International Journal of Advanced Engineering Research and Science (IJAERS)
ISSN: 2349-6495(P) | 2456-1908(O)
Vol-8, Issue-2; Feb, 2021
Journal Home Page Available: https://ijaers.com/
Journal DOI: 10.22161/ijaers
Article DOI: https://dx.doi.org/10.22161/ijaers.82.17

Action of *Matricaria Recutita* in the Management of Oral Mucositis in Animal Model: Systematic Literature Review

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Received: 26 Oct 2020;
Received in revised form:
15 Jan 2021;
Accepted: 29 Jan 2021;
Available online: 14 Feb 2021

***Keywords*— Oral Mucositis, Matricaria, Chamomile, Fluorouracil, Inflamatory citokynes.**

***Abstract*—** *Oral mucositis comprises an acute inflammatory condition frequent in cancer patients.To date, therapeutics have only alleviated the clinical aspect of lesions. Chamomile stands out as one of the most used plants in the world for medicinal purposes, as it has several beneficial characteristics. The aim of this study was to evaluate the effect of topical chamomile in the oral mucositis with clinical and/or histological parameters in an animal model. It was a systematic review, which sought articles of the "experimental study" in an animal model according to the PRISMA parameters. The databases used were PubMed, Cochrane Library, and Bireme. Crossing descriptors were selected from DeCs/MeSh with the operators AND and OR, and the ARRIVE strategy was applied. The search found 43 publications. After all the refinement steps, two articles evaluating the effects of the fluid extract of chamomile (Ad-Muc®) on chemo-induced oral mucositis were selected. The total sample included 141 female hamsters and the two studies used the same methodology to induce the lesion. The results showed that, applying chamomile in oral mucositis in hamsters was effective, both from a clinical ($p < 0.0001$) and histological parameters, with a significant reduction in pro-inflammatory cytokines ($p < 0.05$). The ARRIVE strategy, 15 recommendations were implemented out of 20 criteria in both studies.The application of topical chamomile in the treatment of chemo-induced oral mucositis in hamsters seems to be recommended due to the clinical/histopathological results demonstrated and its capability to reduce the levels of some pro-inflammatory cytokines.*

I. INTRODUCTION

Oral mucositis (OM) comprises an acute inflammatory condition frequent in cancer patients undergoing myeloablative cytotoxic chemotherapy and/or radiotherapy in the head and neck regions. Clinically, it manifests as erythematous areas, painful ulcers, pseudomembranes, edema, and hemorrhage [1,2]. Its presence directly interferes with the patient's general health, further developing severe complications, such as dysgeusia, dysphagia, opportunistic infections, in addition to increasing treatment costs, which may require the change or even interruption of antineoplastic treatment, with a direct consequence on tumor response and patient survival [3].

The mechanism of action of OM is not completely elucidated; however, it is known that inflammatory reactions arising from this condition occur due to a complex series of interactions between molecules and direct/indirect cell events that affect the epithelial and submucosal tissues of the oral mucosa [1,4]. Although the pathogenesis of OM is a dynamic process, Sonis [5,6] proposed the sequence of its biological development basing on five phases: initiation, generation of messenger signals, signaling and amplification, ulceration, and healing. The initiation phase occurs immediately after exposure to antineoplastic therapy, directly damaging the epithelial cells DNA and the underlying connective tissue, simultaneously forming reactive oxygen species (ROS). In the generation of messenger signals, a series of transcription factors are activated, especially the nuclear factor *kappa B* (NF-κB), which induces the expression of genes encoding pro-inflammatory cytokines, such as tumor necrosis factor α (TNF-α), interleukin 1ß (IL-1ß) and interleukin 6 (IL-6). In the signaling and amplification phase, these cytokines have a direct harmful effect on the cells of the oral mucosa and indirectly amplify cellular signaling. The ulcerative phase is the most important from a clinical parameter, as it comprises the phase of painful symptoms associated with loss of function. In the healing phase, ulcers heal spontaneously after the end of antineoplastic treatment, through signals from the extracellular matrix.

To date, therapeutics have alleviated the clinical aspect of lesions, reduced infections, and painful symptoms associated with OM, since no therapy is capable of preventing or completely treating this condition [7]. For this reason, the continuous search for new agents that act effectively in the management of OM has become important for the scientific community, consequently increasing studies focusing on natural agents. Natural medicine proposes that the possible therapeutic effects of herbal medicines, including analgesic, anti-inflammatory, and tissue repair actions make these products well tolerated, which has provided a progressive increase in their consumption and recommendation [8]. Chamomile, also known as *Matricaria Chamomilla L.*,*Chamomilla recutita (L.)* Rauschert, *Matricaria recutita L.*, and *Matricaria suaveolens L.*, stands out as one of the most used plants in the world for medicinal purposes, as it has several beneficial characteristics with its anti-inflammatory, antimicrobial and sedative properties [9]. Studies carried out in humans [10] and animals [4,11,12] recommend chamomile to treat several diseases in the oral cavity, including mucositis, aphthous, and traumatic ulcers.

Thus, this study aimed to carry out a systematic review on the evaluation of the effect of the use of topical chamomile in the management of OM with clinical and histological parameters in an animal model.

II. MATERIAL AND METHODS

It was a systematic literature review carried out in January to August 2020, which aimed to search for articles of the experimental study type in animal model according to the PRISMAparameters (*Preferred Reporting Items for Systematic Reviews and Meta-Analysis*), used to assist in the construction of systematic reviews and meta-analyses [13], and was registered at the PROSPERO database (CRD42020204008). The research used the *PubMed*, *Cochrane Library*, and *Bireme* databases. To maximize the evaluation and use the information presented by the studies, the ARRIVE (*Animal Research: Reporting In Vivo Experiments*) strategy was used, which is based on guiding essential information that is necessary in animal studies in order to improve researchers' communication, make the study reproducible, orderly, transparent, and accurate [14].

The relevant and specific question for this study was, "Is topical chamomile capable of preventing and/or treating oral mucositis in an animal model?" To do so, the DeCs/MeSh descriptors and free terms were crossed using the Boolean operators AND & OR. The research strategy included only terms related to chamomile, oral mucositis, radiotherapy, chemotherapy, radiotherapy, and chemotherapy, as described in Table I.

Inclusion criteria

Experimental studies in animals were included, in which OM was induced by chemotherapy, radiotherapy in the head and neck region or both, and the therapeutic approach for this condition was exclusively topical chamomile in different concentrations, without association with other therapeutic agents. As for the language, only studies in

English were selected; however, no restriction for the publication period were putted, given the scarcity of studies on this theme.

Table I: The search strategy with selected descriptors.

Mucositis	("Mucositis" OR Mucositides OR "Stomatitis" OR Stomatitides OR “Oral Mucositis” OR “Oral Mucositides” OR “Oromucositis” OR “Oromucositides”). ('mucosa inflammation' OR 'mucosa irritation' OR 'mucositis' OR 'Mucositides' OR 'Oromucositis' OR 'Oromucositides' OR 'cancrum oris’ OR ‘denture stomatitis’ OR ‘mouth epithelium inflammation’ OR ‘mouth inflammation, ulcerative’ OR ‘mouth inflammation, ulcerous’ OR ‘mouth mucosa inflammation’ OR ‘oral inflammation, ulcerative’ OR ‘stomatitis ulcerativa’ OR ‘stomatitis ulcerosa’ OR ‘stomatitis, OR ‘stomatitis, ulcerative’ OR ‘stomatitis, ulcerous’ OR ‘ulcerative mouth inflammation’ OR ‘ulcerative oral inflammation’).
Chamomile	(“Chamomile” OR “Chamomiles” OR “Chamomilla recutita” OR “Matricaria” OR “Matricaria chamomilla” OR “Marticaria recutita” OR “Matricarias” OR “Chamomillas” OR “Matricaria recutitas”). (‘Chamomille tea’ OR ‘Chamomille infusion’ OR ´Chamomiles tea’ OR ‘Wild camomille’).

Source: own authorship.

Exclusion criteria

Studies whose therapeutic approach systemic use of chamomile, and studies with human beings were excluded. Theses, dissertations were also not included, because according to the scale of scientific evidence in the Cochrane Manual for Systematic Reviews of Interventions, these modalities fit with a low level of scientific evidence [15].

Selection of articles

Articles were selected by analyzing the title, abstract, and full text, based on the previously established criteria. Two examiners (JD and GM) performed the selection independently in the previously selected databases. In case of disagreement between them, a third author would be requested, which was not necessary. Data were extracted using the inclusion and exclusion criteria and according to ethical aspects, clear methodology, and presence of results. Duplicate articles were considered only once.

Data extraction

Two examiners (JD and GM) performed the data extraction by searching for the following variables in each study: main author and collaborators, year and country of publication; study’s objective, total sample (n) and sample description, methodology, chamomile characteristics (concentration, dosage, application days), characteristics of the comparative groups (concentration, dosage, application days), evaluated parameters (clinical, histological), and main results.

III. RESULTS

The initial database search found 43 articles addressing the use of topical chamomile in OM induced in animals. After the first analysis, this number reduced to 28 articles by excluding duplicate texts. After applying the inclusion/exclusion criteria, 25 articles were removed by reading the title and abstract. Three articles were read in full, and of these, only two met the inclusion criteria after all stages of search selection and refinement according to the flowchart in Figure 1, based on the PRISMA model [13].

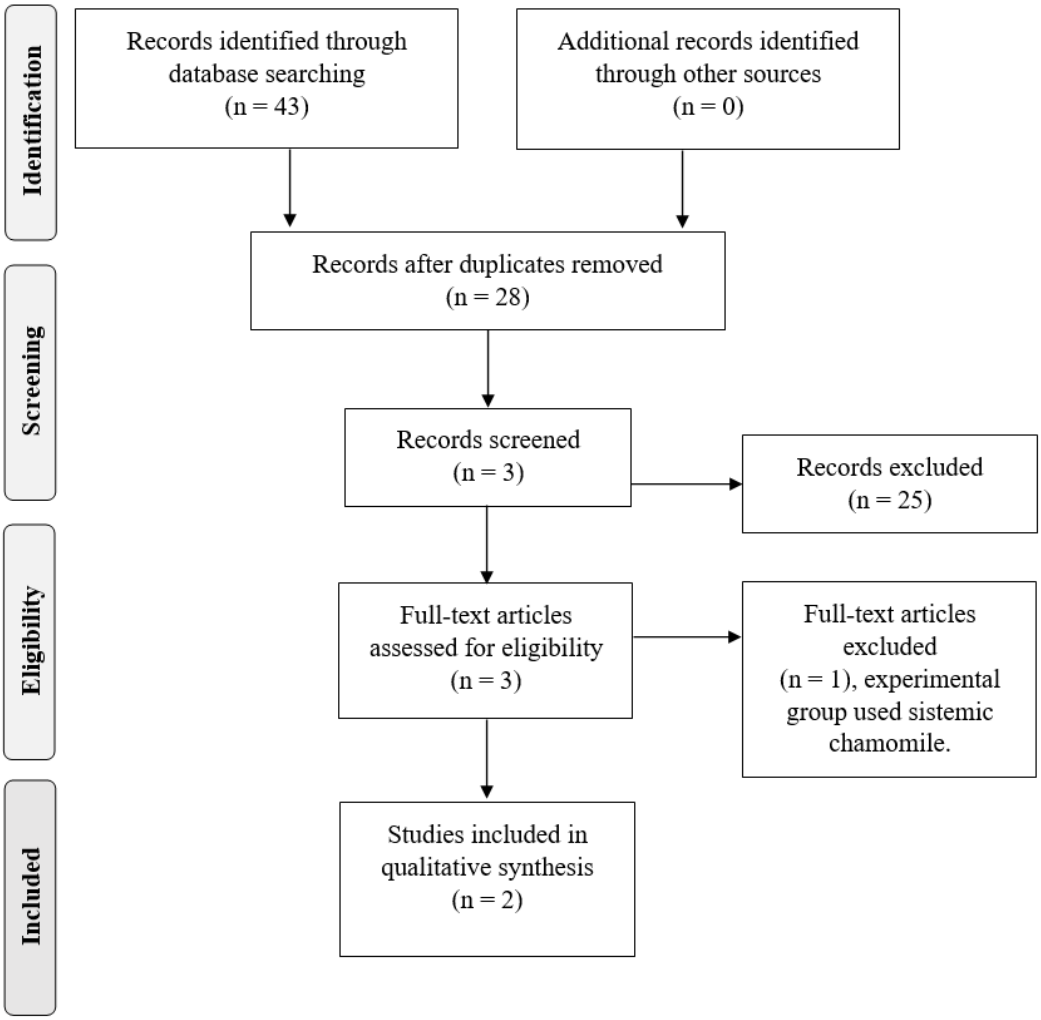

Figure 1: Flowchart of identification to selection of articles.

Two studies that compared the effects of chamomile in OM in hamsters, using clinical parameters [12] and histological [4,12], were then used to prepare this review. Pavesi *et al*. (2011) [12], evaluated clinical healing with a scoring system ranging from zero to three, proposed by Lima *et al.* (2005) [16]. Both publications performed a histological analysis; however, Pavesi *et al*. (2011) [12], using a graduation scale,evaluated the presence of inflammatory infiltrate, vasodilation, hyperemia, bleeding, ulcer, and abscess with hematoxylin & eosin and Sirius red histological staining techniques. Curra *et al.* (2013) [4], performed a qualitative and semi-quantitative analysis of pro-inflammatory cytokines IL-1β and TNF-α according to the criteria established by Grundtman *et al.* (2007) [17], with the immunohistochemical staining technique. The authors consolidated the results, as shown in Table II.

Both were carried out by the same research group. These articles used a total of 141 animals, all of which were female hamsters. Both studies used the same methodology to induce OM in animals, which was based on the administration of intraperitoneal injection of 60 mg/kg of chemotherapy 5-fluorouracil on day zero of the experiment, and on day two, an infusion of 40 mg/kg of the same antineoplastic agent. The induction of the wound in the cheek mucosa followed the same protocol for both studies, in which a sterile needle was used on days 3 and 4 after the chemotherapy administration. The application of the chamomile started on the day 5 of the experiment for the two studies. Regarding the form of presentation and use of chamomile, both studies standardized in an identical way, which included the use of the ointment with 100 mg of fluid extract of chamomile, commercially known as Ad-Muc®. The application occurred with a flexible cotton swab, twice a day (morning and night), as described in Table II [4,12].

As for the outcome of the selected studies, the application of topical chamomile in chemo-induced OM in hamsters was effective, from both a clinical [12] and histological parameters [4,12]. The study by Pavesi *et al.* (2010) [12] performed a clinical and histopathological analysis in all

four periods evaluated and the fluid extract group of chamomile (Ad-Muc®) revealed to be superior in relation to the corticosteroid group (Celestone®) and in the group without treatment (Control), with statistical significance ($p<0.0001$). In addition, in some animals of the corticoid group, bacteria can be colonized in ulcers on the 8th, 10th, 12th and 14th day of evaluation. In the study by Curra *et al*. (2013) [4], histological analysis showed that pro-inflammatory cytokines were found in all groups; however, on day 10 of the experiment, the fluid extract of chamomile had a lower score compared with the corticosteroid group, with statistical significance ($p<0.05$). Nonetheless, it showed no difference in relation to the group without treatment.

Regarding the application of the ARRIVE strategy, notably, in the two studies [4,12], 15 recommendations were implemented out of 20 previously established criteria, with little limitation in both methodologies, which makes them reproducible, transparent articles, ordered logically, well conducted and with precise objectives. Table II shows the criteria that were not considered.

Table II: General characteristics of the included studies (ICS, UFBA, 2020).

AUTHOR COUNTRY OF STUDY	PURPOSE	SAMPLE (n) AND SAMPLE DESCRIPTION	METHODS	HOW TO USE CHAMOMILE	CONTROL GROUP OR COMPARISON GROUP	EVALUATED PARAMETERS	OUTCOMES	GUIDELINE ARRIVE
Curra *et al.* [4] Brazil Experimental	To evaluate the presence and intensity of pro-inflammatory cytokines (IL-1β and TNF-α) during the development of OM after infusion with chemotherapy 5-FU.	36 adult female hamsters allocated in three groups: Group I Control (n = 12), without treatment; group II (n = 12), fluid extract of chamomile (Ad-Muc®); Group III (n = 12), corticosteroid betamethasone elixir (Celestone®).	After induction of OM in the cheek mucosa, the products were applied. Three animals per group were sacrificed on days 0, 5, 10, and 14, removing the cheek mucosa for analysis.	Topical chamomile (Ad-Muc®): for each 1g of ointment: 100 mg of fluid extract of *Chamomilla recutita (L.)*Rauschert, twice a day(morning and night).	Group I (without treatment) and Group III (corticosteroid betamethasone elixir, Celestone®— standard treatment), twice a day (morning and night).	Qualitative and semi-quantitative histological analysis were performed. In the qualitative analysis, the distribution and location of IL-1β and TNF-α protein was recorded. In the semi-quantitative analysis, the quantification of IL-1β and TNF-α was performed at the site close to the injury, based on the percentage of stained tissue, as proposed by Grundtman *et al*. (2007).	According to the qualitative analysis, the distribution and location of IL-1β and TNF-α were similar in all groups, with the diffuse distribution in the connective tissue. In adipose and epithelial tissue, the result was negative for both proteins. According to the semi-quantitative analysis, the peak of IL-1β was found on day 10 in all groups; however, in the group II, the score was significantly lower ($p<0.05$) compared with the other groups. The semi-quantitative analysis of TNF-α had peak incidence on day 5 in all groups. On day 10 of the experiment, group II was superior to group III, according to the levels of TNF-α ($p = 0.0304$). However, it did not differfrom Group I.	Total: 15/20

Pavesi *et al.* [12] Brazil Experimental	To evaluate clinically and histologically the effect of topical chamomile in 5-FU-induced OM.	105 female hamsters divided into three groups: Group I: Control (n = 35), without treatment; Group II: (n = 35), fluid extract of chamomile (Ad-Muc®); Group III: (n = 35) corticosteroid betamethasone elixir (Celestone®).	After induction of OM in the cheek mucosa, the products were applied. Three animals per group were sacrificed on days 0, 2, 5, 8, 10, 12, 14, and 16 of the experiment, removing the cheek mucosa for histological analysis.	Topical chamomile (Ad-Muc®): for each 1g of ointment: 100 mg of fluid extract of *Chamomilla recutita (L.)*Rauschert, Twice aday(morning and night).	Group I (without treatment) and Group III (corticosteroid betamethasone elixir, Celestone®-standard treatment), twice a day (morning and night).	Macroscopic analysis: erythema, hyperemia, bleeding, ulcer, and abscess. Histological parameters: inflammatory infiltrate, vasodilation, hyperemia, areas of bleeding, ulcer,and abscess. Lima *et al*. (2005) proposed the two graduation scales, with a score from 0 (absent) to 3 (severe).	Clinically and histopathologically, groups I and III had more severe OM throughout the experiment when compared with group II. On experiment days 8, 10, 12, and 14, groups I and III demonstrated severe histological changes ($p < 0.0001$) in relation to group II, with extensive areas of ulcer and bleeding, severe hyperemia and edema, and diffuse inflammatory infiltrate. Group II showed mild hyperemia and inflammatory infiltrate, in addition to the absence of ulcers.	Total: 15/20

IV. DISCUSSION

This study aimed to carry out a systematic literature review on the effectiveness of using topical chamomile in the management of OM, based on clinical and histological parameters with experimental studies in animal model. The two studies included in this review suggest that applying the fluid extract of chamomile in lesions of MO chemo-induced by 5-fluorouracil contributed to the process of tissue repair and anti-inflammatory action [4,12].

Concerning the application of Guideline ARRIVE, the two studies presented similar results, with the presence of 15 items out of 20 [4,12]. This is probably because both studies belong to the same research group. Among the unidentified items, we highlight the lack of justification for choosing the animal model and the identification of whether there was a sample calculation.

According to the methodology used for the induction of OM, the form of use and presentation of chamomile, in addition to the sample description, the two studies adopted the same criteria, which favors the analysis of the results in a more reliable way. This is because the technique and the lesion induction were the same, as well as the sample, which included female hamsters that were subdivided into three groups: negative control (without treatment), positive control (betamethasone elixir, Celestone®) and experimental with chamomile (Ad-Muc®). That is, the evaluation of the tissue repair process followed the same pattern for all selected studies, which favors their analysis.

The studies differ in the pattern of histological analysis performed to assess the presence of inflammatory infiltrate. In the study by Pavesi *et al*. (2010) [12], the evaluation occurred with vasodilation, hyperemia, bleeding, ulcer, and abscess by the conventional staining technique of Hematoxylin & eosin and Sirius red. On the other hand, in the study by Curra *et al*. (2013) [4], the immunohistochemistry technique was adopted for qualitative and semi-quantitative measurement of specific pro-inflammatory cytokines that are known to manifest themselves in OM [1,5,6]. Although the techniques employed are different, it is worth mentioning that these analyses complement and do not contradict each other, as both allow the identification of tissue elements, which provide diagnosis. In case of the need to identify specific tissue elements, special immunohistochemistry techniques are used.

The study by Pavesi *et al.* (2010) [12] was the only one who underwent clinical analysis of chemo-induced OM among the groups. The results revealed the superiority of the fluid extract of chamomile in relation to the negative control group and the topical corticosteroid group, in

which the group treated with the natural agent developed a milder OM during the entire experiment. This result corroborates studies in which a clinical reduction of lesions of non-infectious origin occurred in the oral cavity, such as mucositis and traumatic ulcers through studies carried out in humans [10,18] and animals [11].

The clinical analysis revealed that the animals started to develop OM on day 5 after the infusion of 5-fluorouracil, with a peak of clinical [4,12] and histological [12] ulceration on the 10th day. These results corroborate with a previous study in humans, in which the clinical development of OM occurred around the 10th day, with variation between 7 to 14 days after the infusion of the chemotherapy [10]. Thus, the use of an animal model in an attempt to reproduce the findings in humans is justified, as the period of development of OM is similar for the two species.

Microscopic parameters were assessed by both studies. In accordance with histological analysis with conventional staining, Pavesi *et al*. (2010) [12] found that the use of chamomile in all periods of evaluation promoted mild hyperemia and inflammatory infiltrate, in addition to the absence of ulcers when using topical corticosteroids, which presented areas with ulcers, hemorrhage, severe hyperemia, and edema, in addition to infiltrate diffuse inflammatory disease, with a predominance of neutrophils. Complementarily, Curra *et al*. (2013) [4] with a semi-quantitative analysis of IL-1β and TNF-α, demonstrated that both pro-inflammatory cytokines were found in all groups; however, on the 10th day after the chemotherapy infusion, the chamomile group had a significantly lower score in relation to the other groups, which strengthens the theory about its anti-inflammatory effect. In general, the increase in these cytokines occurs because mucositis comprises a dynamic inflammatory phenomenon [1,5]. In a double-blind, placebo-controlled study conducted by Oton-Leite *et al*. (2015) [19], an increase in the expression of IL-1β e TNF-α was found with the technique of collecting unstimulated saliva, which was diluted in a phosphate-buffered saline solution containing a protease inhibitor, during the OM phase in humans. Although using different samples to identify the presence of cytokines, these studies consolidate the theory about the complex pathophysiology of mucositis proposed by Sonis, in 2004 [5], with the triggering of a series of biological events, which stimulate the expression of these pro-inflammatory cytokines in the initial phases of generation of messenger signals, increasing considerably in the subsequent signaling and amplification phase, in which these cytokines have a direct and indirect harmful effect on the cells of the oral mucosa. This theory can also be verified in the study by Curra *et al*. (2013) [4], in which the expression of IL-1β and TNF-α are visible from the histological parameters from the fifth day after infusion, representing the initial stages of mucositis histopathogenesis.

Regarding the final evaluation period of the mucositis lesion, the study by Pavesi *et al.* (2010) [12] followed up until the 16th day, while Curra *et al*. (2013) [4] evaluated until the 14th day after chemotherapy drug infusion. Regarding the analysis intervals, Pavesi *et al*. (2010) [12] evaluated eight different moments of the experiment (days 0, 2, 5, 8, 10, 12, 14, and 16), while Curra *et al*. (2013) [4] reduced this analysis to days 0, 5, 10, and 14, totaling four periods. Although the performance of multiple analyses has given additional results, with emphasis on the beginning of the peak of mucositis occurring on the eighth day after infusion [12], the four-period approach was enough, as it was able to obtain conclusive and similar results [4]. In both studies, the number of inflammatory cells reduced after application of the fluid extract of chamomile, and Curra *et al*. (2013) [4] observed that the period of greatest reduction in inflammatory cytokines occurred at the peak of mucositis severity (day 10 post-infusion), which emphasizes the action of chamomile on this repair process in lesions of chemo-induced mucositis.

The possible reasons for the favorable effect of topical chamomile on chemo-induced OM in hamsters, according to the studies, are that its medicinal properties are already proven, which includes anti-inflammatory, analgesic, and antimicrobial action [9,20]. According to studies carried out in animals [11] and in humans [10,18], this natural agent has shown to be effective as an adjunct therapy in the management of chemo-induced mucositis due to its beneficial actions, with emphasis on the ability to inhibit the production of cyclooxygenase-2 (COX-2). However, in the study by Fidler *et al*. (1996) [21], the results obtained did not find that topical chamomile was able to decrease the severity of OM induced by 5-fluorouracil in humans. A similar result can be seen in the recent systematic review by MASCC/ISOO, in which the scarcity of clinical studies with the use of chamomile in cancer patients was observed, and due to limited evidence, no guideline was possible [22]. The two studies included in this review demonstrated that the fluid extract of chamomile proved to be superior in relation to the corticosteroid group betamethasone elixir, both from a clinical and histopathological point of view, with a significant decrease in the inflammatory infiltrate, in addition to IL-1β and TNF-α, proving the anti-inflammatory effect of this natural agent.

The findings in the experiments may be contradictory because of the form of presentation of chamomile.

According to Fidler *et al*. (1996) [21], chamomile was administered three times a day as a mouthwash by diluting 30 drops of concentrated chamomile (ASTA Médica, Incorporated, Hackensack, NJ) in 100 mL of water for 14 days, starting on the first day of the cycle with 5-fluorouracil for the treatment of solid tumors. Regarding studies in humans demonstrating a positive effect of chamomile, dos Reis *et al*. (2016) [10] adopted the application of the infusion by preparing 10g of chamomile flower in 400 mL of water, which was later transformed into ice cubes and applied to the oral cavity for 30 minutes, starting five minutes before starting the infusion with 5-fluorouracil for the treatment of solid tumors. Braga *et al*. (2014) [18] used concentrations of 0.5%, 1%, and 2% of liquid chamomile extract from dehydrated flowers and strictly controlled in the form of mouthwash in adults submitted to conditioning for hematopoietic stem cell transplantation under different chemotherapy regimes. Patients were instructed to use 10 mL of the rinse for one minute, twice a day. The 1% group demonstrated a lower incidence, intensity and duration of OM compared to the control. In the studies selected [4,12], fluid extract of chamomile was used, where each 1g of ointment contained 100 mg of fluid extract of *Chamomilla recutita (L.)* Rauschert. The application occurred with a flexible cotton swab twice a day in the hamsters. The positive results suggest that the presentation form was a positive factor, given that the fluid extract has the capacity for greater adhesion in the oral cavity for a longer time.

Some variables must be discussed for the respective findings. Associating cryotherapy with chamomile may have benefited the study by Braga *et al*. (2014) [18]. This mechanism alone already prevents the mucositis induced by antineoplastic agents with a short half-life, such as melphalan and 5-fluorouracil, with local vasoconstriction, according to the mucositis management guideline proposed by MASCC/ISSO [7]. Thus, evidence shows that both cryotherapy and chamomile promoted the prevention of mucositis, that is, the beneficial effect was enhanced by the combination of these two therapies. In the studies of this review [4,12], topical chamomile was exclusively analyzed, excluding articles that addressed the association of therapies. The fluid extract was used in animals at room temperature, which strengthens the theory that its beneficial effect is due to the inherent properties of this agent because of phenolic compounds, mainly flavonoids, with emphasis on aspegenine, quercetin, patuletin, luteolin, and its glycosides [23,24].

According to the literature, the anti-inflammatory action of chamomile has a positive effect in relation to the healing process. Countless substances make up this natural agent, such as chamazulene, alpha bisabolol, bisabolol oxides, spirometers, and flavonoid compounds [23]. According to Braga *et al.* (2014) [18], the amount of aspegenin-7-glycoside, which represents a flavonoid compound, determines the anti-inflammatory activity of chamomile. These data can be confirmed with the study by Curra *et al*. (2013) [4], in which the levels of pro-inflammatory cytokines IL-1β and TNF-α reduced significantly in the group in which 100 mg of fluid topical chamomile extract was used.

Despite the analgesic potential of chamomile due to its ability to inhibit COX-2 [10,18], the experiments in the studies did not report information on analgesia and pain. This aspect can be justified by the fact that the evaluations were performed on animals. Although the analysis of this symptom in hamsters has limitations, notably, in the study conducted by Pavesi *et al*. (2010) [12], weight reduction was significantly less in the chamomile group compared with the negative control group, which may suggest a possible analgesic effect of this agent, with reduced interference in the feeding of the animals in this group. In a complementary way, studies in humans have demonstrated its analgesic effect by the application of a questionnaire [10], or by the decrease in the use of opioid analgesics in the group that used chamomile [18].

Considering that cancer patients generally use several medications due to their systemic impairment associated with the increased costs generated, the search for low-cost alternatives is necessary, which favors studies aimed at the use of chamomile. Allied to this fact, natural products are well tolerated by the body, which has led to a progressive increase in consumption [23], as shown by the study by Braga *et al*. (2014) [18], in which 84% of patients rated the chamomile mouthwash pleasant, and in the study by dos Reis *et al.* (2016) [10], in which the cryotherapy performed with chamomile infusion promoted approval of 85% of patients.

V. CONCLUSIONS

It is worth mentioning that tissue repair in the oral cavity of humans is more complex to be studied when compared to experimental animals, which requires further studies *in vivo* to make it possible to standardize specific therapeutic parameters for clinical use of chamomile topical in mucositis.

Conclusively, topical therapy with fluid extract of chamomile can be considered in the treatment of OM in hamsters as it showed positive clinical and histopathological results and the ability to reduce the levels of some pro-inflammatory cytokines. It is also a natural agent with easy access and low cost, although few studies that have evaluated this therapeutic resource are available.

Thus, scientific production on this topic should be encouraged, as it aims at determining useful protocols of this resource for the oncological population.

ACKNOWLEDGMENTS

The authors would like to gratefully acknowledge the financial support of the Bahia Research Foundation (scholarship FAPESB).

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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