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SYSTEMATIC REVIEW

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Plant extracts used in Brazil for treatment of oral ulcers and mucositis: systematic review

Extratos vegetais utilizados no Brasil para tratamento de úlceras orais e mucosite: revisão sistemática

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ABSTRACT

Objective: To identify and analyze plant extracts used in Brazil for the treatment of oral ulcers and oral mucositis. **Material and Methods:** A systematic review was registered in PROSPERO (CRD 42018102184) and performed following the PRISMA protocol. The databases searched were PubMed, Web of Science, Scopus, Lilacs, Scielo, the Brazilian Dentistry Library. Manual searches were also performed. **Results:** Initially, 440 studies were found, of which 392 were excluded after reading the titles and abstracts. A total of 29 articles were read in full and 11 studies were excluded, resulting in 18 articles included in the systematic review. Nine plant species were identified in five clinical trials and 13 *in vivo* studies, with *Chamomila recutita* being the most used (33.3% of the studies). *Chamomila recutita* showed more promising results for analgesic, anti-inflammatory, and healing properties. *Calotropis procera* latex significantly decreased ($p<0.05$) inflammatory mediators, such as TNF-α and IL-1β in oral mucositis induced in rats. *Eupatorium laevigatum* showed anti-inflammatory activity and analgesic action on oral ulcers. *Carapa guianensis Aubl.* reduced the severity and painful symptoms of oral mucositis and exhibited better results compared to the use of low power laser. *Curcuma longa L* accelerated re-epithelialization and resolution of inflammatory processes. *Spondias mombin* reduced oxidative stress and inflammation caused by oral mucositis and helped on healing it. Extracts of *Aloe barbadensis Miller* or *Aloe vera* showed anti-inflammatory action but did not help in the healing process of oral ulcers. *Copaifera reticulata* Ducke oil did not induce improvement in the healing process, nor did it show an anti-inflammatory effect. *Malva sylvestris* did not show an anti-inflammatory action on oral lesions in humans or rats. The assessment of methodological heterogeneity showed the impossibility of performing a meta-analysis. Risk of bias varied from low to high. **Conclusion:** The plant species most used and with the best results for the treatment of oral ulcerations and oral mucositis was *Chamomilla recutita*. *Spondias mombin L.*, *Curcuma longa L.*, *Carapa guianensis* Aubl and *Calotropis procera* showed good results in the treatment of oral mucositis, while *Eupatorium laevigatum* was efficient in the treatment of ulcers of traumatic origin. *Malva sylvestris*, *Copaifera reticulata* Ducke, and *Aloe barbadensis* Miller did not exhibit significant results.

KEYWORDS

Medicinal plants; Mucositis; Oral ulcer; Phytotherapy; Plant extracts; Stomatitis.

RESUMO

Objetivo: Identificar e analisar extratos vegetais utilizados no Brasil para o tratamento de úlceras orais e mucosite oral. **Material e Métodos:** Uma revisão sistemática foi registrada no PROSPERO (CRD 42018102184) e realizada seguindo o protocolo PRISMA. As bases de dados pesquisadas foram PubMed, Web of Science, Scopus, Lilacs, Scielo, Biblioteca Brasileira de Odontologia. Buscas manuais também foram realizadas. **Resultados:** Inicialmente, foram encontrados 440 estudos, dos quais 392 foram excluídos após a leitura dos títulos e resumos. Um total de 29 artigos

foram lidos na íntegra e 11 estudos foram excluídos, resultando em 18 artigos incluídos na revisão sistemática. Nove espécies vegetais foram identificadas em cinco ensaios clínicos e 13 estudos *in vivo*, sendo a *Chamomila recutita* a mais utilizada (33,3% dos estudos). A *Chamomila recutita* apresentou resultados mais promissores quanto às propriedades analgésicas, anti-inflamatórias e cicatrizantes. O látex de *Calotropis procera* diminuiu significativamente ($p<0,05$) os mediadores inflamatórios, como TNF-α e IL-1β, na mucosite oral induzida em ratos. *Eupatorium laevigatum* apresentou atividade anti-inflamatória e ação analgésica em úlceras orais. *Carapa guianensis Aubl.* reduziu a gravidade e os sintomas dolorosos da mucosite oral e apresentou melhores resultados em comparação com o uso do laser de baixa potência. *Curcuma longa L.* acelerou a reepitelização e resolução de processos inflamatórios. *Spondias mombin* reduziu o estresse oxidativo e a inflamação causadas pela mucosite oral e ajudou na sua cicatrização. Extratos de *Aloe barbadensis Miller* ou *Aloe vera* apresentaram ação anti-inflamatória, mas não auxiliaram no processo de cicatrização de úlceras orais. O óleo de *Copaifera reticulata Ducke* não induziu melhora no processo cicatricial, nem apresentou efeito anti-inflamatório. *Malva sylvestris* não apresentou ação anti-inflamatória em lesões orais em humanos ou ratos. A avaliação da heterogeneidade metodológica mostrou a impossibilidade de realizar uma meta-análise. O risco de viés variou de baixo a alto. **Conclusão:** A espécie vegetal mais utilizada e com melhores resultados para o tratamento de ulcerações orais e mucosite oral foi a *Chamomilla recutita*. S*pondias mombin L., Curcuma longa L., Carapa guianensis Aubl e Calotropis procera* apresentaram bons resultados no tratamento da mucosite oral, enquanto *Eupatorium laevigatum* foi eficiente no tratamento de úlceras de origem traumática. *Malva sylvestris, Copaifera reticulata Ducke* e *Aloe barbadensis Miller* não apresentaram resultados significativos.

PALAVRAS-CHAVE

Plantas medicinais; Mucosite; Úlcera oral; Fitoterapia; Extratos vegetais; Estomatite.

INTRODUCTION

Oral ulcers have a variety of clinical characteristics and are classified based on the evolution period (acute or chronic), the number of lesions (single or multiple), and etiological factors (local or systemic), such as traumatic ulcers and recurrent aphthous stomatitis [1]. Oral mucositis (OM) is a common outcome in patients undergoing cancer treatment [2], whose probable mechanism of action is the development of complex biological events mediated by inflammatory cytokines, which cause ulceration and destruction of the epithelial barrier [3] and make the underlying connective tissue unprotected and vulnerable to external aggression [4] as well as other oral ulcers.

These oral lesions can decrease the patient's quality of life, causing pain and discomfort, leading to the impairment of some functions such as chewing, swallowing, speaking, and taste [5,6]. OM can become a limiting factor for cancer treatment and may cause its interruption [7] or serve as a gateway for the proliferation of bacteria, fungi, and viruses in an already debilitated patient [8].

The absence of a standard protocol for the treatment of OM and oral ulcerations points to the need for further studies with possible effective and more accessible interventions [9]. The most used measures are based on palliative care, such as good oral hygiene, use of mouthwashes, anti-inflammatories, and low power laser [8,10].

Natural treatment with medicinal plants is an affordable option for patients who already use several medications, as it has fewer side effects and lower cost compared to conventional medications [11,12]. It is known that plants have long since been used for various purposes, including the prevention and treatment of diseases [13].

Brazil has an extensive territorial area and biodiversity, with a great variety and quantity of plant species with medicinal potential [14]. It also has a good adaptation of plant cultures from different parts of the world that, when cultivated in Brazil, can have different properties [15]. Knowledge on plants and natural products with therapeutic potential is important both for their historical-cultural value and for information about their correct indication, use, and commercialization [16]. Thus, this systematic review aimed to identify and evaluate herbal medicines or plant extracts used in Brazil for the treatment of oral ulcers and mucositis.

MATERIALS AND METHODS

Protocol registration and reporting guidelines

This systematic review followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, the PRISMA statement [17]. A protocol was registered, under the number CRD 42018102184,

in the International Prospective Register of Systematic Reviews (PROSPERO).

Definition of the clinical question

The clinical question of the systematic review was: "What are the most effective medicinal plants used in Brazil for treatment of oral ulcerations and mucositis"? A PICO question is depicted in Table I.

The strategies for the searches performed on 09/17/2022 are presented in Table II.

Randomized or non-randomized clinical trials as well as animal studies assessing interventions with plant extracts or herbal medicines used in Brazil for the treatment of oral alterations characterized by ulcerations or oral mucositis were used as inclusion criteria. Meeting abstracts, qualitative studies, editorials and expert opinions were excluded.

Article selection and data extraction

The article selection process was carried out by two reviewers independently. Inter-examiner agreement was verified by applying the Kappa index (0.798) after reading 10% of the studies retrieved in the searches. Divergences were discussed and resolved by consensus. In the first phase, the studies were identified in the databases following the inclusion criteria applied to titles and abstracts. In the second phase, the full texts were obtained and analyzed based on the same eligibility criteria. The references meeting the eligibility criteria were included.

The two researchers independently and qualitatively evaluated each included study using an evaluation form with data on the following items: author; year of publication; study design; characteristics of the participants; oral alteration; inclusion criteria; medicinal plant, clinical/ macroscopic/ microscopic aspects analyzed and results.

Risk of bias assessment

The risk of bias was estimated for each selected study according to the method used. Clinical trials were evaluated using the tool for risk of bias assessment of the Cochrane collaboration (Cochrane Handbook for Systematic Reviews of Interventions) to judge the following items: selection bias composed of random sequence generation and allocation concealment; performance bias due to blinding of participants and raters; incomplete outcomes, selective reporting of results, and other biases (absence of sample calculation, standard deviation or confidence interval, inadequate statistical analysis, and observation period incompatible with the purpose of the study) [18]. The evaluation of *in vivo* studies carried out in animals was performed using the SYRCLE tool, assessing selection bias (sequence generation, baseline characteristics, allocation concealment), performance bias (random housing, blinding),

Table I - Description of the PICO strategy used to develop the clinical question

ACRONYM	DEFINITION	DESCRIPTION
P	Participants	Cancer patients, healthy patients and animals with induced oral mucositis or oral ulcers due to mechanical trauma
I	Intervention	Treatment with medicinal plants in Brazil
C	Comparison	No treatment / treatment with placebo or anti-inflammatory
O	Outcome	Clinical and histopathological characteristics of the lesions, reduced incidence of oral lesions, degree of severity and symptomatology

Table II - Search strategy used in the databases

Databases	Keywords combined with Boolean operators
Pubmed/Medline/Lilacs/Web of science/Scielo/Brazilian Dentistry Library	(phytotherapy OR "herbal drug" OR "plant extract" OR plant OR "medicinal plant" OR pharmacognosy OR ethnobotany OR ethnomedicine OR ethnopharmacology OR "flower essences" OR "natural product") AND (mucositis OR mucositides OR stomatitis OR stomatitides OR oral ulcer) AND (Brasil OR Brazil OR Brazilian)
Scopus	(phytotherapy OR "herbal drug" OR "plant extract" OR plant OR "medicinal plant" OR pharmacognosy OR ethnobotany OR ethnomedicine OR ethnopharmacology OR "flower essences" OR "natural product") AND (mucositis OR mucositides OR stomatitis OR stomatitides OR "oral ulcer") AND (Brasil OR Brazil OR Brazilian)

detection bias (random outcome assessment, blinding), attrition bias, reporting bias, and other sources of bias [19]. For each item of both tools, the study could exhibit high risk of bias, low risk of bias or unclear risk of bias.

Synthesis of results

The evaluation of methodological heterogeneity showed the impossibility of carrying out a meta-analysis, since the articles exhibited different methods and varied characteristics in relation to the medicinal plants used.

RESULTS

The search resulted in 440 potentially relevant references. The main results found are described in the Prisma Flow Diagram (Figure 1). After evaluating the titles and abstracts, 29 publications were selected. After the complete assessment of the 29 articles, literature reviews, an *in vitro* study and an *in vivo* study with diabetic wounds were excluded. Thus, 18 articles were included in the qualitative analysis [3,20-36].

Most articles reported *in vivo* studies (n = 13, 72.2%) performed with wistar rats or hamsters [3,25-36] and five articles were clinical trials (27.8%) [20-24]. Regarding plant species, nine different types were tested. *Chamomilla recutita* was the most used (n = 7, 38.8%) [3,21-23,25,27,34]. *Aloe barbadensis* Miller (n = 2, 11.1%) [29,30], *Copaifera reticulata* Ducke (n = 2, 11.1%) [31,32], *Calotropis procera* (n = 2, 11.1%) [26,35], *Carapa guianensis* Aubl. (n = 2, 11.1%) [24,33], *Eupatorium laevigatum* Lam (n = 1, 5.5%) [20], *Malva sylvestris* (n = 1, 5.5%) [28], *Curcuma longa* L (n = 1, 5.5%) [34] and *Spondias mombin* (n = 1, 5.5%) [36] were also tested.

A total of 232 patients were evaluated in the randomized clinical trials. Of these, 112 patients had been included in studies analyzing the effectiveness of *Chamomilla recutita* [21-24], 60 patients had been included in studies assessing *Eipatorium laevigatum* Lam [20], and 60 had been included in studies evaluating *Carapa guianensis* Aubl [24] (Table III).

The animals used in the *in vivo* studies were hamsters (n = 473) and rats (n = 390), totaling

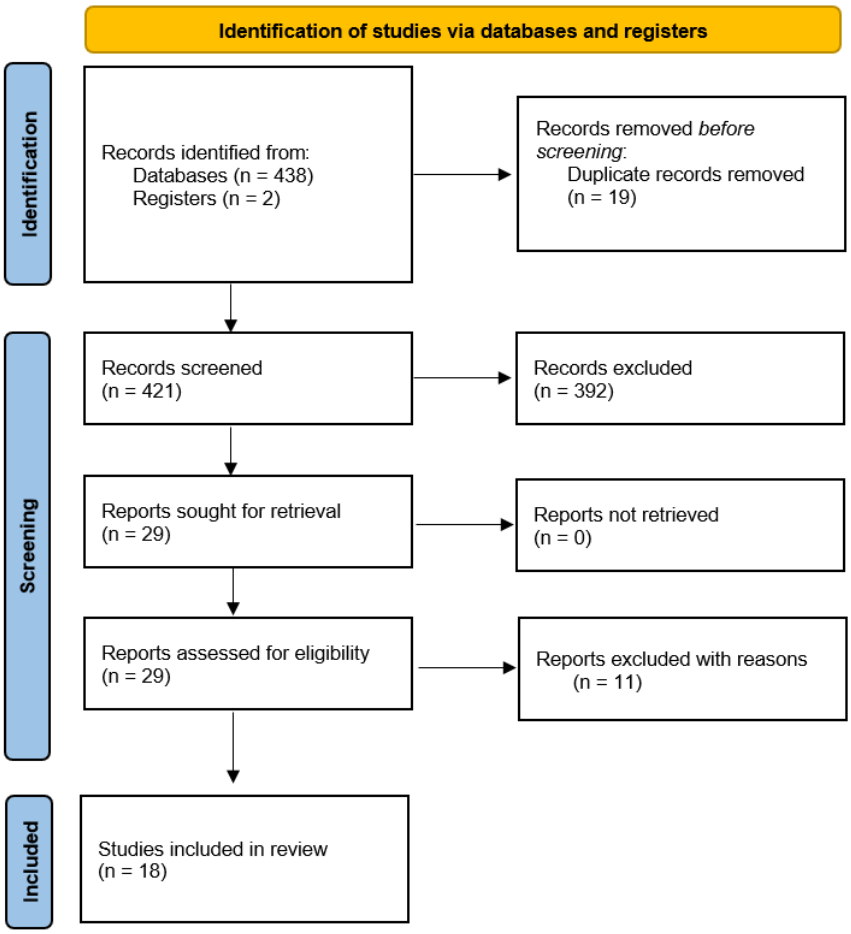

Figure 1 - PRISMA Flow Diagram for inclusion of articles in the systematic review.

Table III - Characteristics of clinical trials included in the systematic review

Authors (year)	Comparison groups	Oral alteration	Plant Extract (popular name)	Analyzed variables	Results
Paulo et al. (2000) [20]	60 patients TG: *Eupatorium laevigatum* Lam CG: triamcinolone 0.1% orabase	Oral ulcer (aphtha) at an early stage	*Eupatorium laevigatum* Lam (*mata-pasto* or *cambará-falso*) 3 times/day for 5 days	Clinical characteristics of buccal ulcers and Pain	Clinical characteristics of buccal ulcers Cure: CG: 26.7% and TG: 40%; Slight improvement: CG: 30% and TG: 36.7%; non-improvement: CG: 43.4% and TG: 23.3%. Pain Alleviated in pain: CG: 33.3% and TG: 70% (p=0.01).
Ramos-e-Silva et al. (2006) [21]	34 patients TG: AdMuc® No CG	Oral lesions of non-specific cause (aphtha)	*Chamomile recutite* (chamomile) Topical application of AdMuc®	Pain relief assessed VAS before application (T1), after 5 minutes (T2), 10 minutes (T3) and 15 minutes (T4).	Treatment efficiency of 82%. Pain relief after topical application (VAS) in T1 (113.49), T2 (75.84), T3 (48.43) and T4 (36.25) were statistically significant (p <0.05).
Braga et al. (2015) [22]	40 patients CG- Chlorhexidine 0.12% TG1 Chamomile 0.5% TG2 Chamomile 1% TG3 Chamomile 2%	Oral mucositis	*Chamomile recutite* (chamomile) extract Mouthwash in three concentrations	Incidence and intensity of oral mucositis using the oral toxicity measurement scale (WHO).	Incidence of mucositis: TG2 had 30% incidence of ulcers, TG3 60%, TG1 70% and CG 90% (p = 0,01). Intensity of the mucositis: TG2 had mean of 0.7 intensity of mucositis, TG1 and TG3 mean of 1.6 each and CG mean of 2.1 (p = 0.01). Duration of Mucositis: TG2 had average duration of 1.9 days, TG1 and CG 5.7 days each and TG3 6.9 days (p = 0.01).
Reis et al. (2016) [23]	38 patients TG: Cryotherapy with chamomile CG: Cryotherapy with plain ice	Induced oral mucositis (5-FU 425 mg/m^2 and leucovorin 20 mg/m^2)	*Chamomile recutite* (chamomile) Infusion (10g of chamomile flowers prepared in 400 ml of water)	Assessment of oral mucosa 8, 15 and 22 days after chemotherapy. Occurrence and intensity of oral mucositis (WHO) and pain in the mouth (VAS)	Day 8: Assessment of the oral mucosa: TG had 0% and CG had 16% ulceration (p =0.10). Pain: TG had 0.6 level of pain and CG 2.3 (p=0.02). Day 15: Assessment of the oral mucosa: TG and CG with similar results. Pain: TG had 0.9 level of pain and CG 2.3 (p=0.09). Day 22: Assessment of the oral mucosa: TG and CG with similar results. Pain: TG and CG with similar results. 30% of TG patients and 50% of CG patients developed oral mucositis at some point during treatment. TG patients never developed grade 2 or higher mucositis.
Soares et al. (2021) [24]	60 children (6-12 years old) TG- andiroba CG-Laser	Oral mucositis in patients undergoing chemotherapy	*Carapa guianensis Aubl (andiroba)*	OM severity degree (WHO) and Pain level (Wong-Baker visual analogue scale) in days 1 to 9.	Days 1, 2, 5-9: OM severity: TG and CG with similar results. Pain: TG and CG with similar results. Day 3: OM severity: TG and CG with similar results. Pain: TG presented 0.7 and CG 1.0 (p = 0.031). Day 4: OM severity: TG had fewer lesions than CG (p =0.003). Pain: TG presented 0.5 and CG 0.9 (p =0.003).

Notes: CG: Control group; OM: Oral mucositis; TG: Treatment group; VAS: Visual analog scale; WHO: World Health Organization

863 animals. Chamomile extract presented in ointment and commercialized as Admuc® was used in three studies [3,25,27]. *Aloe barbadensis* Miller [29,37] and *Copaifera reticulata* Ducke extracts [31,32] were analyzed in two animal studies. Latex from *Calotropis procera* [26],

orabase from *Malva sylvestris* L. [28], and oil from *Carapa guianensis* Aubl. [33] were tested in one study each (Table IV).

Risk of bias assessment

The studies of Paulo et al. [20] and Ramos-e-Silva et al. [21] exhibited high risk of bias in the selection of participants and blinding of participants and/or evaluators. The studies carried out by Braga et al. [22], Reis et al. [23] and Soares et al. [24] described, in their methods, the generation of a random sequence, concealment of allocation, blinding of participants and evaluators adequately exhibiting low risk of bias for these items. Figure 2 presents the risk of bias assessment for the clinical trials.

Risk of bias assessment in animal studies showed that all animal samples (rats or hamsters) were homogeneous with accommodation under standard conditions. The risk of bias regarding blinding of trial caregiver and researcher was unclear in the studies carried out by Kovalik et al. [28], Coelho et al. [29], Schmidt et al. [34], Ramos et al. [35], and Sousa Gomes et al. [36]. The risk of bias was low for incomplete results, selective reporting selective, and other sources of bias. The risk of bias was low for random allocation in all studies, except for the study of Freitas et al. [26] and Sousa Gomes et al. [36] (Figure 3).

DISCUSSION

This is the first systematic review carried out with medicinal plants used in Brazil for treatment of oral ulcerations and mucositis. Currently, there are no established therapeutic protocol for these conditions, only methods to alleviate pain and shorten lesion duration [7,8,32,37-39]. Therefore, the exploration of alternative treatments is crucial. Plant species have been used because they have fewer side effects compared to chemical or synthetic drugs [11,12] and there is a growing interest in evaluating their therapeutic effects due to their diverse antioxidant, analgesic, and anti-inflammatory properties [12].

The Brazilian flora is very rich in plant species with therapeutic properties with active principles that need to be explored. The country's fertile soil and climate allow both native and imported plant species to thrive [15]. The variety of species, the knowledge and influence of different cultural heritages strengthens the use for phytotherapeutic purposes, prevention and treatment of diseases, which only contributes to improving the development of studies with this approach [40].

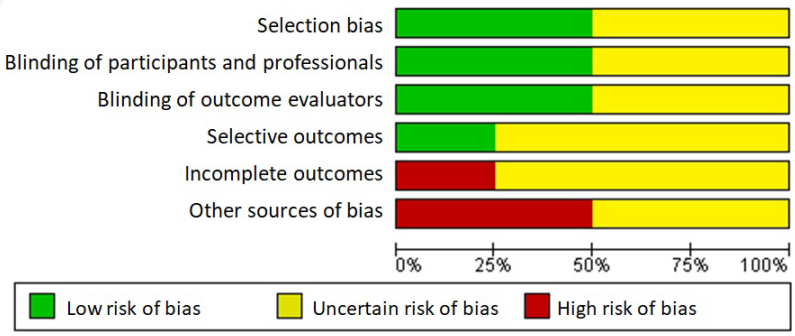

Figure 2 - Assessment of the risk of bias in clinical trials included in the systematic review.

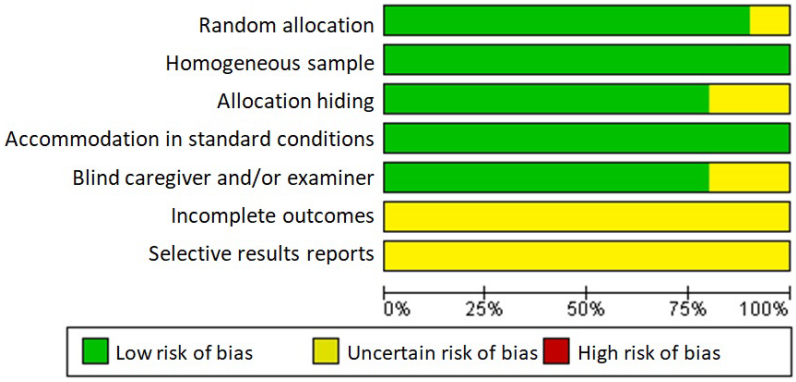

Figure 3 - Assessment of the risk of bias in animal studies included in the systematic review.

This systematic review examined 18 studies on the impact of plant extracts on oral ulcers or mucositis caused by cancer treatment. The review found five clinical trials [20-24] and 13 *in vivo* studies [3,25-36] with nine different plant species. The major number of *in vivo* studies than clinical trials is not surprising, as substances can only be tested on human beings after its properties and effects are thoroughly understood *in vivo* studies [41].

Chamomilla recutita was the most frequently used, appearing in seven studies. *Aloe barbadensis* Miller, *Copaifera reticulata* Ducke, *Calotropis procera* and *Carapa guianensis* Aubl. were present in two studies each and *Eupatorium laevigatum* Lam, *Malva sylvestris*, *Curcuma longa* L and *Spondias mombin* in one study each. Only three plant species were used in clinical trials, *Eupatorium laevigatum* Lam, *Chamomilla recutita* and *Carapa guianensis* Aubl. While *Chamomilla recutita*, *Aloe barbadensis* Miller, *Copaifera reticulata* Ducke, latex from *Calotropis procera*, *Malva sylvestris*, *Carapa guianensis* Aubl., *Curcuma longa* L and *Spondias mombin* were studied in *in vivo* studies, primarily with rats and hamsters.

Table IV - Characteristics of animal studies included in the systematic review

Author (year)	Number and type of animals	Comparison groups	Oral alteration	Plant Extract (popular name)	Analyzed variables	Results
Duarte et al. (2011) [25]	36 wistar rats	TG- 0.04 mL/ day of chamomile ointment CG- placebo	Mouth ulcer due to mechanical trauma	Topical application of chamomile extract (AdMuc®)	Histomorphological analysis: Degree of inflammation, fibroblast count, wound size and epithelialization (3, 7 and 10 days) and percentage of collagen fibers (10 days)	TG and CG had similar results in days 3 and 7. Day 10: degree of inflammation, fibroblast count, and wound size: TG and CG had similar results. TG had a higher degree of reepithelialization than CG (p=0.08). TG had greater degree of collagen fiber formation than CG (p=0.02).
Pavesi et al. (2011) [3]	105 hamsters	TG1- Chamomile TG2- betamethasone corticoid CG- Control without treatment	Induced oral mucositis (5-FU- 60 mg/kg on day 0, and 40 mg/kg on day 2)	Topical application of chamomile extract (AdMuc®)	Weight analysis, clinical and histopathological analysis by degree of mucositis	Weight Analysis: There were no notable weight changes in each group analyzed individually (p=0.3070), but TG1 and TG2 weighed significantly less than the CG (p=0.0004). Clinical analysis: There were no significant changes in the mucositis scores over time for CG (p=0.3742) and TG1 (p=0.6568). However, TG2 which had diminished severity scores over time (p=0.0349). Furthermore, the TG1 group had a 12-fold greater chance of scoring zero (absence of mucositis) than the TG2 (p =0.0001). Histopathological analysis: In each group individually were no significant associations (CG - p=0.2631; TG1- p=0.151; TG2 - p=0.0847). The comparisons between groups revealed that the TG1 exhibited the least degree of mucositis throughout the experiment in comparison to the CG and TG2 groups (p =0.0001).

Notes: 5-FU: 5-Fluorouracil; CG: Control group; CGA: *Carapa guianensis Aubl.* oil; CLX: chlorhexidine; CO: Copaiba oil; MPO: myeloperoxidase test; LP: Laticifer proteins; LPI: Protein fraction I of laticifer proteins; LPII: Protein fraction II of laticifer proteins; LPIII: Protein fraction III of laticifer proteins; LPII-IAA: Protein fraction II treated with iodoacetamide MT: Mechanical trauma; PG: Placebo Group; TG: Treatment Group; VE: Vitamin E.

Table IV - Continued...

Author (year)	Number and type of animals	Comparison groups	Oral alteration	Plant Extract (popular name)	Analyzed variables	Results
Freitas et al. (2012) [26]	90 hamsters	TG1- Normal TG2- MT TG3- MT/5FU TG4- MT/5FU025 TG5- MT/5FU1 TG6- MT/5FU5 TG7- MT/5FU25	Induced oral mucositis (5FU-60 mg/kg on day 1 and 40 mg/kg on day 2) and mechanical trauma	Processed *Calotropis procera* at 0.25, 1, 5 e 25 mg/kg (*Flor de seda*, *algodão de seda* or *queimadeira*)	Macroscopic analysis, histopathological analysis, myeloperoxidase test (MPO) and immunohistochemistry (TNFα, IL-β, iNOS, COX-2)	Macroscopic analysis: TG3 had significant injuries compared to TG1 and TG2 ($p<0.001$). TG4 had significant lesions compared to TG5, TG6, and TG7 ($p<0.05$). On D10, TG6 showed less erythema and no ulcers or abscesses compared to TG1 ($p<0.001$). The other groups did not show significant statistical differences, when compared to each other. Histopathological analysis: Both TG5 ($p<0.05$) and TG6 ($p<0.001$) significantly reduced inflammatory effects, edema, hemorrhage and prevented the formation of ulcers and abscesses in comparison to TG1. The other groups did not show significant statistical differences. Myeloperoxidase test (MPO): TG5 showed a 71% MPO activity ($p <0.01$). The TG6 demonstrated an even stronger result, an 88% of MPO activity ($p<0,001$). The other groups did not show significant statistical differences. Immunohistochemistry: Only TG1, TG2 and TG6 were evaluated: In the inflamed conjunctive tissue, TG6 showed significant increases in the expression of TNF-α ($p<0.001$), IL-1β ($p<0.001$), iNOS ($p<0.05$), and COX-2 ($p<0.05$) compared to TG1. In the epithelial tissue, TG6 only showed a significant decrease in the immunostaining of COX-2 ($p<0.05$) and iNOS ($p<0.05$) compared to TG1.

Notes: 5-FU: 5-Fluorouracil; CG: Control group; CGA: *Carapa guianensis Aubl.* oil; CLX: chlorhexidine; CO: Copaiba oil; MPO: myeloperoxidase test; LP: Laticifer proteins; LPI: Protein fraction I of laticifer proteins; LPII: Protein fraction II of laticifer proteins; LPIII: Protein fraction III of laticifer proteins; LPII-IAA: Protein fraction II treated with iodoacetamide MT: Mechanical trauma; PG: Placebo Group; TG: Treatment Group; VE: Vitamin E.

Table IV - Continued...

Author (year)	Number and type of animals	Comparison groups	Oral alteration	Plant Extract (popular name)	Analyzed variables	Results
Curra et al. (2013) [27]	36 hamsters	TG1- Chamomile TG2- Betamethasone Corticoid CG-Control	Induced oral mucositis (5-FU- 60 mg/kg on day 0, and 40 mg/kg on day 2)	Topical application of chamomile extract (AdMuc®)	Distribution and location of IL-1β and TNF-α proteins Immunostaining of IL-1β and TNF-α and Clinical evaluation on days 0, 5,10 and 14	Distribution and location of IL-1β and TNF-α proteins: Both IL-1β and TNF-α proteins showed a similar distribution and localization, exhibiting a diffuse pattern throughout the connective tissue. The epithelium and adipose tissue were negative for both proteins. Immunostaining of IL-1β and TNF-α and clinical evaluation on days 0, 5,10 and 14: IL-1β: After infusion with 5-FU, all groups discovered a significant increase in immunolabeling for IL-1β ($p < 0.05$). The highest scores were observed in the 10-day period in all groups ($p<0.05$). TG1 showed lower levels of IL-1β D14 in relation to groups CG and TG3 ($p<0.05$). TG1 presented a lower degree of mucositis than CG and TG2 ($p<0.05$). TNF-α: After infusion with 5-FU, all groups showed a significant increase in immunolabeling for TNF-α ($p < 0.05$) and the development of oral mucositis (Days 5–14). However, the TG1 group exhibited a unique pattern of protein expression. This pattern was characterized by an initial increase in tissue levels of TNF-α on Day 5, followed by a significant decrease on Day 10. A subsequent increase was observed on Day 14 ($p = 0.0188$).
Kovalik et al. (2014) [28]	136 rats	TG- Mauve G2- Orabase vehicle GCLX CG- Control	Mouth ulcer due to mechanical trauma	Stems and dried leaves of Malva sylvestris L. 20% in orabase (*malva cheirosa* or *malva silvestre*)	Wound healing area (mm^2) for each experimental time (0 3, 7, 15 and 21 days)	Wound area (macroscopic and histological) and percentage of healing: No statistical significance was found between groups in all periods. However, wound protection can mitigate the impact of physical damage directly at the site of injury.

Notes: 5-FU: 5-Fluorouracil; CG: Control group; CGA: *Carapa guianensis Aubl.* oil; CLX: chlorhexidine; CO: Copaiba oil; MPO: myeloperoxidase test; LP: Laticifer proteins; LPI: Protein fraction I of laticifer proteins; LPII: Protein fraction II of laticifer proteins; LPIII: Protein fraction III of laticifer proteins; LPII-IAA: Protein fraction II treated with iodoacetamide MT: Mechanical trauma; PG: Placebo Group; TG: Treatment Group; VE: Vitamin E.

Table IV - Continued...

Author (year)	Number and type of animals	Comparison groups	Oral alteration	Plant Extract (popular name)	Analyzed variables	Results
Coelho et al. (2015) [29]	72 rats	TG- Aloe Vera CG- Control PG- Placebo (hydro alcoholic extract)	Mouth ulcer due to mechanical trauma	*Aloe barbadensis* Miller (*Aloe vera*) *in 0.5% hydroalcoholic extract 12 / 12h*	Clinical analysis of the area and healing of the wound and histopathological analysis of the reepithelialization and degree of inflammation,on days 1, 5, 10, 14	Clinical analyzes of the area and wound healing: There was no statistical difference between groups. Histopathological analysis of re-epithelialization and degree of inflammation: statistical significance among groups in all periods.
Cuba et al. (2015) [30]	35 wistar rats	TG1- 70% AV TG2- 400mg VE CG- hydroxy-methylcellulose	Mouth ulcer due to mechanical trauma	*Aloe barbadensis* Miller (*Aloe vera*)*70%* and vitamin E gel (VE) ephynal®400mg	Evaluation on days 5 and 7 to verify: inflammatory response by cells and blood vessels (Absent, mild, moderate and intense). Lesion size and weight loss	Inflammatory response, lesion size and weight loss: 5-day period: TG1 and TG2: presented the intensity of the inflammatory process ranged from mild to moderate. TG1: Three animals showed lesions on the tongue. TG2: Two animals showed lesions on the tongue. CG: All animals had moderate intensity inflammation and showed lesions on the tongue, and the size of the lesions was statistically larger compared to the animals to the TG1 e TG2 groups ($p<0,05$). In the 5-day experimental period, there was no weight loss in any animal. 7-day period: TG1 and TG2: The inflammation decreased from moderate to mild. All animals showed complete healing of the lesions. CG: All animals developed an intense degree of inflammation and some degree of ulceration, and the size of the lesions was statistically larger compared to the TG1 and TG2 groups ($p <0.05$). All animals showed weight loss, ranging from 50 to 100 g.

Notes: 5-FU: 5-Fluorouracil; CG: Control group; CGA: *Carapa guianensis Aubl.* oil*;* CLX: chlorhexidine; CO: Copaiba oil; MPO: myeloperoxidase test; LP: Laticifer proteins; LPI: Protein fraction I of laticifer proteins; LPII: Protein fraction II of laticifer proteins; LPIII: Protein fraction III of laticifer proteins; LPII-IAA: Protein fraction II treated with iodoacetamide MT: Mechanical trauma; PG: Placebo Group; TG: Treatment Group; VE: Vitamin E.

Table IV - Continued...

Author (year)	Number and type of animals	Comparison groups	Oral alteration	Plant Extract (popular name)	Analyzed variables	Results
Teixeira et al. (2017) [31]	15 wistar rats	TG- CO GCort- Corticosteroid dexamethasone CG-Control	Mouth ulcer due to mechanical trauma	*Copaífera reticulata* Ducke (Copaiba oil) 200mg/kg/day	Toxicity, qualitative analyzes: edema, inflammatory infiltrate, Immunohistochemical analysis	Negative acute oral toxicity test within 48 hours. TG showed less inflammatory infiltrate compared to CG (p <0.05). TG showed greater anti-inflammatory action and faster repair of the injured area. TG reduced the intensity of the edema (1.8 ± 0.20) compared to CG (2.4 ± 0.4) (p <0.05). TG with reduction of CD68 positive macrophages in comparison to CG (p = 0.04).
Wagner et al. (2017) [32]	96 wistar rats	TG- CO GCort- Corticosteroid CG-Control PG-Placebo	Mouth ulcer due to mechanical trauma	*Copaífera reticulata* Ducke (Copaiba oil)	Animal weight, Clinical analysis of healing process and histopathological analysis in days 3, 5, 10 and 14.	Weight Analysis: On days 3 and 5 there was no significant difference in the weight of the animals. GCort lost more weight than CG (p=0.006) and PG (p=0.02) after 10 days. GCort lost more weight than TG (p=0.01) after 14 days. Clinical analysis of healing process: At day 3, 5 and 10, all animals experienced a similar percentage of wound healing. However, at the 14-day analysis, GCort showed a slower wound healing process (p = 0.007). Histopathological analysis: Did not show differences between groups.
Wanzeler et al. (2018) [33]	122 hamsters	TG1- CGA (100%) TG2- CGA (10%) TG3- CGA (10%refinado) TG4- Cyclophosphamide CG- no treatment	Induced oral mucositis (5-FU- 60 mg/kg on days 0, 5 and 10) and mechanical trauma	*Carapa guianensis Aubl.* (*andiroba*)	Cytotoxicity, genotoxicity, degree of mucositis, histopathological evaluation	Cytotoxicity and genotoxicity: Andiroba did not show cytotoxicity, but genotoxic potential (p <0.001). Degree of mucositis: TG1 showed a significant reduction in the degree of mucositis in relation to the other groups (p<0.005). Histopathological evaluation: TG1 showed reduced inflammatory infiltrate in compared to the group without treatment during the histopathological evaluation (p<0.005).

Notes: 5-FU: 5-Fluorouracil; CG: Control group; CGA: *Carapa guianensis Aubl.* oil; CLX: chlorhexidine; CO: Copaiba oil; MPO: myeloperoxidase test; LP: Laticifer proteins; LPI: Protein fraction I of laticifer proteins; LPII: Protein fraction II of laticifer proteins; LPIII: Protein fraction III of laticifer proteins; LPII-IAA: Protein fraction II treated with iodoacetamide MT: Mechanical trauma; PG: Placebo Group; TG: Treatment Group; VE: Vitamin E.

Table IV - Continued...

Author (year)	Number and type of animals	Comparison groups	Oral alteration	Plant Extract (popular name)	Analyzed variables	Results
Schmidt et al. (2019) [34]	62 golden Syrian hamsters	CG-Control PG-Placebo TG1- *Chamomilla recutita* TG2- *Curcuma longa* L.	Mechanical trauma Induced oral mucositis (5-FU-60 mg/kg on day 0, and 40 mg/kg on day 2)	TG1 - Chamomile extract (AdMuc®) TG2 - mucoadhesive formulation containing *Curcuma longa* L. extract	Clinical and histopathological analysis, Inflammatory process, immunostaining of TGF-β1 in the epithelial lining.	Clinical Analysis: All animals exhibited Oral Mucositis (OM) on Day 5. On Day 8, the TG1 group showed a milder form of OM compared to the CG ($p < 0.05$) and PG ($p < 0.01$) groups. TG2 revealed less severe OM compared with CG ($p < 0.01$) and PG ($p < 0.001$). No differences were observed among groups on Days 10 and 14. Histopathological Analysis: No differences were observed among groups on Days 5. At Day 8, TG1 and TG2 demonstrated accelerated re-epithelialization in comparison to CG ($p < 0.001$) and PG ($p < 0.001$). At Days 10 and 14, all groups showed re-epithelialization coverage of all of the wound thickness. The only statistically significant difference observed at day 10 was between PG and TG2 ($p < 0.05$). Inflammatory Process: No differences were observed among groups on Day 5. At Day 8, CG and PG showed similar scores with predominance of diffuse acute inflammation. TG2 and TG1 revealed a significant reduction and chronification of inflammation process comparing with CG ($p < 0.05$; $p < 0.001$) and PG ($p < 0.01$; $p < 0.001$). At Day 10, TG1 and TG2 still demonstrated a lower inflammatory process compared with the PG ($p < 0.05$). At Day 14, all groups presented resolution and healing (reduction or disappearance of chronic inflammation). Immunostaining of TGF-β1: At Day 8, the TG2 exhibited significantly lower labeling of this cytokine compared with PG ($p = 0.019$) and CG ($p = 0.019$). At Days 5, 10 and 14, no difference was found among groups.

Notes: 5-FU: 5-Fluorouracil; CG: Control group; CGA: *Carapa guianensis Aubl.* oil; CLX: chlorhexidine; CO: Copaiba oil; MPO: myeloperoxidase test; LP: Laticifer proteins; LPI: Protein fraction I of laticifer proteins; LPII: Protein fraction II of laticifer proteins; LPIII: Protein fraction III of laticifer proteins; LPII-IAA: Protein fraction II treated with iodoacetamide MT: Mechanical trauma; PG: Placebo Group; TG: Treatment Group; VE: Vitamin E.

Table IV - Continued...

Author (year)	Number and type of animals	Comparison groups	Oral alteration	Plant Extract (popular name)	Analyzed variables	Results
Ramos et al. (2020) [35]	64 male Golden Sirius hamsters	TG- *Calotropis procera* latex protein samples (LP, LPI, LPII, LPIII and LPII-IAA) CG-Control PG-Placebo	Mechanical trauma Induced oral mucositis (5-FU-60 mg/kg on day 1, and 40 mg/kg on day 2)	*Calotropis procera* (sodom apple)	Lesion area, animal weight, Inflammatory markers, immunohistochemistry.	Lesion area: The LP and LPPII-IAA groups were better and prevented ulceration of the mucosa. Body weight of the animals: The LP, LPII and LPII-IAA groups contributed to avoid the severe effect of 5-FU in terms of survival and body weight gain. Inflammatory markers: The LPII and LPII-IAA groups demonstrated a similar ability to inhibit key inflammatory markers, including the recruitment of inflammatory cells and the release of pro-inflammatory cytokines. Immunohistochemistry: An inhibitory effect of LPII-IAA on IL-1β was observed. Treatments with both LP and LPII-IAA resulted in a decrease in ICAM-1 immunolabeling. An increase in type I collagen fibers was observed in the tissues obtained from animals that underwent either LP or LPII-IAA therapy.
Sousa Gomes et al. (2020) [36]	30 Golden Siryan male hamsters	CG- Control TG1- MT TG2- 5-FU- 60 mg/kg on day 1, and 40 mg/kg on day 2/MT TG3- 50mg/kg *S. mombin* TG4- 100mg/kg *S. mombin* TG5- 200mg/kg *S. mombin*	Mechanical trauma Induced oral mucositis (5FU)	*Spondias mombin* (*caja*)	Macroscopic scores, Histopathological and spectroscopic analyses.	Macroscopic scores: The CG and TG5 presented significantly lower macroscopic scores when compared to TG2 ($p < 0.05$). Histopathological analyses: TG5 exhibited almost complete healing in all animals, areas of re-epithelialization, discrete cell infiltration, absence of hemorrhage, edema, ulcers, and abscesses, significantly lower than TG2 ($p < 0.05$). Spectroscopic analyses: TG5 animals were able to significantly prevent the reduction of total glutathione (GSH) levels compared to the TG2 ($p < 0.01$). Malondialdehyde (MDA) levels were lower in the CG and TG5 when compared to that observed in the TG2 ($p < 0.001$). The estimation of Superoxide dismutase (SOD) was lower in the CG, TG1, TG4 and TG5 compared to the TG2 ($p < 0.05$). Inflammatory cytokine IL-1β was significantly lower in the CG and TG5 ($p < 0.05$) compared to TG2. TNF-α was significantly reduced in the CG and TG5 ($p < 0.0001$), and in the TG1 compared to TG2 ($p < 0.001$).

Notes: 5-FU: 5-Fluorouracil; CG: Control group; CGA: *Carapa guianensis Aubl.* oil; CLX: chlorhexidine; CO: Copaiba oil; MPO: myeloperoxidase test; LP: Laticifer proteins; LPI: Protein fraction I of laticifer proteins; LPII: Protein fraction II of laticifer proteins; LPIII: Protein fraction III of laticifer proteins; LPII-IAA: Protein fraction II treated with iodoacetamide MT: Mechanical trauma; PG: Placebo Group; TG: Treatment Group; VE: Vitamin E.

Chamomilla recutita is native from Europe but widely grown globally and is common in Brazil's South and Southeast regions [22]. It has been the plant species with the most promising results among the clinical trials [21-23] and studies with animals [3,25,27]. This is likely due to its phytochemical compounds, which include β-farnesene, chamomillol, spiroether, chamomillaester, glycosides such as aesculin, scopolin, fraxin, isofraxidin-7-hexoside, caffeoylquinic acids, and phospho- and glyceroglycolipids found in its roots [42].

Chamomile was tested in each clinical trial under different pharmacological presentation: ointment form commercialized as AdMuc® and applied topically; mouthwash in three concentrations (0.5%, 1%, and 2%); and infusion with subsequent freezing for use in cryotherapy. In all forms of use, chamomile extract showed good results. In the study evaluating mouthwashes (in concentrations of 0.5%, 1%, and 2%) in patients with hematopoietic stem cell transplantation, the reduction in the incidence of oral mucositis as well as its intensity and duration in the group treated with 1% chamomile extract was observed [22]. The incidence of oral mucositis was also lower in patients undergoing cryotherapy with ice made from chamomile infusion [23]. Although the effects of cryotherapy on prevention, reduction of injury time, and severity of oral mucositis have been previously described [43,44], the association of chamomile improved the results of conventional cryotherapy. Chamomile gel was also effective in relieving pain in patients with traumatic ulcers [21]. More research is encouraged.

Eupatorium laevigatum is used in folk medicine for wound healing and as an antifungal [45]. Its methanolic extract contains alkaloids, steroids, phenols, tannins, and flavonoids [46]. Patients with oral ulcers had less pain after five days of treatment with the extract of *Eupatorium laevigatum* when compared to the control group [20].

Aloe barbadensis Miller or, more commonly, *Aloe vera* (AV), a plant from Northeast Africa and the Mediterranean region, was adapted to hot climates, such as in Brazil. It has numerous antioxidant, anti-inflammatory and healing properties [47,48]. The result in the treatment of lesions on the oral mucosa differed according to the concentration of the extract. While AV hydroalcoholic extract (0.5%) did not promote local effect or improvement in wound healing [29], 70% AV glycolic extract reduced the inflammatory process and the severity of lesions [37]. The results show the need for further studies exploring the different application vehicles and concentrations of AV.

Copaiba oil-resin is often used orally or topically as an anti-inflammatory and healing agent [49,50]. Studies with different forms of administration confirmed these effects [51]. Oral administration reduced the chronic inflammatory infiltrate and macrophage activity in oral lesions [31]. However, when topically applied to lesions on the dorsum of the tongue, copaiba oil did not accelerate the healing process of the lesions despite not having any relevant side effects [32]. Future research on the different routes of administration of copaiba oil is recommended to obtain better results in the treatment of ulcerations of the oral mucosa.

Calotropis procera, from the *Asclepiadace* family is native to Africa, India, and Persia, and commonly found in Northeast Brazil. The plant's latex, once processed, yields lactifer proteins, a clean, water-soluble substance. Phytochemical analysis of this extract revealed the presence of alkaloids, cardiac glycosides, tannins, flavonoids, steroids and/or triterpenes. Phytomodulator lactic acid proteins were extracted from the plant and injected into hamsters at a concentration of 5 mg/kg to evaluate the efficacy in the treatment of mucositis induced by 5-FU injections. The results showed a significant reduction in the secretion of inflammatory mediators, such as TNF-α and IL-1β [26]. The effect of Calotropis procera phytomodulatory lactiferous proteins on different protein fractions was evaluated and the new fractions (Protein fraction I - PI, Protein fraction II - PII, Protein fraction II treated with iodoacetamide - PII-IAA and Protein fraction III – PIII.) were more homogeneous than the original lactiferous proteins (chitinases, proteases and osmotins) and, therefore, obtained greater efficacy for the treatment of oral mucositis. The result of the study showed that PII-IAA is the most effective candidate of latex proteins for therapeutic use by returning the clinical integrity of the group, comparable to that of a healthy group [35].

Malva sylvestris, a *Malvaceae* family plant, is widely used in Latin American and

Brazilian folk medicine for its anti-inflammatory, antiseptic, diuretic, and expectorant properties. It aids in wound healing and treats mucosal inflammation [52] and is used in mouthwashes and dentifrices [53]. However, in the study by Kovalik et al. [28] *Malva sylvestris* did not show anti-inflammatory action on oral lesions in rats.

Carapa guianensis Aubl. is an Amazonian tree, whose seeds are used in the production of an oil of commercial value. This oil, known as Andiroba oil, is utilized in traditional medicine and the cosmetics industry due to its anti-inflammatory, healing, and insect repellent properties [54]. Treatment with 100% andiroba oil reduced the degree of OM compared to the other groups studied and was not cytotoxic but had genotoxic potential ($p < 0.001$) [32], deserving further studies. The study of Soares et al. [24] concluded that a 3% concentration andiroba gel used topically every 6 hours reduces the severity and painful symptoms of OM and exhibits better results compared to the use of low power laser, being an accessible and easy-to-use therapeutic alternative, improving the quality of life of cancer patients.

Curcuma longa L, a Southeast Asian species from the *Zingiberaceae* family [55], is a perennial herb used as a spice and yellow dye [34]. It has pharmacological properties like anti-inflammatory, antioxidant, and antitumor effects, and it aids in wound healing, reduces oxidative stress, and modulates anti-inflammatory responses [56]. A mucoadhesive formulation of *Curcuma longa* L accelerated re-epithelialization and resolution of inflammatory processes in OM induced by 5-FU, associated with decreased angiogenesis and TGF-β1 level [34].

Spondias mombin leaves, has phytochemical properties that account for their antimicrobial, antioxidant, hypoglycemic, and antiedematogenic effects. They have been used to treat ailments like lip herpes, conjunctivitis, and urethritis. Sousa Gomes et al. [36] found that oral administration of a hydroethanolic extract from these leaves, at a dosage of 200 mg/kg, reduced oxidative stress and inflammation in hamsters suffering from 5-FU-induced oral mucositis.

Although Brazil is recognized for its vast biodiversity and rich popular culture, a small number of clinical trials have examined the effect of medicinal plants in the treatment of oral disorders. It is known that this type of intervention can provide direct scientific evidence with a lower likelihood of error to clarify a cause-effect relationship [57]. With regard to the treatment of oral ulcers or mucositis, the databases record only nine tested plant species. However, this number is expected to grow in the coming years, given the increasing demand for natural or alternative therapies by both the scientific community and the general population.

This review also points out the need for caution when interpreting the results since the clinical trials presented a moderate risk of bias, and those that evaluated the use of Eupatorium laevigatum Lam [20] and chamomile [21] for the treatment oral ulcers presented high risk of bias in the selection of participants and blinding of participants and/or evaluators. Among the *in vivo* studies, despite all samples being kept under standard conditions, the risk of bias regarding blinding of trial caregiver and researchers was unclear in the studies that evaluated *Malva sylvestris* L. [28] and *Aloe barbadensis* Miller [29] for the treatment of mouth ulcer due to mechanical trauma, and chamomile extract (AdMuc®) [34], *Calotropis procera* [35] and *Spondias mombin* [36] for treatment of induced oral mucositis. The studies that evaluated *Calotropis procera* [26] and *Spondias mombin* [36] for the treatment of Induced oral mucositis presented risk of bias uncertain for random allocation in the study.

CONCLUSION

Among the plant extracts used in Brazil for the treatment of oral ulcers and oral mucositis,

Chamomilla recutita, regardless of the pharmaceutical presentation showed the most promising results. *Spondias mombin* L., *Curcuma longa* L., *Carapa guianensis* Aubl, and *Calotropis procera* also showed good results in the treatment of oral mucositis, while *Eupatorium laevigatum* was efficient in the treatment of ulcers of traumatic origin. *Malva sylvestris*, *Copaifera reticulata* Ducke and *Aloe barbadensis* Miller did not exhibit significant results.

Author's Contributions

LERV: Conception of the work; Data Curation; Formal Analysis; Investigation; Methodology; Project Administration; Software; Supervision; Validation; Visualization; Writing – Original

Draft Preparation; Writing – Review & Editing. PLCE: Conceptualization; Data Curation; Formal Analysis; Investigation; Methodology; Project Administration; Validation; Visualization; Writing – Original Draft Preparation; Writing. LSL: Conceptualization; Data Curation; Formal Analysis; Investigation; Methodology; Validation; Visualization; Writing – Original Draft Preparation; Writing. GVG: Conceptualization; Data Curation; Formal Analysis; Investigation; Methodology; Validation; Visualization; Writing – Original Draft Preparation; Writing. LGA: Conception of the work; Data Curation; Formal Analysis; Investigation; Methodology; Project Administration; Software; Supervision; Validation; Visualization; Writing – Original Draft Preparation; Writing – Review & Editing.

Conflict of interest

The authors have no proprietary, financial or personal interest of any nature or kind in any product, service and/or company presented in this article.

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Regulatory Statement

Nothing to declare.

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