation.[12] As a result, the effectiveness of chemotherapy becomes suboptimal, disrupting the remission period and reducing recovery and child survival,[8,11,12] thereby increasing the cost and ultimately reducing the quality of life of children.[13] These issues can impede cancer treatment and lower survival rates, particularly in immunocompromised children.[14]

Although numerous chemotherapy-induced mucositis treatment options exist, none can entirely prevent or adequately treat mucositis.[13] Elad et al recommend oral care, particularly toothbrushing and gargling, as the primary intervention in treating chemotherapy-induced mucositis. However, the findings of several studies indicate that more research is required to document the expected benefits and risks of various treatment methods. Friend's systematic reviews suggest oral care is the best mucositis treatment. The oral care intervention includes several Methods: brushing, flossing, gargling, and lip care. Various studies related to oral care interventions use varying methods and show varying results. Apart from the various techniques, the agents used in oral care interventions also vary. Various studies are still being debated regarding using oral care agents to prevent and treat mucositis in the pediatric population.[15]

The Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) state that implementing basic oral care protocols is recommended in the pediatric population amidst a lack of high-level evidence studies.[16] MASCC/ISOO also suggests identifying how effective oral care interventions are in the pediatric population with malignancies. Oral care carried out in managing mucositis in children varies greatly.

Several studies show a variety of oral care interventions to manage mucositis in children, such as teeth brushing only,[17] tooth brushing with flossing,[18] mouth washing only,[19] tooth brushing and mouth washing,[12,20] or tooth brushing – mouth washing and lip care.[21] The frequency of oral care in cancer children varies according to the literature. According to the earlier study, oral care can be performed 2–3 times daily, every 4–6 hours, or every 2–4 hours.[22] Thus, MASCC/ISOO encourages additional research to identify oral care intervention in managing mucositis in children, strengthening the current evidence.[16]

Information regarding agents used in oral care interventions in the pediatric population is also important, considering that various agents are used with varying effectiveness in preventing and treating mucositis in children. Chlorhexidine is a widely and frequently used agent in oral care interventions as a mouthwash. However, some studies advise against using this agent.[23] Other agents, such as povidone-iodine, have limited scientific evidence for preventing mucositis. According to Brown and Gupta, most patients notice an unpleasant taste when using these substances in oral care.[24] These substances should not be given over a long period because they may alter the normal bacterial flora in the oral cavity and lead to hyperthyroidism.[24] The agents chlorhexidine (0.12–0.2%) and benzydamine (0.15%), according to the

Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO), have been linked to stinging or burning sensations.[25]

According to the MASCC/ISOO clinical guidelines, using agents such as honey in oral care interventions has a level of evidence suggested for preventing mucositis in general population patients,[25] and special pediatric populations.[16] The MASCC/ISOO panel also believes that honey has promising potential in pediatric patients, but more study is needed to strengthen this evidence.[16] The MASCC/ISOO pediatric sub-analysis panel cited two studies on honey. The first was a placebo-controlled RCT study that used topical honey to treat mucositis in 90 pediatric patients with hematological malignancies undergoing chemotherapy. The study found that *Trifolium alexandrinum*-based honey effectively reduced the healing time of ulcerative mucositis. ($p=0.0005$).[26] However, MASCC/ISOO stated the need for further research to identify the effect of honey on mucositis because MASCC also reported a single RCT reporting the ineffectiveness of topical propolis for the treatment of oral mucositis in pediatric patients (n=40) for hematological and solid cancers.[27]

Several other studies have identified the use of various substances in managing mucositis, including palifermin administration,[28] photobiomodulation,[19] chewing gum, and ketamine. However, in this systematic review study, the focus is more on identifying what kind of oral care interventions are effective in managing mucositis in children, including identifying the agents used in oral care as embedded, that involved the practice of tooth brushing, mouth washing, or lip care.

It is very important to support and strengthen the evidence regarding the implementation of recommended oral care protocols in the pediatric population, as is the mandate of MASCC/ISOO to strengthen the evidence regarding effective oral care protocols in the management of mucositis in children in light of the lack of high-level evidence studies.[16] This systematic review aims to identify oral care interventions used to manage mucositis in children. In addition, the secondary outcome is to identify the effectiveness of the agents used in oral care to reduce the severity of mucositis in children. This systematic review will benefit the field by providing evidence for the efficacy of oral care intervention using specific agents in managing mucositis in children.

Materials and Methods

Study Design

The study design used in this research is a systematic review. The systematic review seeks to inform and assist this process and enable efficient access to evidence for scale-up by synthesizing research from several studies. The framework comprises six fundamental phases, which are as follows: formulating research questions, examining existing literature, filtering studies to identify pertinent ones, evaluating the caliber of investigations, determining each study's outcome measures, and compiling and presenting findings.[29] This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[30] The study protocol was registered on the PROSPERO database (CRD42023456278).

Search Strategy

From July 30, 2023, to December 30, 2023, two independent reviewers examined research articles published between 2014 and 2023 from five databases: PubMed, Embase, Medline, ScienceDirect, and Scopus. This study used a systematic search strategy based on research questions aligned with medical subject headings, phrases, and subject synonym combinations. Boolean operators ("AND" and "OR") were applied to each database. The following keywords and Boolean operators were used: ("children OR pediatric") AND ("cancer OR leukemia OR malignancy") AND ("oral care OR oral hygiene") AND ("mucositis score") AND ("experimental OR randomized trial").

Inclusion and Exclusion Criteria

The articles were chosen for review based on inclusion and exclusion criteria.

Inclusion Criteria

- Population: studies in which the participants are children with cancer up to 18 years old who are undergoing chemotherapy.
- Intervention: oral care intervention using a specific agent. The researchers use the following definition of oral care: Oral care, or basic oral care, refers to all routine activities performed by patients, caregivers, or healthcare providers to manage mucositis in children with cancer who are undergoing chemotherapy. Oral care procedures involve tooth brushing, flossing, mouth washing, lip care, or topical application to the entire surface of the oral mucosa.[25]
- Comparison: control group or standard care.
- Outcome: score or severity of mucositis and other secondary outcomes.
- Study type: experimental studies.
- The article's publication year ranges from 2014 through 2023.

Exclusion Criteria

- Studies on young adults and adult cancer patient.
- Studies for children with other chronic health problems outside cancer.
- Descriptive, cross-sectional, case-control, cohort studies, qualitative studies, feasibility studies, study protocols, conference proceedings, thesis/dissertation, or abstracts.
- Studies in languages other than English.
- Articles with no full text.

Study Selection and Data Extraction

Two reviewers (DG and IN) independently selected the articles from five databases. All search results were imported into the reference management application for data management. Two reviewers independently examined and cross-checked the remaining articles after eliminating any duplicates. A third reviewer (NN) helped resolve disagreements regarding whether to include an article. After the evaluation, the two researchers reached an agreement. The first researcher (IN) who screened the database evaluated the studies based on the relevance of the study title. The reference manager application was used to record studies whose titles and abstracts met the inclusion criteria, and full texts were obtained. Before being transferred to the data extraction table, two independent researchers (IN and AA) evaluated full texts for inclusion criteria and methodological quality. The reviewers (IN, AA, HSM) then extracted data from each article, including the year, study location, study design, sample size and characteristics, the type of oral care-based intervention used, the specific agent used in the oral care intervention, and the findings. The study followed the PRISMA writing guidelines for systematic reviews and meta-analyses (Figure 1).

Quality Assessment

The methodological quality of the included studies was independently assessed by two reviewers (IN, AA) using the Joanna Briggs Institute (JBI) critical appraisal tools for randomized controlled trials and quasi-experiments.[31,32] The JBI includes 13 questions for randomized controlled trials and nine for quasi-experimental investigations. Questions have four possible answers: "Yes", "No", "Unclear" (if no information about the problem is provided), and "Not applicable (NA)" (if the question is incomplete). Each question was scored as "Yes" (1 point), "No" (0 points), "Unclear" (0 points), or "Not relevant" (0 points). Overall, scores range from 0 to 13 and 0 to 9. If there were a disagreement, NN would be involved in resolving the process using JBI guidelines.[31,32]

Risk of Bias

The risk of bias for each article in this study is assessed using the cut-off point established by Viswanathan.[33] Individual studies using experiment designs had a low risk of bias if 70% of answers were "yes", a moderate risk if 50–69% of questions were "yes", and a high risk of bias if "yes" scores were less than 50%. Table 1 summarizes the appraisal's conclusion concerning the risk of bias in each included study.

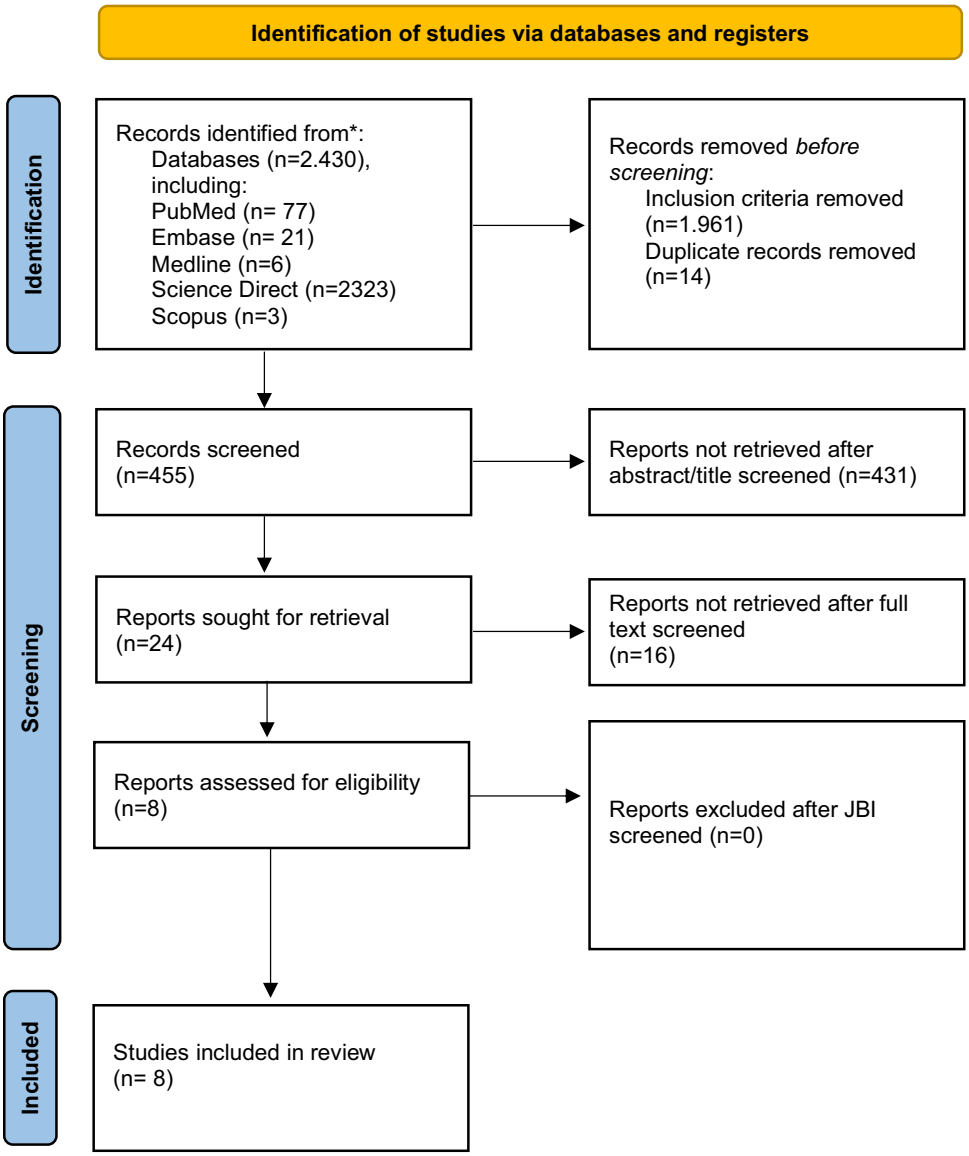

Figure 1 PRISMA Flow Diagram. Adapted from Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated :guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. Creative Commons.[30]

Data Synthesis and Analysis

Two researchers build the data extraction form using the following parameters: (1) author, year, and country; (2) aims; (3) study design; (4) sample characteristics; (5) intervention; (6) outcomes; (7) tools; (8) measurement times; and (9) results of the study (Table 2). Table 3 summarizes the specific oral care intervention carried out in each study, including data extraction: (1) author; (2) study design; (3) cancer type; (4) oral care intervention; (5) oral care agent; (6) doses; (7) sample size; (8) frequency of oral care; (9) length; (10) tools; (11) mucositis score; (12) the effect of the intervention (p-value). The findings are presented as a summary table, followed by a narrative describing the results' similarities and differences.

Results

Eight publications explored oral care interventions in the management of mucositis in children with cancer. Tables 2 and 3 highlight the findings of the analysis. Specific characteristics of the implementation of the oral care intervention can be found in Table 3. Apart from that, Table 3 also contains information about the specific agents used in the oral care

Table 1 The Result of Critical Appraisal for Included Studies

Author, Published Year	JBI Critical Appraisal Tool	Study Design
Al Jaouni et al, (2017)[34]	77% (10/13)	RCT
Alkhouli et al, (2019)[35]	92.3% (12/13)	RCT
Alkhouli et al, (2021)[36]	92.3% (12/13)	RCT
Badr et al, (2023)[37]	92.3% (12/13)	RCT
Bardellini et al, (2016)[38]	84.6% (11/13)	RCT
Raphael et al, (2014)[39]	92.3% (12/13)	RCT
Soares et al, (2021)[40]	84.6% (11/13)	RCT
Kobya Bulut & Güdücü Tüfekci, (2016)[41]	88.8 (8/9)	Quasi-experiment

intervention provided. Based on the findings of this systematic review, the following is an explanation of oral care intervention carried out in managing mucositis symptoms in children with cancer.

Characteristics of Studies

The search yielded 2430 articles. After selection based on inclusion criteria, 455 articles remained: full-text articles in English published between 2014 and 2023, with duplicates removed. Furthermore, 24 articles remained after being eliminated based on title or abstract. The researcher then thoroughly reviewed the full texts of the articles, and eight were ultimately included in this study (Figure 1). Articles were evaluated using the JBI Critical Appraisal Tool, and good article standards exceeded 60% in terms of criteria and topic relevance.

This review includes studies on West Asia, the Mediterranean, Europe, and South America. Table 2 depicts two studies from Syria, one from Saudi Arabia, one from Lebanon, one from Turkey, one from Italy, one from the Netherlands, and one from Brazil. Only one study used a quasi-experimental design, while most used an RCT. Two of the studies involved children with cancer in general, while the other six included children with leukemia. This study identified both primary and secondary outcomes. The primary outcome in this study is the degree of mucositis identified using the WHO grading scale, Oral Hygiene Index, and The NCI-CTCAE version 3.0 mucositis scoring system. Meanwhile, secondary outcomes identified include pain scale, length of stay, use of analgesics, and quality of life.

Oral Care Intervention

Table 3 shows that the oral care intervention involves several different actions. Four studies involved a complete oral care intervention, including toothbrushing, mouth washing, and lip care (topical application).[34–36,41] One study involved both toothbrushing and mouth washing,[37] one study involved toothbrushing only,[38] one study involved mouth washing only,[42] and one study carried out with topical application in the mouth area.[43] The sample size for each intervention group ranged from 11–32 participants. The frequency with which oral care is carried out varies from 2 times a day,[35,39] four times a day,[36,37,40,41] and the most frequent is six times a day.[34] The length of oral care intervention also varies, mostly being carried out over 5–10 days,[34,37–40,36] 21 days,[41] and the most prolonged intervention was carried out for six weeks.[35]

Oral Care Agents

Table 3 shows that the oral care intervention carried out in each study used a specific oral care agent. Three studies used honey as an oral care agent,[34,37,41] three studies used olive oil,[35–37] one study used toothpaste contains saliva enzymes, essential oils, proteins, and colostrum extract (Bioxtraâ),[38] one study used Caphosol mouth rinse,[39] one study used Aloe vera,[36] and one study used Andiroba.[40] This product is used for toothbrushing, mouth washing, and lip care or lubrication in the lip and oral cavity. Based on the findings of this systematic review, the following explanation is provided for the effectiveness of oral care agents on mucositis scores in children with cancer.

Table 2 The Primary Feature of the Systematic Review Included Studies (n=8)

Author, Year, Country	Aim	Study Design	Sample Characteristic	Intervention	Outcomes	Tools	Measurement Time	Results
Al Jaouni et al, 2017, Saudi Arabia.[34]	To evaluate the efficacy of using local Saudi honey as an integrative approach in prophylaxis and treatment of chemo/radiotherapy-induced oral mucositis (grades III and IV) among pediatric cancer patients.	RCT	Forty pediatric cancer patients are undergoing chemo/ radiotherapy. n=20 (intervention) n=20 (control).	Control group: routine oral hygiene using Lidocaine, Mycostatin, and Daktarin for mouthwash. Intervention group: routine oral hygiene using topical application of pure honey for mouth and lip care.	The severity of oral mucositis	The World Health Organization's (WHO) oral toxicity	Three times (before and after treatment, a week a	There was a significant difference between the experimental (honey) and the control group (p=0.02). The experimental group had a 20% incidence rate of grade III and IV oral mucositis versus 55% in the control group. In the experimental group, the length of stay decreased (p=0.001), while the weight gain percentage increased (p=0.001).
Alkhouli et al, 2019, Syria.[35]	This study aimed to identify the efficacy of topical olive oil application to delay or alleviate chemotherapy-induced oral mucositis (OM) in children with acute lymphoblastic leukemia.	RCT	22 children with acute lymphoblastic leukemia aged 4 to 6 years old were randomly assigned to one of two groups: olive oil group (n=11), and sodium bicarbonate 5% group (n=11).	Control group: oral care, including tooth brushing and mouth washing using sodium bicarbonate 5%. Intervention group: oral care, including tooth brushing and topical application, using olive oil for mouth and lip care.	The severity of oral mucositis	The World Health Organization (WHO) mucositis grading scale combines clinical features with the patient's ability to eat or drink.	Eight times (once weekly for eight weeks, during the induction and consolidation phases of chemotherapy)	During the eight weeks, the olive oil group had the highest percentage of grade (0) OM. Furthermore, the olive oil group has no grade (4) OM. The olive oil group had less severe oral mucositis than the sodium bicarbonate group, with a statistically significant difference from the second to the eighth week of the study phase (p<0.05).

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Table 2 (Continued).

Author, Year, Country	Aim	Study Design	Sample Characteristic	Intervention	Outcomes	Tools	Measurement Time	Results
Alkhouli et al, 2021, Syria.[35]	To assess the efficiency of Aloe Vera and Olive Oil in managing chemotherapy-induced oral mucositis.	RCT	Thirty-three children with acute lymphoblastic leukemia, aged between 6 and 9 years, were receiving chemotherapy and were experiencing grade 3 or grade 4 oral mucositis.	Group A: 70% Aloe Vera solution for mouth washing (n=11) Group B: Extra Virgin Olive Oil for mouth and lip topical application (n=11). Group C: 5% sodium bicarbonate solution mouth washing (n=11).	The severity of oral mucositis	The World Health Organization (WHO) mucositis grading scale.	Two times (pretest and ten days after intervention)	Both aloe vera (p=0.007) and olive oil (p=0.002) had shown a statistically significant difference in oral mucositis grades before and after the intervention. In contrast, the sodium bicarbonate group showed no significant difference (p=0.414).
Badr et al, 2023, Lebanon.[37]	To compare the efficacy of honey or olive oil on the severity and pain of OM in children with leukemia and OM to placebo (standard care) and to determine which of the two interventions is more beneficial.	RCT	Forty-two children with leukemia received high-dose chemotherapy. n=17 (intervention for honey) n=13 (intervention for olive oil) n=12 (control group).	Group 1: tooth brushing and mouth washing using 2.5 cc of certified Manuka honey. Group 2: tooth brushing and mouth washing using 2.5 cc of extra virgin olive oil. Group 3 (control): tooth brushing and mouth washing using 5cc of 3% sodium bicarbonate and 5cc Rinsidin.	The severity of oral mucositis and pain score.	The World Health Organization (WHO) mucositis grading scale and Visual analog scale (VAS).	Twice (pretest and seven days after intervention).	Children who received the honey had less severe OM (p=0.00) and less pain (p=0.00) than the control group. Children who received the olive oil had less pain than the control group (p=0.00), although not lower than the honey group.
Bardellini et al, 2016, Italy.[38]	To compare the impact of a fluoride toothpaste with salivary enzymes, essential oils, proteins, and colostrum extract versus a fluoride toothpaste without menthol on oral hygiene and quality of life (QoL) in children with oral mucositis (OM) grade 1 or 2 receiving chemotherapy for acute lymphoblastic leukemia.	RCT	64 children with acute lymphoblastic leukemia were divided into two groups at random: Group A (Bioxtraâ toothpaste) (n=32) Group B (fluoride toothpaste without menthol) (n=32).	Group A: Brush the tooth using the roll-on technique of Bioxtraâ toothpaste. Group B: toothbrush using roll-on technique using fluoride toothpaste without menthol.	Oral hygiene grade and quality of life.	Oral Hygiene Index (OHI), The Oral Health Impact Profile (OHIP-14).	Twice (pretest and eight days after intervention).	A significant difference (p< 0.001) between the mean of the OHI-s in group A and group B. The overall OHIP-14 scores were not associated with using one or the other toothpaste (p=0.33). Although the use of Bioxtraâ toothpaste does not affect the QoL of children undergoing chemotherapy, it may be recommended as clinically effective in improving the oral hygiene grade.

Raphael et al, 2014, Netherland.[39]	To find out whether Caphosol can be used to treat oral mucositis.	RCT	Pediatric cancer patients aged 4–18 years old. n=15 (intervention) n=14 (control)	Control group: mouth washing using NaCl 0.9% four times daily. Intervention group: mouth washing using Caphosol four times daily.	The severity of mucositis, pain, and other parameters (use of analgesics, obtained blood cultures, and need for tube or parenteral feeding).	The NCI-CTCAE version 3.0 mucositis scoring system and	Twices (pretest and the number of days with OM> grade 1).	The total duration of mucositis showed a trend to be longer in the Caphosol group (p=0.069) The number of days in pain was significantly higher in the Caphosol group (p=0.04), although the peak pain level was comparable between groups. Analgesics use was significantly longer by those in the Caphosol group (p=0.035)
Soares et al, 2021, Brazil.[40]	To evaluate the therapeutic effects of andiroba gel (Carapa guianensis Aubl) on the symptom- atology and evolution of OM in children with leukemia who underwent chemotherapy.	RCT	60 patients of both genders with leukemia, with age ranging from 6–12 years. The patients were divided into two study groups: the andiroba group (n=30) the laser group (n=30).	Intervention group: oral hygiene procedure and topical application of Andiroba orobase 3%. Laser group: daily treatment with a low-frequency red laser.	The degree of mucositis and the degree of pain.	The World Health Organization (WHO) mucositis grading scale and the Wong-Baker scale.	The Mucositis score was assessed daily for 11 days, while the pain score was evaluated daily for nine days.	The OM scores in the andiroba group were lower on all days compared to the laser group, indicating that the andiroba group had less severe OM than the laser group (p<0.05) The current study found that the andiroba group experienced less pain than the laser group (p<0.05). Thus, andiroba gel outperformed low-power laser in terms of analgesic potential.

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Table 2 (Continued).

Author, Year, Country	Aim	Study Design	Sample Characteristic	Intervention	Outcomes	Tools	Measurement Time	Results
Kobya Bulut & Güdücü Tüfekci, 2016, Turkey.[41]	To assess the effect of oral care with honey on children undergoing chemotherapy for the prevention and healing of oral mucositis	Quasi experiment	Seventy-six children who receive chemotherapy for leukemia. n=37 (intervention) n=39 (control)	Control group: routine oral care using standard care for mucositis: Phase 0 and Phase 1: mouth care with sodium bicarbonate (NaHCO3); Phase 2: mouth care with NaHCO3, vitamin E, ranitap, and tantum; Phases 3 and 4: mouth care with NaHCO3, vitamin E, ranitap, tantum, mukostatin (triflucan), glycerin and novacaine. If there were improvements during phases 3 and 4, glutamine and nephrogen were added to the mouth care formula. Intervention group: routine oral care using standard care for mucositis, in addition to using honey as a mouthwash and topical application for three weeks.	The severity of mucositis.	World Health Organization Mucositis Assessment Scale (WHOMAS)	Six times (day 1st, 4th, 8th, 12th, 16th, 21 th).	The results showed that the OM degrees of the children in the honey group before OM occurred gradually decreased after the first day of honey use. There was a significant difference between the follow-up days and OM degrees ($p<0.05$). The OM degrees of the children in the control group gradually increased on the fourth, eighth, and twelfth days but decreased slightly on the sixteenth and twenty-first days. The difference in follow-up days and OM degrees was statistically significant ($p=0.001$). In contrast, the degree of OM in the honey group was significantly lower after the fourth follow-up day, and the difference between the experimental and control groups was significant.

Table 3 Characteristics of Oral Care Intervention

Study	Study Design	Cancer Type	Oral Care Intervention	Oral care Agent	Sample Size	Doses	Frequency	Length	Tools	Outcomes	p-value
Al Jaouni et al, 2017, Saudi Arabia.[34]	RCT	Various	Toothbrushing + lip care + topical application	Honey	20	N/A	Six times daily	N/A	WHO grading scale	A significant reduction of oral mucositis, associated Candida, and aerobic pathogenic bacterial infections was noted in patients in the honey treatment group.	0.02
Alkhouli et al, 2019, Syria.[35]	RCT	Leukemia	Toothbrushing + lip care + topical application	Olive Oil	11	5 mL	Two times daily	Six weeks	WHO grading scale	The olive oil group had less severe oral mucositis than the sodium bicarbonate group.	0.022
Alkhouli et al, 2021, Syria.[36]	RCT	Leukemia	Toothbrushing + lip care + topical application	Aloe Vera Olive Oil	11 11	70% Aloe vera	Four times daily	Ten days	WHO grading scale	Aloe Vera and Olive Oil have significant differences in the management of chemotherapy-induced oral mucositis compared to sodium bicarbonate treatments.	0.007 0.002
Badr et al, 2023, Lebanon.[37]	RCT	Leukemia	Toothbrushing + Mouthwash	Honey Olive Oil	17 13	2.5 cc honey 2.5 cc olive oil.	Four times daily	Seven days	WHO grading scale	Children who received the honey had less severe mucositis and less pain than the control group. Children who received the olive oil had less pain than the control group, although not lower than the honey group.	0.001 0.001
Bardellini et al, 2016, Italy.[38]	RCT	Leukemia	Toothbrushing	Fluoride toothpaste (Bioxtraâ) with salivary enzymes, essential oils, proteins, and colostrum extract	32	A pea-sized amount of toothpaste	N/A	Eight days	Oral Hygiene Index	Bioxtraâ toothpaste may be recommended as clinically effective in improving the oral hygiene grade but does not affect the QoL of children undergoing chemotherapy.	<0.001

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Table 3 (Continued).

Study	Study Design	Cancer Type	Oral Care Intervention	Oral care Agent	Sample Size	Doses	Frequency	Length	Tools	Outcomes	p-value
Raphael et al, 2014, Netherland.[39]	RCT	Various	Mouthwash	Caphosol mouth rinse	15	N/A	Two times daily	Five days	The NCI-CTCAE version 3.0 mucositis scoring system.	The total duration of mucositis, the number of days in pain, and analgesic use were significantly longer in the Caphosol group.	>0.05
Soares et al, 2021, Brazil.[40]	RCT	Leukemia	Topical application on oral cavity	Andiroba gel	30	Andiroba gel 3%	Four times daily	Six days	WHO grading scale	A statistically significant reduction in the degree of OM was observed on the fourth, fifth, and sixth days and in the pain scores on the second, third, and fourth days in the andiroba group after the manifestation of OM, compared to the laser group.	<0.05
Kobya Bulut & Güdücü Tüfekci, 2016, Turkey.[41]	Quasi experiment	Leukemia and Lymphoma	Toothbrushing, Mouthwash, lip care, topical application	Honey	37	1gr/kg body weight.	Four times daily	21 days	WHOMAS grading scale	Regular oral care with honey for children undergoing chemotherapy for hematological cancers prevents mucositis and also accelerates recovery of it when it is started after mucositis onset.	<0.05

Honey

Three of the eight reviewed studies used Honey as an agent in oral care. Several studies have shown that using honey has a positive effect on reducing mucositis scores. Al Jaouni et al found that using local Saudi honey on 20 participants in the intervention group resulted in a 35% reduction in grades III and IV oral mucositis in the treatment group (p=0.02) with an NNT (Number Needed to Treat) of 2. This study also found that oral mucositis patients in the treatment group had a significantly shorter hospital stay than those in the control group. Furthermore, Badr et al used manuka honey as an oral care agent to treat mucositis, applying it to the oral mucosa three times a day by an assigned nurse until healing, which lasted seven days. On day 7, the children who received honey (group 1) had a milder grade of oral mucositis, according to the WHO scale, than the control group (F=5.18, p=0.01).

The other study was conducted by Bulut, who administered natural and standardized flower honey to the experimental group in addition to routine and standard oral care provided in the clinic following each chemotherapy session.[41] The study found that children in the honey group experienced a gradual decrease in oral mucositis after the first day of use. There was a significant difference in the degree of OM between follow-up days ($p< 0.05$). The level of OM in control group children increased gradually on days 4, 8, and 12 but decreased slightly on days 16 and 21. There was a significant difference ($p<0.001$) between follow-up days and OM grade.

Olive Oil

Three of the nine articles reviewed used olive oil as a treatment for oral mucositis.[35–37] Based on these three studies, it can be concluded that using olive oil as a topical agent in oral care effectively lowers mucositis scores in cancer children undergoing chemotherapy.

Andiroba

Carapa guianensis Aubl, commonly known as Andiroba, is a tree belonging to the Meliaceae family. It is large and is generally found in the Amazon region. Andiroba is one of the Amazon region's most widely used medicinal plants. It has been used by indigenous peoples and local populations for many years in managing upper respiratory tract infections, dermatitis, skin lesions, secondary skin lesions, boils, abrasions, rheumatism, and as a muscle relaxant. Soares et al found that andiroba gel at a concentration of 3% is the only active substance in the gel composition.[40] The intervention was performed by administering andiroba oral-based 3% to each patient's lesion four times daily (every six hours), following oral hygiene procedures. After applying andiroba oral-based, avoid eating or drinking for at least 60 minutes. As a result, andiroba can effectively reduce the severity and symptoms of oral mucositis pain while showing better Results.

Toothpaste

Toothpaste is an oral care ingredient that is used in conjunction with brushing. Special toothpaste containing fluoride, salivary enzymes, essential oils, proteins, and colostrum extract have been proposed to treat oral mucositis, particularly in cases of xerostomia. One study examined two types of toothpaste for oral care in patients with oral mucositis.[38] The first toothpaste is Bioxtra Toothpaste, which contains saliva enzymes, essential oils, proteins, and colostrum extract. It's the second tooth, specifically fluoride toothpaste without menthol. The quality of life and severity of mucositis were evaluated in this study. The findings revealed that using specific toothpastes like Bioxtra in children with grade 1 or 2 oral mucositis had no significant impact on their quality of life, but it significantly impacted their oral hygiene.

Caphosol

Caphosol is a mouthwash that can help prevent or treat mucositis. One study examined the efficacy of Caphosol mouthwash in pediatric patients by measuring the mucositis grade score and the patient's pain threshold.[39] As a result, the number of hospital days with a mucositis score >grade 1 did not differ significantly between the two study groups: the intervention group with Caphosol and the control group with NaCl 0.9%. The Caphosol group had a longer mean duration of mucositis. Despite similar peak pain levels, the Caphosol group had significantly more pain days. Caphosol users took their analgesics for longer. This study shows that Caphosol is ineffective in treating pediatric patients with oral mucositis caused by cancer therapy.

Aloe Vera

Aloe vera is a plant in the Asphodelaceae family that has been used in medicine, cosmetics, and skincare products. The active components of aloe vera gel include enzymes, vitamins, minerals, hormones, and amino acids. Alkhouli et al investigated the efficacy of aloe vera gel in treating mucositis in children with cancer.[36] This study used an oral sponge to administer the agents used in the three groups (olive oil, aloe vera, and sodium bicarbonate) four times daily for ten days. All children were instructed not to drink, eat, or gargle for 1.5 hours after receiving the agent. According to the findings of this study, the group that received aloe vera gel saw their mucositis score decrease from grade 3 to grade 2 on the WHO oral mucositis grading scale. This result is inferior to that of olive oil but superior to that of sodium bicarbonate. This study concluded that aloe vera is effective for the management of mucositis.

Primary Outcomes

The primary outcome of oral care-based intervention in the management of mucositis in children is a reduction in the severity of mucositis in children. This decrease in the severity of mucositis is characterized by a reduction in score or grading, a decrease in the degree of pain due to mucositis, and a shorter total duration of mucositis. This study found that oral care interventions containing honey effectively reduced the severity of mucositis,[34,41] and the pain associated with mucositis.[37] Meanwhile, three studies that used olive oil in oral care procedures showed that olive oil could reduce the severity of mucositis. It was found that children who received the olive oil had less pain than the control group,[35,36] although not lower than the honey group.[37]

The use of Aloe vera in oral care is also beneficial in managing mucositis, as evidenced by findings indicating differences in mucositis grading before and after Aloe vera administration.[36] Another oral care agent that statistically shows an effect in reducing the severity of mucositis is fluoride toothpaste (Bioxtraâ), which is effective in improving the oral hygiene grade,[38] and Andiroba gel, which can significantly reduce the degree of mucositis and pain caused by mucositis.[40] This study also found that the total duration of mucositis, number of days in pain, and use of analgesics were significantly higher in the Caphosol group.[39] Caphosol rinse is not recommended for the management of mucositis in children.

Secondary Outcomes

This study identified several secondary outcomes from oral care interventions using specific agents in the management of mucositis in children. The secondary outcomes are the child's quality of life and the use of analgesics. Bioxtraâ toothpaste may be recommended as clinically effective in improving the oral hygiene grade, but it does not affect the QoL of children undergoing chemotherapy.[38] Meanwhile, the use of Caphosol rinse as a mouth washing agent in oral care has not been proven to reduce the degree of mucositis, thereby increasing the number of days in pain and analgesics use.[39]

Discussion

Oral mucositis is a painful consequence of chemotherapy as a cancer treatment. This disease progresses from redness of the oral mucosa to intractable ulceration that causes pain, discomfort, and the inability to eat or drink.[44] Among the oral complications of chemotherapy, oral mucositis (OM) is the most debilitating side effect. Oral mucositis associated with immunosuppression can cause serious and potentially life-threatening consequences that interfere with treatment and the patient's quality of life.[38]

Oral mucositis can significantly reduce a patient's quality of life, emphasizing the importance of managing oral health. Mucositis management consists primarily of pain management with topical and oral analgesics/anesthesia and anti-inflammatory agents, systemic use of antifungal drugs, and, most importantly, oral care (daily oral care).[45] Basic oral care refers to all routine actions to reduce bacterial load in the oral cavity, prevent infection, and provide comfort. Oral care practices include mechanical cleaning (brushing and flossing), mouthwash, and lip care.[25]

Our study found that an oral care intervention program carried out in the management of mucositis has several variations. Several studies have completed basic oral care, including mechanical cleaning (brushing), mouth washing, and lip care. However, most of the oral care programs in the included study were incomplete, and they only included brushing teeth alone, mouth washing alone, topical application, or a combination of the three. In fact, MASCC/ISOO recommends that children's mucositis be managed with complete basic oral care, which includes brushing teeth, gargling,

and lip care. This aims to promote optimal oral health to prevent or alleviate mucositis symptoms. The finding of this study shows that oral care intervention is beneficial for the primary outcome, specifically the degree of mucositis, and is beneficial for secondary outcomes, such as pain score, duration of mucositis, and use of analgesics. This cannot be separated from the frequency, duration, and comprehensiveness of the oral care procedure interventions and the effects of the specific agents used in the oral care procedures.

An important finding from this systematic review is that the interventions provided varied in terms of the time and duration of the intervention. This systematic review revealed an important finding: the interventions varied in time and duration. The frequency of oral care varies from two to six times per day. The study highlights that oral care is performed with only one action (in this case, mouthwash) and at a low frequency (twice per day) despite the specific agent Caphosol not affecting or decreasing the severity of mucositis.[39]

The main finding of this study concerns the efficacy of agents used in oral care interventions. This study discovered that the following oral care agents are effective in reducing the severity of mucositis in children: honey, olive oil, aloe vera, Andiroba gel, and Fluoride toothpaste with salivary enzymes, essential oils, proteins, and colostrum extract (Biodextra). Meanwhile, Caphosol did not significantly reduce the severity of mucositis.

Another notable finding is that oral care interventions using specific, appropriate agents, such as honey, olive oil, aloe vera, andiroba gel, and salivary enzyme-containing toothpaste, not only improve the main outcome, namely the severity of mucositis but also improve the outcomes. Others include decreased pain intensity, analgesic use, mucositis duration, and the number of days of pain caused by mucositis.

Honey has long been known to have calming properties and is recommended for treating oral mucositis. Honey is a by-product of floral nectar. Honey has excellent antimicrobial properties, low pH, and high osmolarity. The enzyme oxidase converts glucose into non-cytotoxic hydrogen peroxide at high concentrations. Honey lowers prostaglandin levels in lesions, increases nitric oxide concentrations, and has anti-inflammatory and antioxidant properties.[46] Studies on using honey in the management of mucositis have yielded positive results. In one study, patients with head or neck cancer were instructed to gargle with 20 mL of honey three times a day and then swallow it. The study concluded that this application relieved oral mucositis pain.[47] Other studies have found that honey reduces the severity of oral mucositis.[48,49]

Three studies have shown that olive oil is effective for treating oral mucositis.[35–37] Olive oil reduces the severity of oral mucositis in children and delays its onset. Olive oil's bioactive components and its role in inhibiting many pathobiological steps of oral mucositis may explain its efficacy in prevention. Olive oil is a natural oil derived from olives that contains monounsaturated fatty acids such as oleic acid, which is the most concentrated, followed by palmitic acid, linoleic acid, and stearic acid. Apart from fatty acids, phenolic compounds account for a significant portion of olive oil's composition. Monounsaturated fatty acids inhibit inflammation by influencing biomarkers.[50] Olive oil can form a layer on the oral mucosa, improving lubrication, reducing microorganism retention, and increasing saliva buffering capacity.[51] Ahmad et al found that olive oil leaf extract effectively treated chemotherapy-induced mucositis by decreasing the expression of several pro-inflammatory cytokines.[52]

Furthermore, this study discovered that andiroba gel is an effective oral care agent for reducing mucositis scores. *Carapa guianensis Aubl*, also known as andiroba, is a large *Meliaceae family* tree commonly found in the Amazon region.[43] Andiroba is one of the most widely used medicinal plants in the Amazon. Indigenous peoples and residents have used it for many years to treat upper respiratory tract infections, dermatitis, skin lesions, secondary skin lesions, boils, abrasions, rheumatism, and muscle relaxants. Soares et al found that starting treatment with andiroba significantly reduced the severity of oral mucositis on the fourth, fifth, and sixth days, as well as the level of pain on the second, third, and fourth days ($p<0.05$).[40] The andiroba group's oral mucositis scores were also lower on other days. Furthermore, on the eighth day of follow-up, no patients in the andiroba group reported pain, resulting in an average pain score of zero. Again, on the ninth day of follow-up, no patient in the andiroba group demonstrated symptoms of oral mucositis. Other study reported additional evidence supporting andiroba oil's therapeutic potential, indicating that its use reduces the severity of oral mucositis and speeds up the healing process.[43]

Aloe vera is another effective treatment for mucositis. Aloe Vera has numerous beneficial properties. Aloe vera suppresses inflammation by reducing macrophage adhesion, which interferes with the responsible cytokines and aids in wound healing. Topical application of Aloe Vera and olive oil was influential in treating oral mucositis.[36] No significant

differences were found between *Aloe Vera* versus olive oil or Aloe Vera versus sodium bicarbonate. However, the findings of this study are consistent with many previous studies, which found that Aloe Vera effectively prevented or treated chemotherapy-induced oral mucositis.[53]

Some of the agents in this study were used as mouthwash or lip/mouth topical care. However, there is one study that shows that toothpaste contains lysozyme, lactoferrin, lactoperoxidase, colostrum purified stan- dardized extract, sorbitol, xylitol, isoceteth-20, sodium monoflu- orophosphate, hydroxyethylcellulose, sodium benzoate, and titanium dioxide, is beneficial for improving the oral hygiene index in children who experience mucositis.[38] The pathogenesis of chemotherapy-induced OM appears to be related to oxidative stress induced by the treatment. The reactive oxygen species (ROS) cause direct and indirect damage through transcription factors, which induce the production of pro-inflammatory cytokines.[38] Bio-inspired and biomimetic action in toothpaste containing enzymes is effective for oral health care to avoid disrupting the ecological balance in the oral cavity, particularly in conditions like oral mucositis where the oral mucosa should be protected. Bardellini's study mentioned that toothpaste containing salivary enzymes was useful for improving the oral hygiene index, but it did not significantly affect quality of life.[38] This could be because the oral care intervention using toothpaste only lasted eight days; additionally, the study reported that most patients reported not brushing their teeth for at least two consecutive days due to pain and burning, resulting in poor patient adherence. The lack of impact on the child's quality of life may be due to attitudes toward oral care interventions.

Strength and Limitation

This systematic review has some limitations. The majority of the studies in this review are from Asia and Eurasia, particularly Turkey, Lebanon, Saudi Arabia, and Syria. Other studies come from Europe, specifically Italy and the Netherlands, as well as South America, specifically Brazil, so it does not include studies that represent several other continents, such as Africa and Australia, so the diversity of respondents' social and cultural characteristics is limited. This review focuses on oral care interventions and the oral agents that are used within oral care practices. As a result, other studies that used agents administered directly or not integrated into oral care were excluded from this study. This is related to MASCC/ISOO's recommendation that basic oral care protocols be implemented in the pediatric population despite a lack of high-level evidence studies and that agents or products used to manage mucositis be integrated into oral care practices.

Despite its limitations, this study offers several benefits that should be recognized. The study employed a comprehensive search strategy and a systematic data extraction and quality assessment procedure. Aside from that, the majority of the studies included a homogeneous population, specifically children with leukemia, with the exception of two studies involving general child cancer participants. This study identifies the oral care agents used and the type of oral care program implemented in each included study. Aside from that, the severity of mucositis was assessed in this study, with the majority of participants using the same instrument, the WHO mucositis scale. This study also demonstrates that, in addition to the primary outcome, the severity of mucositis, other outcomes such as duration of mucositis, duration of pain, duration of analgesic use, and quality of life of children were identified as effects of oral care-based intervention. Thus, the study's findings provide some strong indications of the role of oral care intervention using appropriate specific in managing mucositis in children.

Conclusion

Our study highlights that oral care interventions are beneficial in managing mucositis among cancer children. This study shows that oral care intervention using specific agents, including honey, vitamin E, olive oil, andiroba gel, aloe vera gel, and toothpaste containing saliva enzymes, essential oils, proteins, and colostrum extract, positively impact mucositis management for children with cancer. This study found that, in addition to reducing the severity of mucositis, oral care intervention with the appropriate specific agent has other benefits, such as lowering pain scores, shortening the duration of mucositis, and reducing the use of analgesics. However, it did not significantly improve the child's quality of life. These findings indicate that an oral care intervention utilizing appropriate specific agents should be implemented to improve cancer care for children with cancer.

Ethics Approval and Content to Participate

This systematic review article involved no subjects; hence, no ethical approval was required or attached.

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Disclosure

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