Bicarbonate versus Alternative Treatments in Chemotherapy Oral Mucositis in Children: A Systematic Review of Randomized Clinical Trials

ABSTRACT

Aims: To investigate the effectiveness of alternative treatments (honey, olive oil, aloe vera) in children with chemotherapy-induced oral mucositis, compared to the use of sodium bicarbonate.
Study design: The study consists of a systematic and qualitative review using the PRISMA 2020 guidelines through a search for articles was conducted in May 2024 in the PubMed, VHL, Embase and Google Scholar databases, with the following terms in the search strategy: Mucositis AND Child AND Chemotherapy AND Clinical Trial, including clinical trials that met the eligibility criteria.
Results: Three randomized clinical trials comparing the use of olive oil, honey and aloe vera with sodium bicarbonate were analyzed and classified as moderate risk of bias. The alternative treatments were effective in reducing oral mucositis and delaying its onset, with statistically significant differences in relation to bicarbonate.
Conclusion: It seems that honey, olive oil and aloe vera may be a promising approach to minimizing the symptoms of this condition, as well as being more accessible and practical options for improving patients' quality of life.

Keywords: Oral mucositis, children, alternative treatment, sodium bicarbonate

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1. INTRODUCTION

Oral mucositis (OM) is a debilitating inflammatory condition of the oral mucosa that can affect patients undergoing cancer chemotherapy and/or radiotherapy.1,2 It is characterized by ulceration and inflammation, causing erythema, intense pain, dysphagia and consequent weight loss, local infection, as well as a reduction in the quality of life of affected patients.2,3 Studies show that around 40% of patients undergoing chemotherapy can develop MO, and around 90% when combined with radiotherapy.1,2,4 The incidence of malignant tumors varies according to age group. In children aged 0 to 14, the rate is around 40.6 per million person-years,5,6 which is three times higher than in adults.7 This is due to the higher proliferative fraction of basal cells in children.6

Nowadays, alternative medicine is increasingly being used in various areas of health, including dentistry. Alternative practices such as music therapy, homeopathy, aromatherapy and herbal medicine represent a set of medical care that acts as a complement to conventional treatments, providing greater well-being and quality of life to patients.8

There is no consensus on the most effective preventive and therapeutic strategies for OM, however, laser therapy, analgesics, anti-inflammatories, antibiotics and medications are commonly used.9,12 According to Devi et al,13 the most common treatment today is gargling with warm water, salt and sodium bicarbonate four times a day, associated with oral hygiene. Another preventive approach includes daily oral assessment, oral hygiene every four hours, application of 0.12% chlorhexidine with a disposable sponge and moisturizing gel for the mucosa and lips.13

Alternative therapies promote a significant reduction in the severity of OM. The literature identifies cryotherapy, the use of amifostine, hydrolytic enzymes, ice chips and the electrolytic solution Caphosol.14,15 The use of integrative methods such as honey, extra virgin olive oil and aloe vera (Aloe barbadensis Miller) stands out.14 These methods are promising due to the properties present in each product used, as well as the fact that they have been used since ancient times for medicinal purposes.4 Honey, olive oil and aloe vera have significant results due to their healing, antioxidant, anti-inflammatory and antimicrobial properties.10,16

Although all these available therapies have been identified, there is no standard treatment for OM.9,12 Although there is a need to improve knowledge about its prevention and treatment, the literature is still scarce.9 Therefore, the lack of an effectively effective, valid and accessible system for preventing and treating OM in children raises the need for more evidence. Therefore, this study aims to present a qualitative systematic review on the effectiveness of alternative treatments with aloe vera, olive oil and honey compared to sodium bicarbonate in the treatment of OM in pediatric patients undergoing chemotherapy, as more accessible and promising alternatives.

This systematic review addresses a critical knowledge gap, providing high-quality evidence to inform clinical practice and guideline development for the management of chemotherapy-induced oral mucositis in pediatric cancer patients. The findings contribute to the advancement of evidence-based medicine, shaping the future of pediatric oncology care.

2. MATERIAL AND METHODS / EXPERIMENTAL DETAILS / METHODOLOGY

This study is a systematic, qualitative literature review using the PRISMA 2020 guidelines.17 The following question was posed: Are alternative treatments with honey, olive oil and aloe vera effective in treating oral mucositis in children compared to sodium bicarbonate? Thus, the PICOS strategy (Population/Patient, Intervention, Comparator and Outcomes, Study design) consists of: Patient: Children undergoing chemotherapy with oral mucositis, Intervention: Alternative treatments (honey, olive oil and aloe vera) for oral mucositis, Comparison: Sodium bicarbonate, Outcomes: Efficacy, prevention and impact on the quality of life of the children in the clinical trials, Studies: Clinical trials in children. Research Ethics Committee approval was not required as this article is a literature review.

2.1 Search strategy

An electronic search for articles was carried out in May 2024, with no restrictions on language, date of publication or country of origin. The databases used were: PubMed, VHL and Embase, with the following terms in the search strategy: Mucositis AND Child AND Chemotherapy AND Clinical Trial. In addition, Google Scholar (gray literature) was searched. The references of the included articles were reviewed to cover possible additional studies that were not found in the initial search.

2.2 Eligibility criteria

Clinical trials in children, randomized or not, that used alternative treatments such as honey, olive oil and aloe vera for oral mucositis due to chemotherapy, compared to the use of sodium bicarbonate, were included. Other types of studies were excluded.

2.3 Study selection

A detailed evaluation of the articles selected for the study was carried out, taking into account the objectives of this research. Initially, searches were carried out in the predefined databases, according to the search strategies. All the results were entered into the citation manager for inclusion in the Rayyan program, where duplicates were excluded, and

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the title and abstract were read, excluding the articles that did not meet the criteria. Subsequently, the selected studies were read in full and included or excluded after independent peer review (HCS, MFSM). When there was no consensus among the peers regarding the inclusion or exclusion of a study, a third reviewer (GFR) was consulted. The following parameters were observed: author/year, study design, sample size, interventions (alternative treatments and use of sodium bicarbonate), results/conclusions.

The CONSORT (Consolidated Standards of Reporting Trial) guidelines were used to assess the quality of clinical trials. The following criteria were established: sample size, randomization, allocation concealment, blinding and loss to follow-up.[18] The criterion was considered adequate "A" when it was reported by the authors and explained; if it was only mentioned and not explained, it was established as "B"; and "C" if it was not mentioned. The studies were classified into levels of quality of evidence: I (high), II (moderate) and III (low). The clinical trial that met all the criteria with an "A" classification or only one "B" was given level I. A study in which all items were rated "A" or "B" and only one item with a "C" was classified as level II. Finally, it was classified as level III when more than one item received a "C" rating.[19]

2.4 Protocol and Registration

The review was organized based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. It was also registered in the PROSPERO international prospective registry of systematic reviews with the registration code CRD42024549591.

3. RESULTS AND DISCUSSION

Initially, 271 articles were found in the databases. After removing duplicates, 214 articles were selected based on titles and abstracts. A total of 38 studies remained for full-text evaluation, and three articles were selected for the final qualitative synthesis work as shown in the flowchart (Figure 1).

Figure 1: Flowchart demonstrating article screening

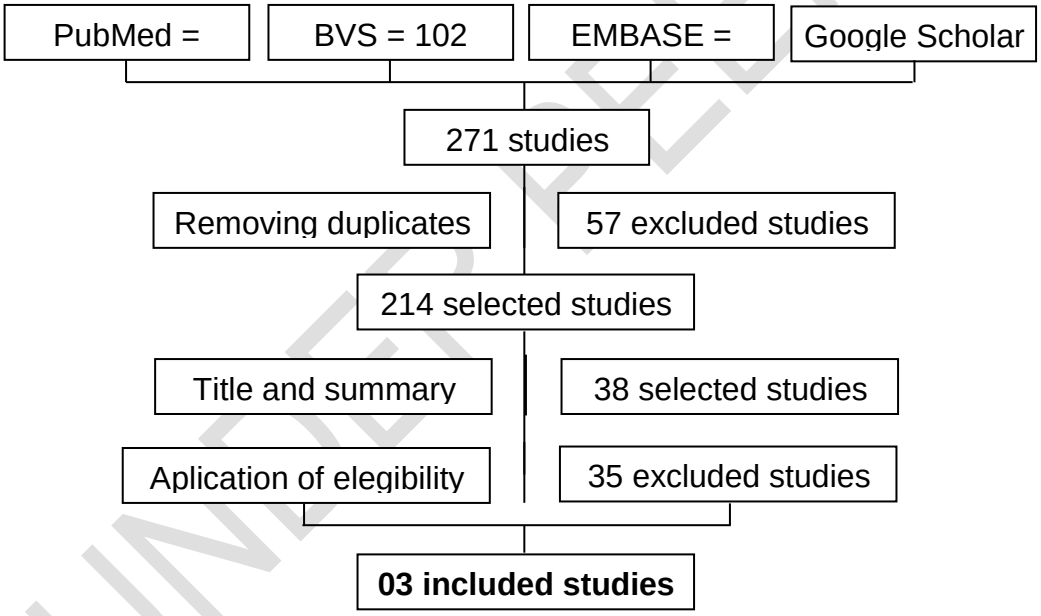

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Table 1: Characteristics of the Selected Studies

Author / Year	Study Design	Sample	Interventions	Evaluations / Follow-up	Results / Conclusions	Country
Alkhouli *et al.*, 2019	RCT Triple Blind	24 patients MA: 4/6 years	CG: NaHCO3 5% TG: Olive Oil Topical use	WHO Scale 1x / week for 2 months	1 week: TG = CG 2 week: TG ≠ CG (Better olive oil)	Australian
Alkhouli *et al.*, 2019	RCT Triple Blind	26 patients MA: 3/6 years	CG: NaHCO3 5% TG: Aloe Vera Solution 70% Topical use	WHO Scale 1x / week for 2 months	Between groups: TG = CG in weeks 1,5,6,8 TG ≠ CG in weeks 2,3,4,7 (Aloe Vera best)	New Zealand
Badr *et al*., 2022	RCT Single Blind	26 patients MA: 3/6 years	CG: NaHCO3 3% TG1:Honey TG2: Olive Oil EV Mouthwash	WHO Scale Pain: VAS Every day until cure or day 7	TG1 / TG2 = OM less severe and less pain than CG	Middle East

Reference: Belém et al., 2021. Abbreviations: RCT = Randomized Clinical Trial EV = Extra Virgin, VAS = Visual Analogue Scale, CG = Control Group, TG = Test Group, MA = Mean Age, OM = Oral Mucositis, NaHCO3 = Sodium Bicarbonate, WHO = World Health Organization.

The three studies selected[3,10,16] were Randomized Clinical Trials (RCTs) in which the age of the participants ranged from 3 to 17 years and the sample size ranged from 24 to 42 patients. All the studies described how the sample size was calculated.

The efficacy of olive oil was investigated in two studies.[10,16] In one of these, delayed OM was observed,[11] while the other compared the efficacy of olive oil and honey on severity and pain.[4] Aloe vera, on the other hand, was evaluated in palliative care.[3] These studies differed in the application of the substances and all used the World Health Organization rating scale to assess the oral mucosa during the interventions.[310,16]

The three studies compared alternative treatments to 5% sodium bicarbonate in the prevention of chemotherapy-induced OM. According to the data analyzed in the study by Alkhouli et al,[10] there was less severity of the lesions in the olive oil group and a statistically significant difference in relation to sodium bicarbonate. Furthermore, in the olive oil group, OM started later, also with a statistically significant difference. Therefore, olive oil delayed the onset of OM compared to sodium bicarbonate. The study covering honey and olive oil obtained results compatible with the previous study, as both obtained less severe OM and less pain compared to the sodium bicarbonate group,[3] with statistically significant differences. Similarly, the use of Aloe Vera has shown superior results to sodium bicarbonate in reducing the severity of OM and delaying the appearance of lesions.[16]

The three articles presented a moderate and medium level of scientific evidence as shown in table 2.[3,10,16]

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Table 2: Classification of Levels of Evidence and Justifications

Author / Year	Sample Calculation	Randomization	Allocation concealment	Blinding	Losses in follow-up	LE
Alkhouli *et al.*, 2019	**A**: reported calculation	**A**: by computer (www.random.org)	**C**: NM	**A**: Triple Blind	**A**: reported and explained	II
Alkhouli *et al.*, 2019	**A:** reported calculation	**A**: by computer (www.random.org)	**C**: NM	**A**: Triple Blind	**A**: reported and explained	II
Badr *et al*., 2023	**A**: reported calculation	**A**: by a statistician not involved in the study	**C**: NM	**B**: Single Blind	**A**: reported and explained	II

Reference: Belém et al., 2021. Abbreviations: LE = Level of Evidence, NM = Not Mentioned

This review aimed to evaluate the effectiveness of alternative treatments with olive oil, honey and aloe vera compared to sodium bicarbonate in the treatment of OM in pediatric patients undergoing chemotherapy. Based on the established eligibility criteria, three studies were found that used these therapies compared to the most common treatment. Thus, following the criteria previously established for assessing methodological quality, all three articles were classified as level II scientific evidence, i.e. moderate risk of bias.

Based on the bibliographic reference of this review, studies[3,10,16] were classified as Level II evidence, due to the lack of reporting of allocation concealment, resulting in a "C" classification in this aspect. However, the other criteria such as sample calculation, randomization, blinding and loss to follow-up were adequately reported, receiving an "A" rating. Allocation concealment is crucial to avoid bias in the selection of research groups and to mitigate the overestimation of results.[21]

Several supportive therapy options are currently available for the prevention and treatment of OM. However, these therapies have limitations and are not completely effective.[1,22,23] The treatment commonly used combines oral hygiene with gargling with a solution of warm water, salt and sodium bicarbonate, administered four times a day.[13] Sodium bicarbonate acts as an alkalizing agent, reducing irritation and inflammation of the oral mucosa, as well as having antiseptic properties, which promotes pain relief, better healing and prevention of infections.[24,25]

Olive oil, extracted from the fruit of the olive tree, has active components that aid wound healing and can be applied both topically and systemically.[16] One RCT demonstrated the efficacy of olive oil in the management of OM, with significant improvements observed after treatment.[16] Additional observational studies highlight the beneficial role of olive oil in the treatment or prevention of OM.[26,27] These findings corroborate the results of the studies reviewed, indicating that OM was less severe in patients treated with olive oil compared to sodium bicarbonate.

Honey has antioxidant, anti-inflammatory and antimicrobial properties, promoting rapid tissue healing, which makes it effective for patients with chemotherapy-induced OM.[28] Studies have shown a significant reduction in symptom severity and length of hospital stay,[29] in line with the results of Badr et al.[3] After reviewing 17 RCTs, Yang et al.[30] concluded that honey as an adjuvant treatment for OM is safe and effective. In addition, a RCT involving 150 children showed greater efficacy of honey compared to chlorhexidine,[31] while observational studies also confirm its efficacy compared to analgesic and antiseptic gel.[7,32] This evidence highlights honey as an effective, accessible and low-cost treatment, as does Badr et al.[3]

Aloe vera, a medicinal plant used for thousands of years, has various therapeutic properties, including analgesic, antifungal, anti-inflammatory, antiproliferative, anticancer and immunomodulatory actions.[33] These actions probably contributed to the positive results observed in the study,[15] consistent with other studies. A clinical trial in patients with lymphoma and leukemia demonstrated a reduction in the intensity and pain of OM by topical application of aloe vera,[34] supported by in vitro studies suggesting wound healing.[35] Also, a systematic review with meta-analysis confirmed the benefits of aloe vera in reducing the severity of OM.[36]

However, three RCTs found no significant differences when using aloe vera to treat chemotherapy-induced MO.[37,39] In one of these studies, there was no improvement in tolerance to radiotherapy and no reduction in mucositis or pain.[37] In the other two, despite there being no significant difference compared to placebo, benefits were observed in the relief of MO and side effects.[38,39]

As mentioned in the previous paragraphs, studies were found with promising results in the use of alternative treatments, but some limitations were identified. The scarcity of scientific literature on integrative practices in the treatment of OM, the lack of studies with a high level of evidence and the absence of a standard protocol. Therefore, there is a need for more careful clinical trials in the description of their methods and greater attention to the use of herbal medicines in the treatment of OM. Nevertheless, the lack of a consolidated protocol for the treatment of OM reinforces the importance of new studies to establish more robust therapeutic guidelines.

However, this study stands out for its many strengths. Firstly, it is a systematic review that carried out a thorough search of the literature, including up-to-date studies. In addition, only RCTs were considered, which significantly raises the level

of relevance, since these studies are considered the gold standard in scientific evidence, providing scientific rigor, control and minimization of bias, resulting in a more reliable and relevant analysis for clinical practice.
One of the limitations of this study was the lack of primary studies on the subject, thus encouraging new randomized clinical trials to be developed. Such alternative practices can provide better well-being, reduce discomfort and improve the quality of life of patients during treatment.

4. CONCLUSION

Based on this systematic review, although the studies investigating alternative treatments (honey, olive oil and aloe vera) presented a moderate risk of bias, they demonstrated effectiveness compared to the most common treatment (sodium bicarbonate) in the management of MO in pediatric patients undergoing chemotherapy. These alternative therapies not only offer a promising approach to minimizing the symptoms of the condition, but may also represent more accessible and viable options for improving the quality of life of these patients.

Disclaimer (Artificial intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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REFERENCES

1. PULITO C, CRISTAUDO A, PORTA CL, ET AL. ORAL MUCOSITIS: THE HIDDEN SIDE OF CANCER THERAPY. J EXP CLIN CÂNCER RES. 2020; 39(210): 1-15. DOI: 10.1186/S13046-020-01715-7

2. COLELLA G, BOSCHETTI CE, VITAGLIANO R, ET AL. INTERVENTIONS FOR THE PREVENTION OF ORAL MUCOSITIS IN PATIENTS RECEIVING CANCER TREATMENT: EVIDENCE FROM RANDOMISED CONTROLLED TRIALS. CURR ONCOL, 2023; 30(1):967-980. DOI: 10.3390/CURRONCOL30010074

3. BADR LK, EL ASMAR R, HAKIM S, ET AL. THE EFFICACY OF HONEY OR OLIVE OIL ON THE SEVERITY OF ORAL MUCOSITIS AND PAIN COMPARED TO PLACEBO (STANDARD CARE) IN CHILDREN WITH LEUKEMIA RECEIVING INTENSIVE CHEMOTHERAPY: A RANDOMIZED CONTROLLED TRIAL. J PEDIATR NURS, 2023; 70(1):E48-E53. DOI: 10.1016/J.PEDN.2022.12.003

4. SANT ANA G, NORMANDO AGC, DE TOLEDO I. ET AL. TOPICAL TREATMENT OF ORAL MUCOSITIS IN CANCER PATIENTS: A SYSTEMATIC REVIEW OF RANDOMIZED CLINICAL TRIALS. ASIAN PAC J CANCER PREV, 2020; 21(7):1851-1866. DOI: 10.31557/APJCP.2020.21.7.1851

5. FOUCHER-ESTLIAROVA E, COLLOMBET M, RIES LAG, ET AL. INTERNATIONAL INCIDENCE OF CHILDHOOD CANCER, 2001-10: A POPULATION-BASED REGISTRY STUDY. LANCETA ONCOL, 2017; 18(6):719–31. DOI: 10.1016/S1470-2045(17)30186-9

6. DOCIMO R, ANASTASIO MD, BENSI C. CHEMOTHERAPY-INDUCED ORAL MUCOSITIS IN CHILDREN AND ADOLESCENTS: A SYSTEMATIC REVIEW. EUR ARCH PAEDIATR DENT, 2022; 23:501–511. DOI: 0.1007/S40368-022-00727-5

7. MUNIZ AB, HOLANDA MAR, ABREU KN, ET AL. ORAL MUCOSITIS IN CHILDREN WITH CANCER: DIFFICULTIES OF EVALUATION AND EFFECTIVE THERAPY. RESEARCH, SOCIETY AND DEVELOPMENT, 2021; 10(11):1-10. DOI: 10.33448/RSD-V10I

8. LITTLE JW. COMPLEMENTARY AND ALTERNATIVE MEDICINE: IMPACT ON DENTISTRY. ORAL SURG ORAL MED ORAL PATHOL ORAL RADIOL ENDOD, 2004 ;98(2):137-45. DOI: 10.1016/J.TRIPLEO.2004.05.011.

9. DINIZ GS, FELÍCIO LMP, GUIMARÃES JP. INFLUENCE OF LOW-LEVEL LASER ON ORAL MUCOSITIS TREATMENT IN YOUNG CANCER PATIENTS UNDERGOING CHEMOTHERAPY: A SYSTEMATIC REVIEW. REVISTA GAÚCHA DE ODONTOLOGIA, 2023; 71:1-9. DOI: 10.1590/1981-86372023004520230028

10. ALKHOLI M, LAFLOUF M, ALHADDAD M. EVALUATION OF THE EFFECTIVENESS OF OLIVE OIL TO PREVENT CHEMOTHERAPY INDUCED ORAL MUCOSITIS: A RANDOMIZED CONTROLLED CLINICAL TRIAL. PEDIATRIC DENTAL JOURNAL, 2019; 29(3):123–131. DOI: 10.1016/J.PDJ.2019.08.001

11. CIDON U. E. CHEMOTHERAPY INDUCED ORAL MUCOSITIS: PREVENTION IS POSSIBLE. CHINESE CLINICAL ONCOLOGY, 2018; 7(1):6-11. DOI: 10.21037/CCO.2017.10.01

12. GARROCHO-RANGEL JÁ, HERRERA-MONCADA M, MÁRQUEZ-PRECIADO R, ET AL. ORAL MUCOSITIS IN PAEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS RECEIVING METHOTREXATE-BASED CHEMOTHERAPY: CASE SERIES. EUROPEAN JOURNAL OF PAEDIATRIC DENTISTRY, 2018; 19(3):239-242. DOI: 10.23804/EJPD.2018.19.03.13

13. DEVI KS, ALLENIDEKANIAB A. THE RELATIONSHIP OF ORAL CARE PRACTICE AT HOME WITH MUCOSITIS INCIDENCE IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA. COMPREHENSIVE CHILD AND ADOLESCENT NURSING, 2019; 42(1):56–64. DOI: 10.1080/24694193.2019.1577926

14. ALLEN G, LOGAN R, GUE S. ORAL MANIFESTATIONS OF CANCER TREATMENT IN CHILDREN: A REVIEW OF THE LITERATURE. CLIN J ONCOL NURSE, 2010; 14(4):481-490. DOI: 10.1188/10.CJON.481-490

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15. BOURDELIN M, DAGUINDAU E, LAROSA F, ET AL. LA MUCITE POST-ALLOGREFFE DE CELLULES SOUCHES HÉMATOPOÏÉTIQUES: FACTEURS DE RISQUE, CONSÉQUENCES CLINIQUES ET PRÉVENTION. PATHOL BIOL, 2015; 63:106-110. DOI: 10.1016/J.PATBIO.2014.11.001

16. ALKHOULI M, LAFFOUL M, ALHADDAD M. EFFICACY OF ALOE-VERA USE FOR PREVENTION OF CHEMOTHERAPY-INDUCED ORAL MUCOSITIS IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA: A RANDOMIZED CONTROLLED CLINICAL TRIAL. COMPR CHILD ADOLESC NURS, 2021; 44(1):49-62. DOI: 10.1080/24694193.2020.1727065

17. PAGE MJ, MCKENZIE JE, BOSSUYT PM, ET AL. THE PRISMA 2020 STATEMENT: AN UPDATED GUIDELINE FOR REPORTING SYSTEMATIC REVIEWS. BMJ, 2021; 372:71-383. DOI: 10.1136/BMJ.N71

18. MOHER D, HOPEWELL S, SCHULZ KF, ET AL. CONSORT 2010 EXPLANATION AND ELABORATION: UPDATED GUIDELINES FOR REPORTING PARALLEL GROUP RANDOMIZED TRIALS. INT J SURG, 2012; 10(1):28-55. DOI: 10.1016/J.IJSU.2011.10.001

19. TORRES AS, MARTINS OBL, OTONI RP, ET AL. EFFECTIVENESS OF CYANOACRYLATE IN THE TREATMENT OF DENTIN HYPERSENSITIVITY: A SYSTEMATIC REVIEW. INTERNATIONAL JOURNAL OF DENTISTRY, 2023; 1:1-7. DOI: 10.1155/2023/1465957

20. BELEM LM, SILVA LDA, DOUGLAS-DE-OLIVEIRA DW, ET AL. USO DA LASERTERAPIA NO TRATAMENTO DE PACIENTES COM PARALISIA DE BELL: REVISÃO CRÍTICA DA LITERATURA. REVISTA PORTUGUESA DE ESTOMATOLOGIA, MEDICINA DENTÁRIA E CIRURGIA MAXILOFACIAL, 2021; 62(2):81-86. DOI: 10.24873/J.RPEMD.2021.06.832

21. REIS FB, LOPES AD, FALOPPA F, CICONELLI RM. A IMPORTÂNCIA DA QUALIDADE DOS ESTUDOS PARA A BUSCA DA MELHOR EVIDÊNCIA. REV BRAS ORTOP, 2008; 43(6):209-216. DOI: 10.1590/S0102-36162008000600001

22. MÜNSTEDT K, MOMM F, HÜBNER J. HONEY IN THE MANAGEMENT OF SIDE EFFECTS OF RADIOTHERAPY- OR RADIO/CHEMOTHERAPY-INDUCED ORAL MUCOSITIS. A SYSTEMATIC REVIEW. COMPLEMENT THER CLIN PRACT. 2019; 34:145-152. DOI: 10.1016/J.CTCP.2018.11.016

23. KUHN A, PORTO FA, MIRAGLIA P, BRUNETTO AL. LOW-LEVEL INFRARED LASER THERAPY IN CHEMOTHERAPY-INDUCED ORAL MUCOSITIS: A RANDOMIZED PLACEBO CONTROLLED TRIAL IN CHILDREN. J PEDIATR HEMATOL ONCOL, 2009; 31(1):33-38. DOI: 10.1097/MPH.0B013E318192CB8E

24. CAWLEY MM, BENSON LM. CURRENT TRENDS IN MANAGING ORAL MUCOSITIS. CLIN J ONCOL NURS, 2005; 9(5):584-592. DOI: 10.1188/05.CJON.584-592

25. CHENG KK, MOLASSIOTIS A, CHANG AM, WAI WC, CHEUNG SS. EVALUATION OF AN ORAL CARE PROTOCOL INTERVENTION IN THE PREVENTION OF CHEMOTHERAPY-INDUCED ORAL MUCOSITIS IN PEDIATRIC CANCER PATIENTS. EUR J CANCER, 2001; 37(16):2056-2063. DOI: 10.1016/S0959-8049(01)00098-3

26. FOSCOLOU A, CRITSELIS E, PANAGIOTAKOS D. OLIVE OIL CONSUMPTION AND HUMAN HEALTH: A NARRATIVE REVIEW. MATURITAS, 2018; 118:60–66. DOI: 10.1016/J.MATURITAS.2018.10.013

27. PARKINSON L, KEAST R. OLEOCANTHAL, A PHENOLIC DERIVED FROM VIRGIN OLIVE OIL: A REVIEW OF THE BENEFICIAL EFFECTS ON INFLAMMATORY DISEASE. INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES, 2014; 15(7):12323–12334. DOI: 10.3390/IJMS150712323

28. KARIMI Z, BEHNAMMOGHADAM M, RAFIEI H, ABDI N, ZOLADL M, TALEBIANPOOR MS.; ET AL. IMPACTO DO AZEITE E DO MEL NA CICATRIZAÇÃO DO PÉ DIABÉTICO: UM ENSAIO CLÍNICO RANDOMIZADO. CLINICAL, COSMETIC AND INVESTIGATIONAL DERMATOLOGY, 2019; 12:347–354. DOI: 10.2147/CCID.S198577

29. ANDRIAKOPOULOU CS, YAPIJAKIS C, KOUTELEKOS I, PERDIKARIS P. PREVENTION AND TREATMENT OF ORAL MUCOSITIS IN PEDIATRIC PATIENTS: SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS. IN VIVO, 2024; 38(3):1016-1029. DOI: 10.21873/INVIVO.13535

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30. YANG C, GONG G, JIN E. ET AL. TOPICAL APPLICATION OF HONEY IN THE MANAGEMENT OF CHEMO/RADIOTHERAPY-INDUCED ORAL MUCOSITIS: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS. INTERNATIONAL JOURNAL OF NURSING STUDIES, 2019; 89:80-87. DOI: 10.1016/J.IJNURSTU.2018.08.007

31. KONUK SENER D, AYDIN M, CANGUR S, GUVEN E. THE EFFECT OF ORAL CARE WITH CHLORHEXIDINE, VITAMIN E AND HONEY ON MUCOSITIS IN PEDIATRIC INTENSIVE CARE PATIENTS: A RANDOMIZED CONTROLLED TRIAL. JOURNAL OF PEDIATRIC NURSING, 2019; 45:E95-E101. DOI: 10.1016/J.PEDN.2019.02.001

32. SINGH R, SHARMA S, KAUR S, ET AL. EFFECTIVENESS OF TOPICAL APPLICATION OF HONEY ON ORAL MUCOSA OF CHILDREN FOR THE MANAGEMENT OF ORAL MUCOSITIS ASSOCIATED WITH CHEMOTHERAPY. INDIAN JOURNAL OF PEDIATRICS, 2019; 86(3):224-228. DOI: 10.1007/S12098-018-2733-X

33. FERREIRA AS, MACEDO C, SILVA AM, ET AL. NATURAL PRODUCTS FOR THE PREVENTION AND TREATMENT OF ORAL MUCOSITIS - A REVIEW. INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES, 2022; 23(8):4385-4396. DOI: 10.3390/IJMS23084385

34. MANSOURI P, HAGHIGHI M, BEHESHTIPOUR N, RAMZI M. THE EFFECT OF ALOE VERA SOLUTION ON CHEMOTHERAPY-INDUCED STOMATITIS IN CLIENTS WITH LYMPHOMA AND LEUKEMIA: A RANDOMIZED CONTROLLED CLINICAL TRIAL. INT J COMMUNITY BASED NURS MIDWIFERY, 2016; 4(2):119-126.

35. HEGGIE S, BRYANT GP, TRIPCONY L, KELLER J, ROSE P, GLENDENNING M, HEATH J. A PHASE III STUDY ON THE EFFICACY OF TOPICAL ALOE VERA GEL ON IRRADIATED BREAST TISSUE. CANCER NURSING, 2002; 25(6): 442-451. DOI: 10.1097/00002820-200212000-00007

36. LIMA ICGDS, DE FÁTIMA SML, GUEIROS LAM, ET AL. CLINICAL APPLICABILITY OF NATURAL PRODUCTS FOR PREVENTION AND TREATMENT OF ORAL MUCOSITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS. CLINICAL ORAL INVESTIGATIONS, 2021; 25(6):4115-4124. DOI: 10.1007/S00784-020-03743-1

37. SU CK, MEHTA V, RAVIKUMAR L, ET AL. PHASE II DOUBLE-BLIND RANDOMIZED STUDY COMPARING ORAL ALOE VERA VERSUS PLACEBO TO PREVENT RADIATION-RELATED MUCOSITIS IN PATIENTS WITH HEAD-AND-NECK NEOPLASMS. INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY BIOLOGY PHYSICS, 2004;.60:171-177. DOI: 10.1016/J.IJROBP.2004.02.012

38. PUATAWEEPONGA P, DHANACHAIA M, DANGPRASERTA S, ET AL. THE EFFICACY OF ORAL ALOE VERA JUICE FOR RADIATION INDUCED MUCOSITIS IN HEAD AND NECK CANCER PATIENTS: A DOUBLE-BLIND PLACEBO-CONTROLLED STUDY. ASIAN BIOMEDICINE, 2009; 3(4):375–382. DOI:

39. SAHEBJAMEE M, MANSOURIAN A, HAJIMIRZAMOHAMMAD M, ET AL. COMPARATIVE EFFICACY OF ALOE VERA AND BENZYDAMINE MOUTHWASHES ON RADIATION-INDUCED ORAL MUCOSITIS: A TRIPLE-BLIND, RANDOMIZED, CONTROLLED CLINICAL TRIAL. ORAL HEALTH & PREVENTIVE DENTISTRY, 2015; 13(4):309–315. DOI: 10.3290/J.OHPD.A33091

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