ISSN 1695-6141
Revista electrónica trimestral de Enfermería
N°62
Abril 2021
www.um.es/eglobal/

REVISIONES

Effect of Chamomilla Recutita in the oncology patient with oral mucositis: a systematic review

Efecto de Chamomilla Recutita en el paciente oncológico con mucositis oral: revisión sistemática

Efeito da Chamomilla Recutita no paciente oncológico com mucosite oral: revisão sistemática

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https://doi.org/10.6018/eglobal.426451

Received: 3/05/2020
Accepted: 21/12/2020

ABSTRACT:

Objective: To identify through national and international literature the effects of Chamomilla recutita (CR).
Method: A systematic review was chosen which included rigorous analysis of articles, being extremely reliable and of great importance for researchers. The articles analyzed were carefully studied in order to collect data on the potential beneficial effects of the plant in question, in addition to the attempt to verify which method and quantity was necessary to obtain a correct therapeutic application in those with this side effect. At the end of the selection of studies defined by the established criteria, new instruments were applied to validate them, where a quantity of researches that were of entire relevance for this review was reached.
Results: With the analysis of the studies, CR was found in the form of mouth rinses, ointments, tinctures and infusions, all with different forms of concentration, preparation and use. The analysis showed that CR presents a potential therapeutic effect in clinical practice with oncologic and hematologic patients, because it provides ample benefits to this population.
Conclusion: The ways of using CR showed to be effective, however, the method of rinsing and infusion were the studies that most demonstrate beneficial effects to their patients, although all showed

effectiveness. It is suggested future studies to insert this method in the clinical practice of service providers, in order to benefit its users.

Keywords: Stomatitis; Chamomile; Medical oncology; Drug Therapy; Complementary Therapies.

RESUMO:

Objetivo: Identificar através da literatura nacional e internacional os efeitos da *Chamomilla recutita* (CR).
Método: Optou-se por uma revisão sistemática que incluiu a análise rigorosa de artigos, sendo extremamente confiável e de grande importância para pesquisadores. Os artigos analisados foram criteriosamente estudados, para que houvesse uma coleta de dados sobre os potenciais efeitos benéficos da planta em questão, além da tentativa de constatar qual o método e a quantidade necessária para que se pudesse obter uma correta aplicação terapêutica nos portadores deste efeito colateral. Ao final da seleção dos estudos definidos pelos critérios estabelecidos, aplicou-se novos instrumentos para validação deles, onde se chegou a uma quantidade de pesquisas que eram de inteira relevância para a presente revisão.
Resultados: Com a análise dos estudos, foi encontrado a CR em forma de enxaguatórios bucais, pomadas, tinturas e infusões, todas com diferentes formas de concentração, preparação e uso. Constatou-se com as análises realizadas, que a CR apresenta um potencial efeito terapêutico na prática clínica com pacientes oncológicos e hematológicos, pois proporciona amplos benefícios para esta população.
Conclusão: As formas de utilização da CR mostraram-se eficazes, entretanto, o método de enxaguante e infusão foram os estudos que mais demonstram efeitos benéficos aos seus pacientes, apesar de todos demonstrarem eficácia. Sugere-se estudos futuros para que haja inserção deste método na prática clínica dos prestadores de serviços, a fim de beneficiar seus usuários.

Palavras-chaves: Estomatite; Camomila; Oncologia; Tratamento Farmacológico; Terapias Complementares.

RESUMEN:

Objetivo: Identificar los efectos de *Chamomilla recutita* (CR) a través de la literatura nacional e internacional.
Método: Optamos por una revisión sistemática que incluía el análisis riguroso de los artículos, siendo extremadamente confiable y de gran importancia para los investigadores. Los artículos analizados se estudiaron cuidadosamente, de modo que hubo una recopilación de datos sobre los posibles efectos beneficiosos de la planta en cuestión, además del intento de determinar el método y la cantidad necesaria para que se pudiera obtener una aplicación terapéutica correcta en los portadores de este efecto secundario. Al final de la selección de estudios definidos por los criterios establecidos, se aplicaron nuevos instrumentos para validarlos, donde se llegó a una serie de estudios que fueron de máxima relevancia para la presente revisión.
Resultados: Con el análisis de los estudios, se encontró CR en forma de enjuagues bucales, pomadas, tinturas e infusiones, todos con diferentes formas de concentración, preparación y uso. Con los análisis realizados, se encontró que la CR tiene un efecto terapéutico potencial en la práctica clínica con pacientes oncológicos y hematológicos, ya que proporciona amplios beneficios para esta población.
Conclusión: Las formas de usar la CR demostraron ser efectivas, sin embargo, el método de enjuague e infusión fueron los estudios que más demostraron efectos beneficiosos para sus pacientes, a pesar de que todos mostraron efectividad. Se sugiere que los estudios futuros incluyan este método en la práctica clínica de los proveedores de servicios, para beneficiar a sus usuarios.

Palabras clave: Estomatitis; Manzanilla; Oncología; Quimioterapia; Terapias Complementarias.

INTRODUCTION

Abnormal proliferation of cells and subsequent invasion of adjacent tissues is called neoplasia, and this is one of the leading causes of death in the world, and a public health problem [(1)]. It is estimated for the years 2020 to 2022, the occurrence of 625 thousand new cases of cancer in Brazil, for each year of the triennium [(2)]. These patients will be submitted to oncology therapy such as chemotherapy, surgery, hormone therapy and

immunotherapy. Such treatments have the intention of increasing the chances of cure as well as the conservation of the affected tissue [3].

Gastrointestinal tissue cells have greater mitotic capacity, so antineoplastic chemotherapy and radiotherapy can cause acute symptoms such as: mucositis, enteritis, dysgeusia, xerostomia and skin scaling [4]. Mucositis is an inflammation of the mucous membrane of the gastrointestinal tract, which can go from the mouth to the anus, and its first symptoms can appear already in the second week of oncologic treatment [5]. The pathophysiology of mucositis is divided into four 4 phases: inflammatory (increasing the vascularization of the site), epithelial (reduction of cellular mitoses), ulcerative (occurs the scaling of the epithelium) and curative (occurs the renewal of cells and as a consequence the healing) [6].

The patient with oral mucositis (OM) is debilitated due to a decrease in food intake, caused mainly by pain, which influences the healing process. Chamomilla recutita (CR), popularly known as chamomile, is a plant native to Europe and acclimatized in some regions of Asia and Latin America, being widely cultivated throughout the world. In Brazil, it is highlighted in the South and Southeast of the country, and is considered a medicinal plant used for therapeutic purposes for centuries [7], However, its therapeutic use in traditional medicine is recent and gradual, so one wonders: what is the production of scientific literature on the effect of CR in patients with oral mucositis and in oncologic treatment? The answer to this question may influence the patient's experience with health care.

Thus, the objective was to identify, through national and international literature, the effects of CR in oncologic patients with oral mucositis.

METHODOLOGY

This was a Systematic Review study (SR) which consists of one of the methods used for literature review, this being an important resource of evidence-based practice. For the elaboration of the stages of SR, we used the protocol PRISMA 2016/2018 [8, 9].

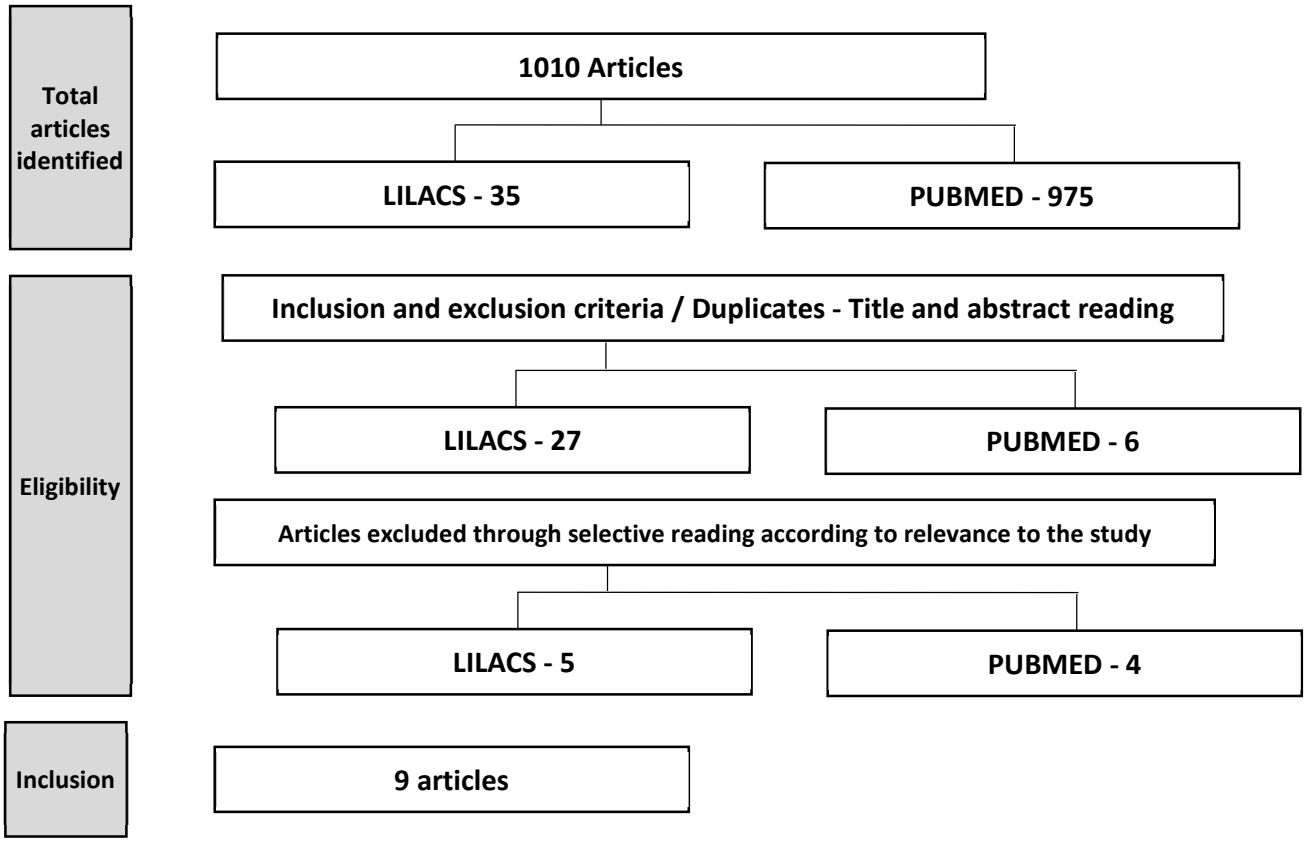
For the elaboration of the clinical question the PICO strategy was adopted, in which P represents patient/problem, I of intervention, C of comparison and O of outcomes/disclosure, being these fundamental components for the SR [10]. For this P study it meant: What the national and international literature addresses the use of CR for oncologic patients with oral mucositis; I: CR use; C: there was no comparison; and O: reduction of the inflammatory process.

Data was searched via Internet in the free access databases, using the following databases: National Library of Medicine (PUBMED) and Latin American Caribbean Literature on Health Sciences (LILACS). The controlled descriptors were delimited according to each base, and were used due to the high number of articles identified. The following associated descriptors were used: **LILACS: "***Stomatitis or Matricaria or chamomile and medical oncology*"; "*Stomatitis and Matricaria*"; "*Matricaria and medical oncology*"; "*Chamomile and medical oncology*", "*Stomatitis and chamomile*". **PUBMED: "***Stomatitis* [mesh] *and Matricaria* [mesh] *and neoplasms* [mesh]"; "*Stomatitis* [mesh] *and Matricaria* [mesh]"; "*Stomatitis* [mesh] *and medical oncology*", "*Matricaria and medical oncology*". The search was carried out from April to May 2019.

In the first stage of research, the articles were surveyed with the proposed descriptors in the databases, being identified 1010 productions, of which 975 articles were in the PUBMED database and 35 articles in the LILACS database. In the second stage, the titles of the articles and abstracts were analyzed, excluding the duplicate articles among the databases used and which dealt with the use of CR, however not for oral mucositis. Also, review articles and articles that did not address the proposed topic were excluded, totaling 33 selected articles. In the third stage the critical evaluation of the studies was carried out, and finally, in the fourth stage, the careful reading of the complete articles and their qualitative analysis were applied for the extraction of the data, at this moment 24 articles were excluded that although they treated CR for the treatment of oral mucositis, they made use of other associated components, being CR one more substance involved in the pharmacological solution, soon it became a confounding factor, because it was not possible to identify if the positive/negative effect was of CR or of the other associated components, therefore the selection ended with nine articles. It should be noted that all steps were performed in pairs, and in cases of disagreement between the reviewers, there was discussion in order to decide on the inclusion or exclusion of the article.

The Kappa Test was used [11], which deals with the level of agreement between the reviewer pairs that acted in the selection of the articles, and the result obtained was 0.96, which means almost perfect agreement between the reviewers. The process of search and selection of the articles can be observed in figure 1.

Figure 1. Flowchart of operationalization of the revision according to PRISMA, Chapecó, Santa Catarina, Brazil, 2020.



Source: Developed by the authors.

The data was extracted using the URSI tool [12], and the articles were evaluated according to quality criteria, and randomized clinical trials were evaluated according to the CONSORT Instrument (37 items for evaluation) [13], for the experimental studies the Warnock instrument was used [14] (24 items for evaluation), and finally, to evaluate the case study the instrument CARE checklist version 2013 was applied (30 items for evaluation) [15]. This information is present in table 1.

Table 1. Summary of the quality evaluation of the selected studies, Chapecó, Santa Catarina, Brazil, 2020.

Author/ Year	Level of Evidence	Absolute Value	% meeting the quality criteria
CONSORT			
Braga, *et al*. 2015	II	25	67.5
Ardakani, *et al*. 2016	II	28	75.6
Marucci, *et al*. 2017	II	24	64.8
Fidler, *et al*. 1995	II	21	56.75
Warnock - evaluation of experimental studies			
Pavesi, *et al*. 2010	II	18	72
Seyyede, *et al*. 2014	II	21	84
Reis, *et al*. 2016	II	20	80
Curra, *et al*. 2012	II	17	68

CARE Checklist			
Mazokopakis, *et al*. 2003	IV	19	63.3

Source: Developed by the authors.

The articles used for this systematic review meet more than 50% of the quality criteria in the instruments used, which implies that the evidence produced in this study is reliable for practical application in health. We also inform that, in order to meet the ethical precepts in research, the articles selected when cited in the text were referenced.

RESULTS

The selected corpus of studies was produced by nurses, doctors and dentists. The concentration area is health sciences, with application in humans and animals. The investigations occurred in Asia (two studies), Europe (two studies), South America (four studies) and North America (one study), varying from the years 1995 to 2017, published in English and Portuguese. The synthesis of the information extracted from the studies can be observed in the table 2.

Table 2. Summary of studies selected for systematic review, Chapecó, Santa Catarina, Brazil, 2020.

Evidence	Sample	Substance	Main results
1 [16]	40 participants candidates for HSCT	CR solution at 0.5%, 1% and 2% (*apigenin-7-glucoside* per ml of production)	Only the 1% dose showed a reduction in the incidence, intensity, and duration of oral mucositis compared to the control group. The formulation was well tolerated by patients and safe. There were no adverse effects.
2 [17]	60 patients submitted to HSCT, divided into two groups	Mouthwash with 1% peppermint oil, 1% CR dry extract and 96% alcohol. The placebo was similar in taste, smell and color, 0.02% edible red dye, 0.5% chlorophyll color, 13% 96% alcohol, 71.5% sterile distilled water and 15% mint *pulegium* aroma	The treatment group had lower degrees compared to the placebo. In terms of pain, xerostomia and dysphagia, there was a significant decrease in the rinse group. It was observed that the rinse group required fewer interventions compared to the placebo group.

3 [18]	105 hamsters divided into 3 groups. Group I - no treatment (control); group II - CR treatment (Ad-Muc®); and group III - corticoid treatment (betamethasone elixir - Celestone ®)	Each gram of ointment contains 100mg of CR fluid extract, glycerol, lanolin alcohols, ketoestearyl alcohol, sodium petrolatum, xanthan gum, methylparaben, peppermint essence, myrrh tincture, mineral oil, sodium saccharin and purified water.	The CR group had 12 times more chances to mark absence of mucositis than the corticoid, the control group did not differ. Analysis of histopathological findings revealed that the CR group exhibited a lower degree of mucositis compared to the other groups.
4 [19]	76-year-old female, carrier of rheumatoid arthritis. The treatment was a combination of corticosteroid (5mg/day), methotrexate (MTX) (10mg/ week) and folic acid (5mg/ week).	Liquid preparation for CR cheek adding 8 grams of dried flowers to 1000 ml of boiling water, covering and leaving in infusion for 15min.	Patient presented mucositis grade 3. On the 13th day of hospitalization the oral mucositis was moderate (note 2: erythema, ulcers, able to eat solids) and was completely healed within four weeks.
5 [20]	36 patients diagnosed with Recurrent aphthous stomatitis (RAS). Triple blind.	Group A received CR dye and group B placebo (both produced by a pharmacological research center). The patients were instructed to apply to ten drops of the product three times a day.	CR significantly reduced the healing period, number of injuries, pain and burning sensation.
6 [21]	101 participants tested rinses that could prevent the development of mucositis in patients undergoing head and neck CPB chemotherapy.	The experimental group rinse had propolis, aloe vera, calendula and CR as its ingredients. In the placebo honey was added and the same resulting excipients in a solution similar to	The authors report that CR, aloe and vera, calendula and propolis are ineffective in preventing acute grade 3 mucositis. These natural agents can have other beneficial effects, such as shortening the time to cure the mucosa, which

		the experimental in color, flavor and density.	was not screened in this study. mucositis degree 2. The frequency
7 [22]	38 patients divided into two groups who received chemotherapy with *5-fluorouracil and leucovorina*.	Control group received an ice cup made with pure water, and the CR group received an ice cup made with CR infusion at 2.5%. The infusion was made with 400mL of water and 10 g of flowers.	The CR group did not develop ulceration was 16% in the control group vs. 0% in the CR group. The occurrence of oral mucositis and pain was also lower in the CR group.
8 [23]	36 female Hamsters- Syrian divided into three groups.	Group I - no treatment (control); Group II - CR treatment (Ad-Muc®); and Group III - corticosteroid treatment (Celestone® betamethasone elixir). Each gram of the ointment contained 100 mg of CR fluid extract.	Topical treatment with CR leads to a decline in IL-1b and TNF-a levels, associated with less severe oral mucositis.
9 [24]	164 patients in their first 5- FU cycle	The *chamomilla*/ placebo was administered 3x a day for 14 days. In the CR group, 100ml of water was used and 30 drops of concentrated CR were added. The participant chewed 100ml of solution.	The results do not support the hypothesis that CR can decrease the 5-FU rate and reduce mucositis. Further studies are indicated to try to find new methods to decrease mucositis induced by 5-FU.

Source: Developed by the authors.

DISCUSSION

The OM is a clinical occurrence that promotes difficulties in the progression of oncologic treatment, therefore, it is important to identify the effectiveness of CR in this scenario. With the analysis of the studies, we found a variety in the types of interventions,

variations in concentrations of pharmacological solutions, forms of preparation and clinical management.

All studies presented evidence on the beneficial effects of CR, such as shortening the time of mucosal recovery due to its anti-inflammatory potential and fewer medical interventions. In addition, some limitations were observed (sample size, dropout during the development of the studies, and no pairing between males and females recognized as an important element for analysis of treatment effectiveness), but the authors always recommended the development of other studies to strengthen the evidence produced. Among the forms of presentation found are oral rinses, ointments, tinctures and infusions.

In studies 1[16] and 2[17], Mouth rinses based on CR extract with a concentration of 1% in candidates for hematopoietic stem cell transplantation, and patients in chemotherapy and radiotherapy for the treatment of head and neck cancer were used. Benefits were found such as reduced incidence and intensity of OM, reduced pain and xerostomia. Participants in these studies received high doses of chemotherapy as a pre transplant protocol. The chemotherapy in high doses is a factor causing OM, because the dose of drugs and their administration time refer to the outcome of side effects resulting from treatment [25].

The rinse used in head and neck chemo-irradiation patients in study 6[21], did not use the CR in an isolated way, being added other ingredients in the rinse. Therefore, it was not identified the efficacy in the prevention of OM grade 3 in the patients of this study. However, they emphasize that the solution can shorten the time for mucosa recovery. In a systematic review on the therapeutic effects of CR in situations of human illness, the efficacy of oral rinsing had been identified, which showed beneficial effects for having antimicrobial and anti-inflammatory properties, which are related to the anti-inflammatory effects of apigenin compounds, a flavonoid found in its composition [26].

The oral ointment used in studies 3[18] and 8[23] contained 100mg of CR fluid extract. This formulation was studied in hamsters, which had OM induced by fluorouracil chemotherapy. This chemotherapy is considered an effective drug in cancer treatment because it integrates with DNA and interferes in the synthesis or is incorporated into a new molecule, that is, it presents an anti-cancer action, and for this reason, it becomes cytotoxic and causes damage to the cells present in the human body [27].

The above mentioned studies demonstrate in their participants low degrees of OM and highlight the need to attest the effectiveness of the ointment in humans, although it is already available in pharmaceutical networks. The characterization of CR extracts reveals the presence of phenolic compounds that can be responsible for its antioxidant and antimicrobial activity [28]. One point of concern about the use of the ointment form is its possible commercial value, which may be less accessible for populations with lower purchasing power.

CR infusions used in studies 4[19], 7[22] and 9[24], revealed great potential, and ranged from 8 grams of dried flower and 400ml of water to 10 grams of dried flower and 1 liter of water, and there is also infusion with 100ml of water and 30 drops of CR concentrate. These were used in forms of cryotherapy and infusion for later cheek, both without any side effect or resistance.

In study 4[19] The dried flowers of CR were prepared in infusion and offered to the participant of the study to make cheeks. Her mucositis was caused by a large dose of chemotherapy. In the result of the study, the researchers evidenced that the levels of ulcerations regressed in a short period of time with the cheek. In study 7[22] used the infusion with dry flowers of CR in the form of ice chips before and during the administration of chemotherapy, and report the difference between the CR group and the control with respect to the occurrence of mucositis, pain and ulcerations.

The infusion of water and CR concentrate in ice form was provided to participants in the first cycle of chemotherapy with fluorouracil in the 9th study [24]. The authors found that the form used may decrease the rate of mucositis, but its result was differentiated between men and women.

The researchers [24] highlight the outcome as unexplained, considering that the patients were not differentiated in the stages of research. It shows then, that for this reason, more studies are necessary for the hypothesis to be supported. Despite the opposite result, both conclude that this solution reduces ulcerations, pain and degrees of mucositis, in addition to pointing to CR as a treatment of low cost and wide availability. The form of infusion is facilitated in clinical practice, taking into account that staff training and standardization of the amount of ingredients for its preparation should be established and followed in order to minimize risks to patients.

The CR tincture of study 5[20], presented in drops of CR concentrate, showed benefit in the study by improving the signs and symptoms of patients with recurrent foot-and-mouth lesions, resulting in a greater speed of healing caused by the agents present in CR. What can be discussed in the case of this form of CR is its possible commercial value.

The ways of using CR have proved effective. The method of rinsing and infusion were the studies that most demonstrate beneficial effects to their patients, although all showed effectiveness. However, it is indicated the form of infusion of the CR dry flower, be it for cheek or cryotherapy, because it presents its bioactive components, and besides, it is financially accessible to all the population. The effects of the plant in question are promising and result in low cost and minimal side effects, besides easy application [25].

In the face of evidence on the use of CR, this SR provides a strategic scientific basis for decision-making in the health sector, especially in the practice of nursing care, because it allows the identification of the path taken until the development of current knowledge on the subject. In this perspective, the use of CR in oncologic treatment is considered in order to improve the quality of life of the patients, a characteristic that, currently, has occupied a prominent position, generating guiding elements to give subsidies to make treatment protocols more directive.

CONCLUSION

Based on the evidence investigated, it is understood that CR is effective in the treatment of OM due to its anti-inflammatory action. It is an affordable and easy to prepare herb, which brings advantages to the user and to the public health network, which will provide a better quality of life to the patient affected by OM during or after cancer treatments.

From the identified evidence, it is also possible to affirm that the CR dry flower infusion method is the recommended one to be used in the Single Health System, for the accessibility to the herb, by the non-invasive method of administration, and practicality in the preparation. Its concentration may vary from 6 to 10 grams of dried flower, and from 400 to 1000 ml of water. The infusion can be used as a rinse or as cryotherapy.

CR presented a good anti-inflammatory action index, the cryotherapy method based on the infusion of the flowers of the plant or just the rinse in this same form of preparation, showed greater benefit in the treatment of OM, being able to be standardized in health services without increasing costs to them. This method is practical, low cost and sustainable, besides not exposing the patient to more procedures or medications to alleviate the symptoms resulting from OM.

It is worth mentioning that it was limited to searches in two freely accessible databases for this SR, considering that there may be other evidence not accessed by the authors. Therefore, future studies are suggested to strengthen the evidence produced here, and its use in clinical practice.

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ISSN 1695-6141