Revista Eletrônica
Acervo Saúde
Electronic Journal Collection Health ISSN 2178-2091

Efficacy of apitherapy for the treatment of oral mucositis in cancer patients: a systematic review and meta-analysis

Eficácia de apiterapia no tratamento da mucosite oral em pacientes com câncer: uma revisão sistemática e meta-análise

Eficacia de la apiterapia para el tratamiento de la mucositis oral en pacientes con cáncer: una revisión sistemática y un metanálisis

Fernanda Suely Barros Dantas[1], Katarina Haluli Janô da Veiga Pessoa[1], Tácio Fragoso Pereira[1], Fernanda Gabriela Delfino Ferreira Oliveira[1], Mariana de Moraes Corrêa Perez[1], Sarah Rachel Cavalcante Bezerra Melo[1], Pedro Henrique da Hora Sales[3], Alessandra de Albuquerque Tavares Carvalho[1].

ABSTRACT

Objective: To investigate whether apitherapy is effective in the treatment of oral mucositis in cancer patients. **Methods:** To search the following databases up to July 2024: PubMed/MEDLINE, Scopus, Embase, Web of Science, Cochrane Library, SciELO, and Lilacs. To use Cochrane's Q and Higgins' I² statistics to detect heterogeneity, to apply the Mantel-Haenszel test for data synthesis using RStudio, and to assess risk of bias using the Cochrane Risk of Bias 2 tools. **Results:** To identify 857 articles after the initial search. To apply eligibility criteria and include 18 randomized clinical trials: 11 on honey and 7 on propolis, with low risk of bias in three studies. The meta-analysis did not show statistically significant differences for either agent in the treatment and/or prevention of oral mucositis (P > 0.05). To report high heterogeneity (I² > 65%) in the honey-treated groups for mild, moderate, and severe mucositis. **Final considerations:** To conclude that honey and propolis were not effective in the treatment or prevention of oral mucositis; however, these findings should be interpreted with caution due to the high heterogeneity of some studies.

Keywords: Apitherapy, Oral mucositis, Neoplasms.

RESUMO

Objetivo: Investigar se a apiterapia é eficaz no tratamento da mucosite oral em pacientes com câncer. **Métodos:** Foram realizadas buscas nas seguintes bases de dados até julho de 2024: PubMed/MEDLINE, Scopus, Embase, Web of Science, Cochrane Library, SciELO e Lilacs. As estatísticas Q de Cochrane e I² de Higgins foram utilizadas para detectar heterogeneidade, enquanto o teste de Mantel-Haenszel foi empregado

[1] Universidade Federal de Pernambuco (UFPE), Recife – PE.
[2] Centro Universitário (CESMAC), Maceió - AL.
[3] Universidade Federal de Alagoas (UFAL), Maceió - AL.

SUBMETIDO EM: 8/2025 | **ACEITO EM: 9/2025** | **PUBLICADO EM: 10/2025**

para a síntese dos dados por meio do software RStudio. O risco de viés foi avaliado utilizando a ferramenta Cochrane Riisk of Bias 2. **Resultados:** Após a busca inicial, foram identificados 857 artigos. Aplicando-se os critérios de elegibilidade, 18 ensaios clínicos randomizados foram incluídos nesta revisão, sendo 11 sobre o mel e 7 sobre o própolis, com baixo risco de viés em três dos estudos com mel e própolis. Os resultados da presente metanálise não demonstraram diferenças estatisticamente significativas para nenhum dos agentes no tratamento e/ou prevenção da mucosite oral (P > 0,05). Além disso, foi observada alta heterogeneidade (I^2 > 65%) nos grupos tratados com mel para mucosite leve, moderada e grave. **Considerações finais:** Mel e própolis não se mostraram eficazes para o tratamento ou prevenção da mucosite oral; no entanto, esses resultados devem ser interpretados com cautela, dado que alguns estudos apresentaram alta heterogeneidade.

Palavras-chave: Apiterapia, Mucosite bucal, Neoplasias.

RESUMEN

Objetivo: Investigar si la apiterapia es eficaz en el tratamiento de la mucositis oral en pacientes con cáncer. **Métodos:** Realizar búsquedas en las siguientes bases de datos hasta julio de 2024: PubMed/MEDLINE, Scopus, Embase, Web of Science, Cochrane Library, SciELO y Lilacs. Utilizar las estadísticas Q de Cochrane e I^2 de Higgins para detectar heterogeneidad, aplicar la prueba de Mantel-Haenszel para la síntesis de datos en el software RStudio y evaluar el riesgo de sesgo mediante la herramienta Cochrane Risk of Bias 2. **Resultados:** Identificar 857 artículos después de la búsqueda inicial. Aplicar los criterios de elegibilidad e incluir 18 ensayos clínicos aleatorizados: 11 sobre miel y 7 sobre propóleos, con bajo riesgo de sesgo en tres estudios. El metanálisis no mostró diferencias estadísticamente significativas para ninguno de los agentes en el tratamiento y/o prevención de la mucositis oral (P > 0,05). Informar alta heterogeneidad (I^2 > 65%) en los grupos tratados con miel para mucositis leve, moderada y grave. **Consideraciones finales:** Concluir que la miel y el propóleo no fueron eficaces en el tratamiento o prevención de la mucositis oral; sin embargo, estos resultados deben interpretarse con cautela debido a la alta heterogeneidad de algunos estudios.

Palabras clave: Apiterapia, Mucositis bucal, Neoplasias.

INTRODUCTION

Antineoplastic treatments are utilized in an effort to destroy cancer cells; however, chemotherapy (CT) and radiotherapy (RT) agents are not selective in the cells they target, and often cause damage to healthy, as well as immune, cells (BROWN TJ e GUPTA A, 2020).

Additionally, these therapies often come with toxic side effects, such as oral mucositis (OM), which is a common complication associated with localized treatment. Its severity, however, depends on the type and dose of CT and RT. OM is a toxic inflammatory response of the oral mucosa, resulting in erythema and ulceration of the non-keratinized mucosa, which, in turn, causes significant pain, compromised nutrition, prolonged hospitalization, and bloodstream infections. The intensity and duration of OM are directly linked to the time and type of treatment; however, owing to the aforementioned symptoms, patients may experience delays in treatment, interfering with the administration of the ideal treatment plan. These delays, in turn, can affect the likelihood of the patient experiencing clinical remission or being considered cured (MÜNSTEDT K, e MÄNNLE H, 2019).

OM can be categorized as mild, moderate, or severe; however, there are a variety of scales used to evaluate the symptoms. The World Health Organization (WHO) scale is simple and easy to use in the clinical setting, and, similar to the Radiation Therapy Oncology Group (RTOG) scale, presents four degrees of OM severity. The National Cancer Institute Common Toxicity Criteria (NCI-CTC) scale includes separate objective and subjective analyses, along with five grades, while the Oral Mucositis Assessment Scale (OMAS) is an

objective scale that measures erythema and ulceration at nine sites in the oral cavity, and it is scored from 0 to 3 (LALLA RV, et al., 2008; HAWLEY P, et al., 2014).

Recent studies have focused on the prevention and treatment of oncological treatment-induced OM, and at present, studies are aiming to find new agents that are effective, safe, easy to use and cheap (DAUGĖLAITĖ G, et al., 2019). Apitherapy is a branch of alternative medicine that involves the use of bee products, such as honey, pollen, propolis, royal jelly, and bee venom, also known as apitoxin (WEHBE R, et al., 2019). Some studies have pointed to procedures such as photobiomodulation, oral hygiene, cryotherapy, and the use of honey and/or propolis as improved techniques for the relief of OM-related symptoms (DAUGĖLAITĖ G, et al., 2019; SENER DK, et al., 2019).

Propolis is a pleiotropic substance with anti-inflammatory and antioxidant properties mediated by a variety of compounds, which may explain its role in the formation of granulation tissue and subsequent scarring (AKHAVANKARBASSI MH, et al., 2016). Additionally, propolis contains zinc and iron, which are responsible for collagen synthesis and aid in tissue recovery (SALEHI M, et al., 2018).

Honey exhibits several antimicrobial properties, including high osmolarity, low pH, and conversion to hydrogen peroxide (HAWLEY P, et al., 2014), allowing for the inhibition of microbial activity and an increase in the healing capacity of injuries, surgical wounds, and oral infections (MOTALLEBNEJAD M, et al., 2008).

Honey is a simple, readily available, and inexpensive option for the treatment of patients with OM, as demonstrated by Patil K, et al. (2021), while propolis presents a simple, safe and effective option for the management of OM (BOLOURI AJ, et al., 2015; DASTAN F, et al., 2020).

Based on the aforementioned data, the objective of the present systematic review was to present the apitherapeutic products most commonly used for the treatment of OM and to report their therapeutic effectiveness.

METHODS

Protocol and registration

The present review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (PAGE MJ, et al., 2020). guidelines, and was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42022336793.

Study eligibility criteria

Studies were selected based on the PICOS (Population, Intervention, Comparison, Outcomes, and Study design) framework, as follows: population, patients undergoing CT and RT; intervention, apitherapy products (propolis, beeswax, honey, and/or apitoxin; comparison, placebo, saline/saline solution, and lidocaine; outcomes, efficacy in treating oral mucositis; and study design, randomized clinical trials. The question posed, therefore, was “Is apitherapy effective for the treatment of oral mucositis in cancer patients?”.

The inclusion criteria were as follows: randomized clinical trials using products derived from beekeeping; no association with other active principles; for the prevention and/or treatment of OM induced by CT or RT; published in any language; and without restrictions on sex or age. Studies without full versions, and those that required payment, were excluded.

Information sources and search strategy

Two researchers (KHJVP) and (FSBD) independently searched the following electronic databases for Medical Subject Headings (MeSH) terms, keywords, and free search terms including propolis, bee glue, honey, bee venom, bee products, oral mucositis, stomatitis, radiotherapy, chemotherapy, and cancer: PubMed/MEDLINE; Scopus; Embase; Web of Science; Cochrane Library; SciELO; and LILACS. The Boolean operators “AND” and “OR” were used for associating terms. The final search was conducted in July 2024.

Study selection and data collection

The search was conducted according to the eligibility criteria. There were no disagreements regarding article inclusion, and duplicate studies were excluded using the Mendeley Reference Manager. After the initial search, the titles were screened to exclude articles that did not meet the eligibility criteria. Next, the abstracts were evaluated, based on the type of study, the characteristics of the study population and the intervention evaluated, and the desired outcomes of the studies, as specified above. Finally, the remaining eligible full texts were analyzed using a data extraction form, consisting of a Microsoft Office Excel table containing the following data: author(s); year published; sample size; sex; age group; type of treatment; type of cancer; and conclusion(s).

Risk of bias

The risk of bias for at least one specific outcome from each included study was considered to determine the extent to which the findings were reliable, taking into account that the risk of bias may vary by outcome. The Cochrane Risk of Bias 2 (HIGGINS JPT, et al., 2021).

Tool was used to assess the risk of bias for the randomized clinical trials included in the present systematic review as follows: D1, randomization process; D2, deviations from intended interventions; D3, incomplete data; D4, outcome measurement; D5, description of results; and a global analysis of the risk of bias. Studies were classified, based on their risk of bias, as high, low, or concerning.

Statistical analysis

For dichotomous outcomes, the estimate of an intervention's effect was expressed as the risk r*atio* (RR) with a 95% confidence interval (CI), while for the meta-analysis, Cochrane's Q and Higgins I-squared (I^2) statistics were used to detect heterogeneity, with $P < 0.1$ or $I^2 > 50\%$ being considered statistically significant, and, therefore, a model of random effect. The relevant data were extracted from the studies, and the Mantel-Haenszel statistical method was used to synthesize the data using the RStudio program (BOWDEN J, et al., 2011; ALLAIRE J, 2012).

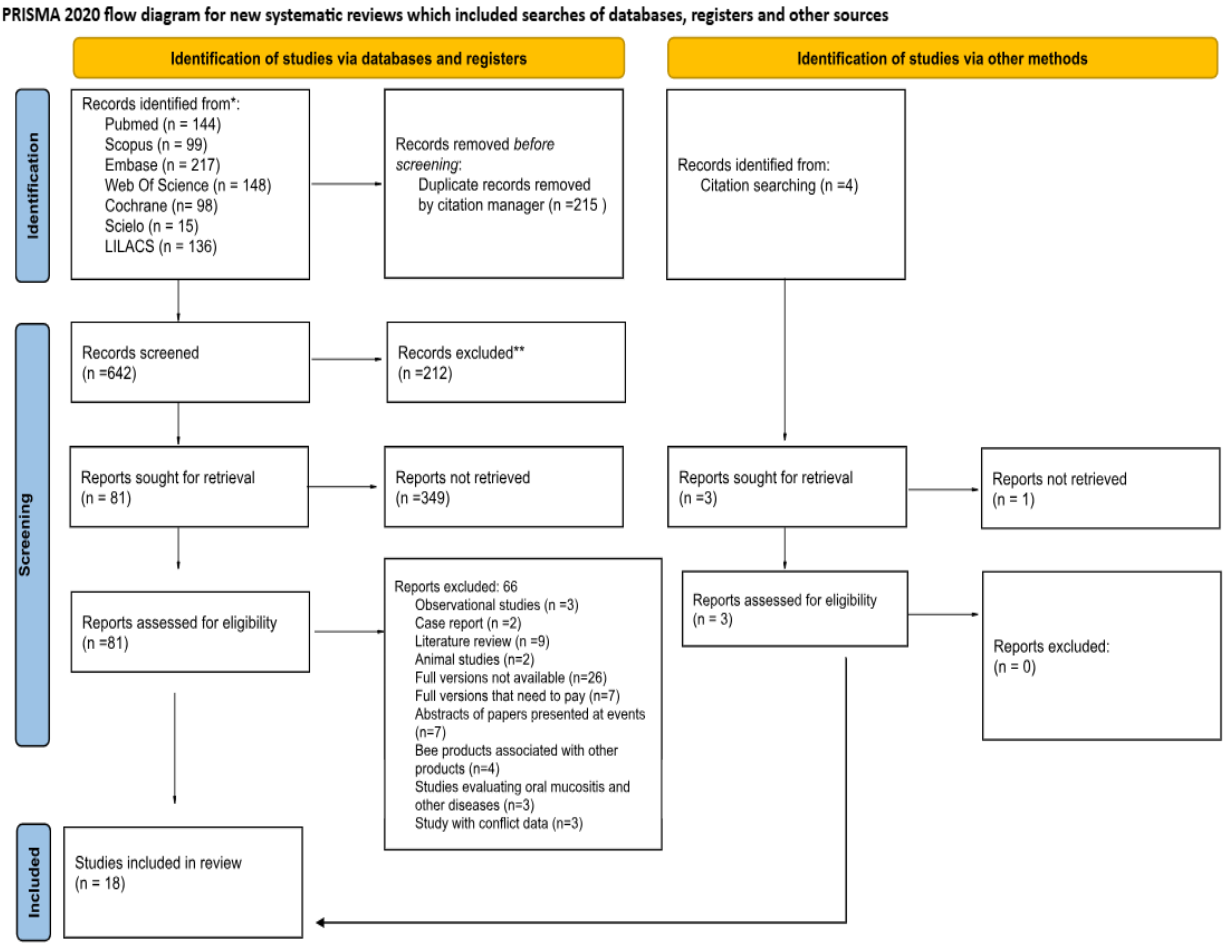
RESULTS

The initial search identified a total of 857 studies – 144 from PubMed/MEDLINE, 99 from Scopus, 217 from Embase, 148 from Web of Science, 98 from Cochrane, 15 from SciELO, and 136 from LILACS. After excluding 215 duplicates, the titles and abstracts of the other 642 articles were screened for eligibility.

The remaining 81 articles were read in full, after which 66 were excluded because they were not randomized clinical trials, only presented an abstract, were not available in full for free, or had confusing data. Studies that used other substances in combination with honey and/or propolis were also excluded, as were those that examined the association of OM with other diseases.

The reference lists of the articles assessed for eligibility were searched, resulting in three more articles having their abstracts screened, one of which was excluded, while the other two were read in full and subsequently selected for the present review. In total, 18 articles were included in the present systematic review – 12 on honey and 6 on propolis, while 5 articles were included in the meta-analysis – 3 in the honey group and 2 in the propolis group. The data regarding study selection are presented as a flowchart (**Figure 1**).

Figure 1 - PRISMA flowchart with the database search process.



Source: Dantas FSB, et al., 2025.

The characteristics of the studies included in the present systematic review are presented in **Table 1**. Propolis was evaluated in 7 studies (AKHAVANKARBASSI MH, et al., 2016; SALEHI M, et al., 2018; BOLOURI AJ, et al., 2015; DASTAN F, et al., 2020; FERNANDES PM, et al., 2022; HAMZAH MH, et al., 2022; TOMAŽEVIČ T e JAZBEC J, 2013), encompassing a total sample population of 197 individuals aged between 1 and 87 years.

Two studies (AKHAVANKARBASSI MH, et al., 2016; HAMZAH MH, et al., 2022) did not report the number of men and women, and the other four (SALEHI M, et al., 2018; BOLOURI AJ, et al., 2015; DASTAN F, et al., 2020; TOMAŽEVIČ T e JAZBEC J, 2013) had more men (76) than women (64). The intervention group had 99 participants, while the control group had 98, all of whom received a placebo.

Honey was evaluated in 11 studies (HAWLEY P, et al., 2014; MOTALLEBNEJAD M, et al., 2008; PATIL K, et al., 2021; BADR LK, et al., 2023; CHARALAMBOUS M, et al., 2018; JAYACHANDRAN S e BALAJI N, 2012; KHANAL B, BALIGA M e UPPAL N, 2010; JAHANBANI MAZRAEH E, et al., 2023; PATIL K, et al., 2022; KHANJANI POUR-FARD-PACHEKENARI A, et al., 2019; UĞUR Ö, et al., 2023), encompassing a total of 814 individuals aged >18 years, also with more men (265) than women (204) in eight studies, while the other four did not report the number of men and women.

The intervention group consisted of 427 participants, while the control group consisted of 387, who received oral hygiene, saline solution, lidocaine, olive oil, benzydamine hydrochloride or a placebo.

Of the studies which evaluated propolis, only Tomazevic and Jazbec (TOMAŽEVIČ T e JAZBEC J, 2013), did not recommend the use of this natural agent for the prevention and treatment of OM. Similarly, Hawley P, et al. (2014) did not observe any positive effects of honey on the treatment or prevention of OM.

Table 1 - Characteristics of propolis and honey studies.

Author/Year	N	Sex	Age (years)	Propolis or honey group	Group control	Treatment and dosage	Type of cancer	Conclusion
Akhavan-Karbassi MH, et al., 2016.	40	NR	≥ 18	Propolis N = 20	Placebo N = 20	Propolis mouthwash (30% extract, Soren Tektoos, Mashhad) – 5 mL of solution was gargled for 60 sec and expectorated. The treatment was carried out 3 times a day (every 8 h) for 7 days.	Head and neck tumors	Propolis was effective and can be used to improve oral health care for patients with OM.
Badr LK, et al. 2022.	42	23 M 19 F	5-17	Honey N= 17	Olive oil N= 13 Control N=12	Each patient was given 2.5 cc of Manuka honey and instructed to swish it slowly in their mouth for one minute and then swallow 3 times a day.	Leukemia	Honey is recommended for the treatment of OM.
Bolouri AJ, et al., 2015.	20	6 F 14 M	15–87	Propolis extract N = 10	Placebo N = 10	Mouthwash (3% extract, SORENTEC) – each patient received 2 bottles of mouthwash and a bottle of normal saline to rinse their mouth prior to using the mouthwash. All of the patients were instructed to rinse their mouths with 15 mL propolis and then swallow 3 times a day for 5 weeks, beginning with their first radiotherapy session.	Head and neck tumors	Aqueous-based propolis extract efficiently prevented and helped cure radiation-induced OM.
Dastan F, et al., 2020.	30	12 F; 18 M	NR	Propolis N = 15	Placebo N = 15	Patients in the test group received 20 mL propolis oral solution (0.8 mg/mL, Soren Tektoos, Mashhad) 3 times a day for 4 weeks, from the first day of radiotherapy. The patients were instructed to brush their teeth and then gargle and rinse their mouth with 20 mL of propolis for 1 min, and swallow the remaining solution.	Head and neck tumors	Effective and safe for the relief of radiation-induced OM.
Charalambous M, et al., 2018.	72	20 F 52 M	≥ 18	Thyme honey N = 36	Saline solution N = 36	Patients were advised to dilute 20 mL of thyme honey in 100 mL of purified water, gargling 3 times a day for 7 weeks, starting the first day of the 4th week of radiotherapy (15 min before and after radiotherapy, and 6 h later)	Head and neck squamous cell carcinoma	Thyme honey had positive effects on the management of radiation-induced OM, as well as on patients' quality of life.
Fernandes PM, et al. 2022.	60	15F 45M	≥ 18	Propolis N= 32	Placebo N= 28	Propolis was given to the test group subjects. While the control group received a placebo. The patient was instructed to apply the product topically to the oral mucosa at	Oral cavity or oropharynx cancer	The topic use of propolis was able to decrease the mean score of OM in key moments of RT

Author/Year	N	Sex	Age (years)	Propolis or honey group	Group control	Treatment and dosage	Type of cancer	Conclusion
						least 6 times a day, every day, including weekends, from the 1st day of RT. Patients were constantly encouraged to continue using the product until the last day of RT.		
Hamzah MH, et al. 2022.	17	NR	Mean age 47	Propolis n=10	Placebo = 7	The experimental group was given a 2.5% propolis mouthwash. All the patients were instructed to rinse their mouths with 7mL (measured using syringe provided) of the assigned mouthwash for 60 seconds and then spit it out. This was done three times per day: on the RT days from Monday to Friday, the patients were instructed to perform the mouth rinse at 30 minutes before starting the RT, at 30 minutes after completing the RT, and then at 6 hours after the RT. During the rest days on Saturday and Sunday, the patients were instructed to rinse their mouths at specific times of 8 am, 3 pm, and 10 pm. These mouth rinses were carried out for 6 weeks simultaneously with the RT protocol.	Nasopharyngeal carcinoma	Propolis mouthwash was effective at reducing the severity of oral mucositis, and its use was proven safe.
Hawley P, et al. 2014.	81	16 F 65 M	NR	Manuka honey N = 40	Placebo N = 41	Honey in a 5 mL gel sachet was swallowed 4 times a day after the use of an oral solution (1 tsp table salt, 1 tsp baking soda in 1 L of tap water, 0.9% saline, and 0.5% sodium bicarbonate). Before swallowing the gel, the oral solution was swished for 30 sec. Patients were also instructed to apply a topical fluoride treatment at bedtime at least 30 min after the honey gel. Treatment started on the first day of radiation and lasted 7 days after the last radiation.	Head and neck tumors	Manuka honey had no impact on reducing the severity of radiation-induced OM.
Jayachandran S & Balaji N, 2012.	60	42 M 18 F	Mean age 53	Honey N = 20	Benzydamine hydrochloride N = 20 Placebo N = 20	The patients were instructed to take 20 ml of natural honey 15 minutes before RT. They were instructed to slowly rinse the honey in their mouths, swish it around for 5 minutes duration, so as to make the honey in contact with the oral mucosa and slowly	Head and neck tumors	Pure natural honey can be an effective agent in managing radiation induced oral mucositis.

Author/Year	N	Sex	Age (years)	Propolis or honey group	Group control	Treatment and dosage	Type of cancer	Conclusion
						swallow so as to make better contact with the pharyngeal mucosa. After 15 minutes and 6 hours after RT, the patients were instructed to slowly rinse the honey in their mouths, swish it around for 5 minutes duration and then swallow.		
Khanal B, et al. 2010.	40	NR	NR	Honey N = 20	Lidocaine N = 20	Honey in 20 mL of gel was swished throughout the oral cavity for 2 min and expectorated, 15 min before and radiotherapy, and once before going to bed.	Oral carcinoma	Topical honey was effective in reducing the severity of radiotherapy-induced OM, and helping to improve the quality of life of cancer patients.
Mazraeh E, et al. 2023.	88	88 F	39 - 53	Thyme honey N=45	Control N= 43	Thyme honey was modified to mucoadhesive oral gel by approximately 3% carbomer 934p, with a proportion of thyme honey in the fnal product as 66%. Patients were prescribed to follow oral hygiene and rinse saline 3 times a day under the supervision of the consultant oral and maxillofacial dentist. Patients in the intervention arm were also advised to apply thyme honey oral gel 2 to 4 times a day	Breast cancer	Thyme honey can be considered as a prophylactic agent for OM and decrease the severity of its symptoms.
Motallebnejad M, et al. 2008.	40	18 F 22 M	NR	Honey N = 20	Saline solution N = 20	Patients were instructed to rinse 20 mL of honey around their mouths and gradually swallow in order to coat the oral and pharyngeal mucosa 15 min before radiotherapy, and again 15 min and 6 h after radiation.	Head and neck tumors	Natural honey was effective in managing radiation-induced OM.
Patil K, et al. 2021.	102	NR	NR	Honey N = 51	Saline solution N = 51	Natural honey (Dabur India, Ltd) was given to test group subjects, who were instructed to apply 4 gm topically using cotton pallet 4 times per day (total of 16 gm/day), after which they were not to consume food for half an hour. The protocol was followed for total of 40 days, including 4 follow-ups every	Head and neck tumors	Topical honey can be used as an adjunct, relieving symptoms and providing effective management of OM.

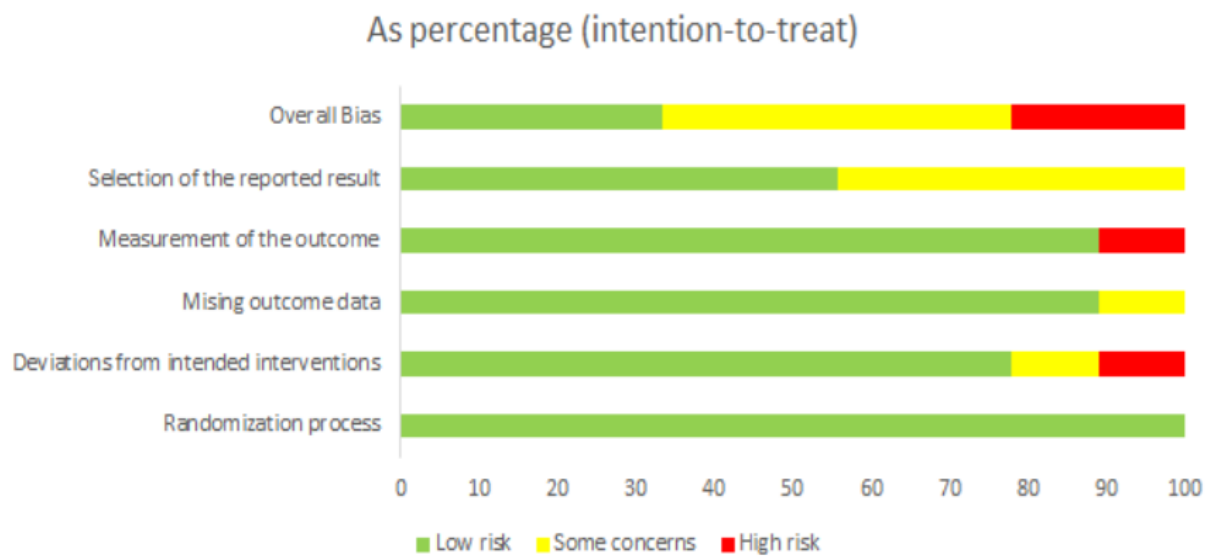
Author/Year	N	Sex	Age (years)	Propolis or honey group	Group control	Treatment and dosage	Type of cancer	Conclusion
						10 days.		
Patil K, et al. 2022.	204	NR	NR	Honey N = 102	Placebo N = 102	Patients were given 20 mL of commercially available Dabur Natural Honey solution (manufactured by Dabur India Limited) and instructed to apply it topically four times daily after radiation (total 20 mL/day). This protocol was followed from the first day of radiotherapy until the end of the 6th week.	Head and neck tumors	Honey can be used in the treatment of OM
Pour-Fard-Pachekenari A, et al. 2019.	53	18 F 35 M	≥ 18	Mouthwash with honey N = 17	Control N =19; Oral hygiene N = 17	Baran-Baghro honey mouthwash (honey-to-water ratio of 1:20) with no bacterial contamination at a of temperature 37 °C was gargled and held in the mouth for 30 sec, so that the solution permeated all parts of the mouth, including the gums and tongue, before and after each meal, and once before bed.	Acute myeloid leukemia	Honey mouthwash was effective in reducing the severity of and preventing OM.
Salehi M, et al. 2018.	50	26 F 24 M	26–72	Propolis N = 25	Placebo N = 25	Patients ingested 50 mg propolis tablets with meals (Soren Tak Toys Pharmaceutical Company) twice daily for three weeks.	Colon cancer	Propolis supplementation played an important role in preventing and improving OM.
Tomazevic T e Jazbec J, 2013.	40	20 F 20 M	1–19	Propolis N = 19	Placebo N = 21	An average of 0.38 g propolis was used for each application with a tip applicator, performed each morning and evening.	Leukemia; Lymphoma; Soft tissue tumors; Bone tumors; Brain tumors	Propolis is not recommended for the treatment of severe OM.
Ugur O, et al 2023.	32	26 M 7 F	32-87	Honey N=16	Sodium bicarbonate N=16	All patients included in the study were instructed to rinse with mouthwash solutions recommended by the clinic for 1 minute, 4 times a day, every 6 hours (4x1), after each meal.	Head and neck tumors	The use of honey was not superior to bicarbonate

Source: Dantas FSB, et al., 2025.

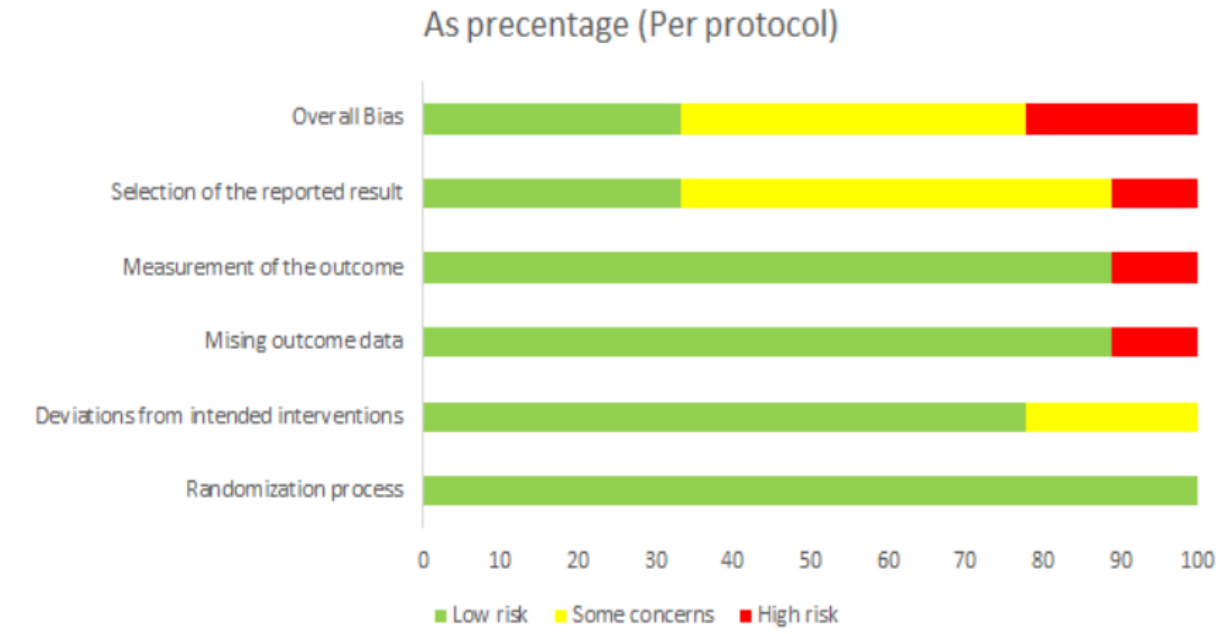
The processes of measuring the outcomes and randomization showed a low risk of bias, both for the intention-to-treat and for each protocol, as shown in **Figure 2**.

Figures 2A and **B** – Presentation of the risk of bias analysis results in a weighted bar chart for each Cochrane Risk of Bias 2.0 domain, based on the intention-to-treat and protocol.

A



B



Source: Dantas FSB, et al., 2025.

Figure 3. A shows the risk of bias assessment results for the studies that used propolis, while **Figure 3B** shows those that used honey. Among the studies on propolis, five raised concerns – Bolouri AJ, et al. (2015), Salehi M, et al. (2018), Dastan F, et al. (2020), Fernandes PM, et al. (2022), and Hamzah MH, et al. (2022) – particularly in the reporting of results and the overall risk of bias assessment domains.

Among the studies on honey, four showed a high risk of deviation from intended interventions – Patil K, et al. (2022), Motallebnejad et al. (2008), Hawley P, et al. (2014), and Uğur O, et al. (2023); however, it should be noted that for this study, the domain of incomplete outcome data raised some concerns. In addition, Patil K, et al. (2021) and Badr LK, et al. (2023) also raised concerns regarding the reporting of results and the overall risk of bias assessment domains.

Figures 3 - A and 3B – Presentation of the results of the risk of bias analysis in a traffic light graph with individual results for each domain of the included studies.



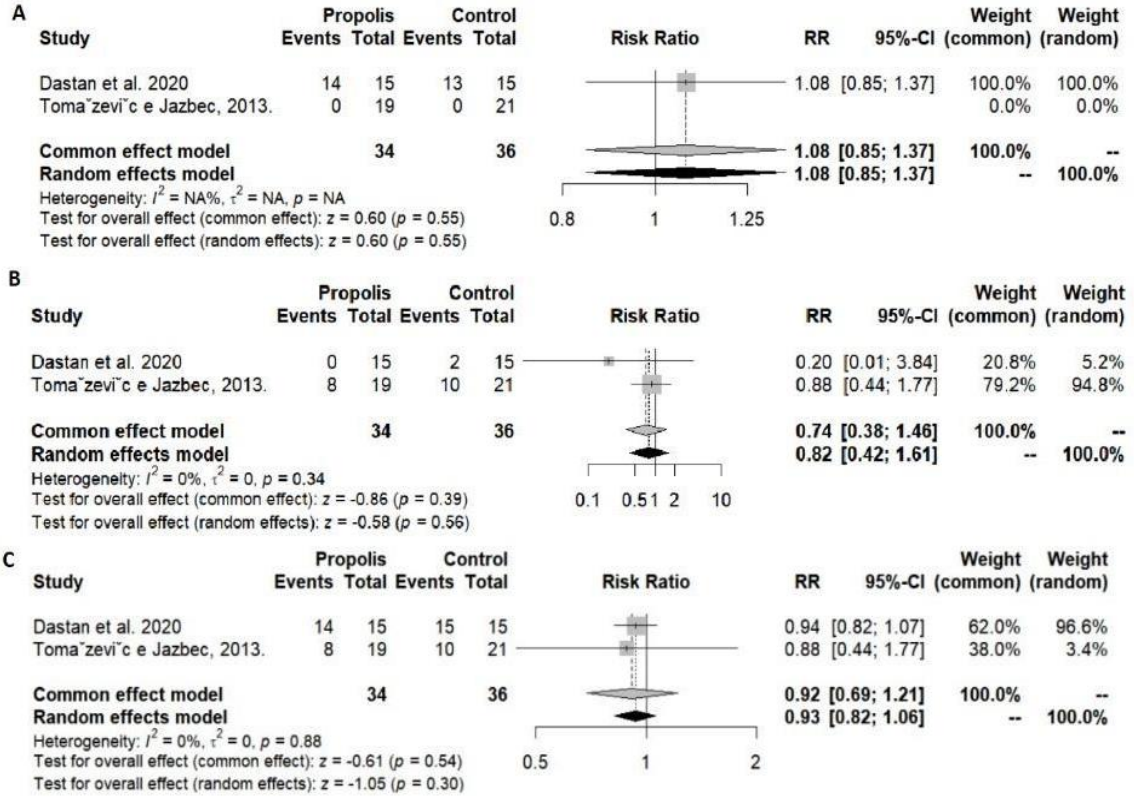
Source: Dantas FSB, et al., 2025.

Meta-analysis

Our meta-analysis included propolis and honey studies that reported the number of treated patients with mild, moderate and severe OM. The action of propolis was evaluated in two randomized clinical trials. The results, presented in **Figure 4**, do not demonstrate statistical significance for the use of propolis in the prevention and treatment of OM ($P > 0.05$). Additionally, the present meta-analysis reported insignificant heterogeneity in both groups.

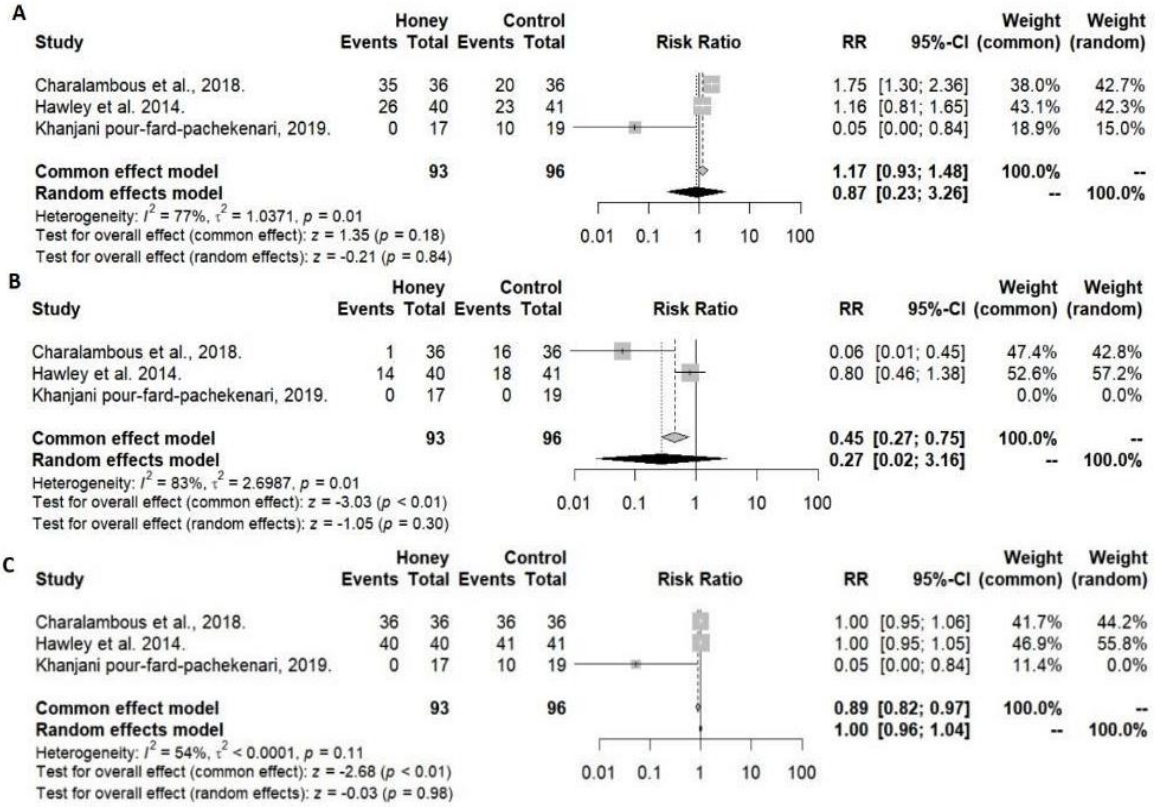
The action of honey was also evaluated in two randomized clinical trials. The results, presented in **Figure 5**, do not demonstrate statistical significance for the use of honey in the prevention and treatment of OM ($P > 0.05$). Additionally, the present meta-analysis reported high heterogeneity among the mild ($I^2 = 77\%$) and moderate-to-severe OM ($I^2 = 83\%$) groups.

Figure 4A - Meta-analysis of propolis for mild OM; **4B** – Meta-analysis for moderate-to-severe OM; and **4C** – Meta-analysis for all participants with OM.



Source: Dantas FSB, et al., 2025.

Figure 5A - Meta analysis of honey for mild OM; **5B** – Meta-analysis for moderate-to-severe OM; and **5C** – Meta-analysis for all participants with OM.



Source: Dantas FSB, et al., 2025.

DISCUSSION

The scales most used by the studies included in this review were those of the WHO (HAWLEY P, et al., 2014; AKHAVANKARBASSI M.H, et al., 2016; SALEHI M, et al., 2018; KHANJANI POUR-FARD-PACHEKENARI A, et al., 2019), the RTOG (HAWLEY P, et al., 2014; CHARALAMBOUS M, et al., 2018; KHANAL B, e UPPAL N, 2010) and the OMAS (AKHAVANKARBASSI MH, et al., 2016; MOTALLEBNEJAD M, et al., 2008). The NCI-CTC scale (BOLOURI AJ, et al., 2015; DASTAN F, et al., 2020) was also used, along with the Oral Assessment Guide (OAG) adapted by Tomazevic T e Jazbec J (2013), which uses three scores to assess five regions of the mouth, swallowing, saliva and voice.

Khanal B e Uppal N (2010) evaluated pure natural honey in gel form with the RTOG scale and observed a reduction in the severity of radiation-induced OM, although their study was the only one to use lidocaine as a control group. Lidocaine is an anesthetic that eliminates pain; however, because it affects the perception of taste, pressure and temperature, its use is limited. The results of the study indicated that severe OM occurred in only 1 of the 20 patients. Patil K e Doggalli N (2021) also evaluated the effects of honey in the treatment of radiation-induced OM and observed that there was no degree of progression of OM to moderate to severe in patients who were treated with honey.

Among the studies that evaluated honey, two types of pure natural honey were used — manuka honey and thyme honey. Hawley P, et al. (2014) used a gel form of manuka honey in their study; however, this format was not well received by the participants, as the gel had a strong taste and a thick consistency, which caused nausea or was made worse by the chemotherapy drugs. As a result of this negative reception, a portion of the study population dropped out of the study.

Charalambous M, et al. (2018) used pure thyme honey filtered before use and reported no difficulty in patients adhering to the treatment protocol. They used the Oral Mucositis Weekly Questionnaire (OMWQ) to assess patients' well-being during treatment and observed that the well-being of the thyme honey group increased after the first month of RT, while in the control group, well-being decreased in the first month, followed by an increase 6 months post-RT.

Pour-Fard-Pachekenari A, et al. (2019) used three study groups — honey mouthwash, specific oral care and oral hygiene with medication (controls). The severity of OM increased in the control group in the third and fourth weeks, while it decreased in the honey group in the same period. When evaluating the patients' weight, significant differences were found between the honey and control groups in the third and fourth weeks, and between the honey and specific oral care groups in the fourth week, showing that the patients in the honey group lost less weight than the other two groups. None of the patients in their study, however, had grade 3 or 4 OM. Motallebnejad M, et al. (2008) observed similar results, because as well as the severity of OM being lower in the honey group, weight loss was also lower than that documented in the control group.

Hao S, et al. (2022), in their systematic review, evaluated the effect of honey for the treatment of OM in pediatric patients. The parameters of their results included the recovery time of OM; the severity; the body weight of the patients; and the result of the isolation of aerobic bacteria and *Candida*. The available evidence shows that honey can significantly reduce recovery time, the occurrence of all grades of radio- and chemo-induced OM and the reduction of grade III and IV OM in pediatric patients, which may cause disagreement with this review since it did not evaluate only pediatric patients. The same review found similar difficulties to the present study, such as significant heterogeneity between the included studies, perhaps due to various regimens, doses, duration, center configurations, and populations enrolled. The quality of the included studies was relatively low and could be a significant source of bias, and each meta-analysis contained a small number of studies.

Co M, et al. (2022) included eight studies in their systematic review and showed that honey was significantly better at reducing the risk of treatment interruptions, weight loss and delay in time to mucositis, but not in the severity of mucositis — converging with the results found in this study — and can be seen as a considerable therapy for reducing treatment interruptions. In this study, oral mucositis was measured using the Radiation Therapy Oncology Group (RTOG), Oral Mucositis Assessment Scale (OMAS) and World Health Organization (WHO) scales, and honey was evaluated in the form of pure natural honey or wild honey from different sources, while the control consisted of normal saline solution and standard treatment or syrup-based placebo.

Tian XY, et al. (2022), in their systematic review, evaluated the effect of honey for the treatment of only grade 3 and 4 oral mucositis in patients with head and neck cancer. The severity of oral mucositis was assessed with a scoring system using the RTOG scale. However, a conclusive finding for the use of honey in patients with HNC has not yet been generated, as in the present study, thus concluding that honey may have the potential to alleviate the severity of radiation-induced oral mucositis, maintain weight and decrease the incidence of OM-related treatment interruption in patients with HNC, based on limited evidence. These results contrast with those found in the review by Lima N, et al. (2021), where the administration of natural products, especially honey, did not result in pain reduction and manuka honey was one of the most prevalent main natural agents for the development of adverse reactions, such as nausea and burning in the oral cavity.

Münstedt K, et al. (2019) highlighted in their systematic review that there is a great deal of controversy regarding the value of honey in managing the side effects of oral mucositis induced by radiotherapy or radio/chemotherapy, although they found that most of the studies evaluated spoke in favor of honey. The most important finding of their review is that the type of honey may have influenced the results, since all the trials with manuka honey showed no advantage, while all the studies with conventional honey revealed positive results. Yang WX, et al. (2022) state that honey treatment for moderate to severe chemo-/radiotherapy-induced oral mucositis is effective and has a great therapeutic effect, and positive results were obtained more frequently with pure natural honey, which is probably the best option to consider when applying the adjuvant therapeutic agent, corroborating the present systematic review and with studies cited above.

Dastan F, et al. (2020) used the NCI Common Terminology Criteria for Adverse Events (CTCAE) scale to assess dysphagia. They found that in the first three weeks of treatment, the degree of dysphagia did not differ significantly; however, in the fourth week, patients in the propolis group showed a reduction in the degree of dysphagia compared to those in the placebo group. This is in line with the results obtained by Bolouri AJ, et al. (2015), who evaluated patients with head and neck cancer undergoing RT, and found that weight loss in the placebo group was significantly greater than in the propolis-treated group, with patients losing an average of 3.4 kg vs. 200 g, respectively.

A double-blind study by Tomazevic T e Jazbec J (2013) evaluated the action of propolis in reducing severe OM in children undergoing chemotherapy; however, this treatment was unsuccessful, as no significant differences were observed in the duration, frequency or severity of OM between the study groups. In addition, four participants did not adhere to the study protocol due to vomiting after applying propolis, one of which was due to the bad taste of propolis. The alcohol used as a solvent in this study, however, may have masked the action of propolis, as it is an irritant. None of the other studies included in this review reported any adverse effects related to propolis (AKHAVANKARBASSI MH, et al., 2016; SALEHI M, et al., 2018; BOLOURI AJ, et al., 2015; DASTAN F, et al., 2020; TOMAZEVIC T e JAZBEC J, 2013).

Salehi M, et al. (2018) evaluated a tablet form of propolis in the treatment of patients undergoing CT, which differed from the other propolis studies (AKHAVANKARBASSI .H, et al., 2016; BOLOURI AJ, et al., 2015; DASTAN F, et al., 2020; TOMAZEVIC T e JAZBEC J, 2013) in that this was the only study in which propolis was administered in tablet form. Salehi M, et al. (2018) observed a significant reduction in the severity of OM in the second and third weeks of treatment. It is worth noting, however, that despite the good results, patients with grade 3 and 4 OM may have difficulty swallowing the tablet and, in these cases, the topical form would be more appropriate.

The majority of studies (HAWLEY P, et al., 2014; AKHAVANKARBASSI MH, et al., 2016; MOTALLEBNEJAD M, et al., 2008; PATIL K e DOGGALLI N, 2021; BOLOURI AJ, et al., 2015; DASTAN F, et al., 2020; CO M, et al., 2022; KHANAL B e UPPAL N, 2010) used apitherapy for the treatment of OM only in patients with head and neck tumors, which, due to the location of the tumor and primary treatment with RT, can result in increased severity and duration of OM (POUR-FARD-PACHEKENARI A, et al., 2019). Of these studies, however, only Hawley P, et al. (2014) did not demonstrate efficacy in reducing the severity of OM.

The meta-analysis of the propolis-treated group in the present study showed no statistically significant results for its use in the prevention and treatment of OM; however, only two studies were included in this analysis, with a limited number of participants (70) and dichotomous results — one study indicated that propolis was effective in mitigating OM symptoms (DASTAN F, et al., 2020), while the other did not (TOMAZEVIC T e JAZBEC J, 2013), and one study (TOMAZEVIC T e JAZBEC J, 2013) involved children and adolescents, while

the other (DASTAN F, et al., 2020) dealt only with adults. Similarly, the meta-analysis of the honey treatment group showed no statistically significant differences in its use in the prevention and treatment of OM; however, only three studies (HAWLEY P, et al., 2014; CHARALAMBOUS M, et al., 2018; POUR-FARD-PACHEKENARI A, et al., 2019) were included in the analysis, and these studies showed a high level of heterogeneity, which may have interfered with the comparison between study participants. Neither the honey nor propolis treatment group showed a pattern in their results, especially in the number of events related to the type of OM (mild, moderate or severe), which led to the exclusion of numerous studies from these meta-analyses.

An inherent difficulty in evaluating CT treatment is that there is no single drug to treat cancer at all levels; therefore, the studies included in this review presented a variety of drugs. Each of these drugs can have different cytotoxicities in the oral cavity; therefore, these factors can interfere with the body's response to OM treatment. In addition, this review was limited by the lack of standardized studies that were sufficient to separate the efficacy of apitherapy based on the type of antineoplastic therapy, with groups treated only with RT or CT and with groups undergoing both RT and CT. However, it is important to highlight apitherapy as a treatment option and to demonstrate the need for new multicentre studies to assess the standardization of treatments with honey and propolis.

A reduction in the occurrence of OM may subsequently offset the additional costs of medical treatment, since patients with OM may require more frequent hospitalizations, dietary support, procedures, examinations and drug intake (BARASCH A e PETERSON DE, 2003). More controlled and standardized studies should be carried out to determine the efficacy of these substances in the treatment of OM.

CONCLUSION

Although honey and propolis can act as adjuvants in the treatment of OM, the results of the present systematic review and meta-analysis have demonstrated that there is insufficient scientific evidence to support the use of such substances in the prevention and treatment of OM.

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