




# Medicinal plants used for the treatment of mucositis induced by oncotherapy: a systematic review

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## Abstract

**Purpose** This systematic review aimed to identify effective medicinal plants for the treatment of mucositis induced by oncotherapy.

**Methods** The clinical question was the following: “Which medicinal plants are effective in the treatment of oral mucositis induced by cancer treatment?” (PubMed, Medline, Web of Science, Scopus, Lilacs, and SciELO). The keywords were the following: 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 chemotherapy OR radiotherapy OR immunotherapy OR cancer OR neoplasm OR neoplasm OR tumor OR tumor. The inclusion criteria for the selection of articles were the type of study design (clinical trials) and the studied population (cancer patients presenting lesions of oral mucositis having undergone treatment with medicinal plants).

**Results** After evaluation of the works, 24 of 893 articles were selected. *Matricaria chamomilla* (chamomilla) presented promising results, such as a reduction in severity and lesion incidence with improved pain symptomatology. The plant extracts *Isatis indigótica*, *Olea europaea*, *Calendula officinalis*, *A. digitatae*, and *M. sylvestris* improved the lesions. Mucotrol™ and QRLYD herbal products improved the degree of severity of the lesions, while SAMITAL® and MUCOSYTE allowed for greater pain control.

**Conclusion** The complementary treatment of oral mucositis in cancer patients, with analgesic and anti-inflammatory actions with lower side effects, is an alternative for healthcare professionals.

**Keywords** Biological products · Cancer · Phytotherapy · Stomatitis

## Introduction

Chemotherapy and radiotherapy are cancer treatment modalities commonly associated with adverse effects, such as inappetence, nausea, vomiting, and mucositis [1]. Oral mucositis (OM), an inflammatory lesion of the mucosa, manifests within 7 to 10 days after cancer treatment [2] and occurs in 40 to 80% of patients treated with chemotherapy and in

practically all those submitted to radiotherapy in the head and neck region [3].

Clinically, oral mucositis appear as mild erythema in the non-keratinised mucosa and progress to ulcers with extremely painful symptoms [3, 4]. They can compromise functions such as speech and swallowing, which reduce the quality of life of the patients [4, 5] and become limiting factors in cancer treatment, as it may be interrupted [6].

Different strategies have been indicated for the treatment of mucositis, such as low-level laser treatment, rinsing with morphine [7]; adequate oral hygiene, the use of antiseptics, analgesics, anti-inflammatories [8]; and cryotherapy [5]. These aim to utilise the palliative effect in the control of pain; however, there is still a need for more studies that evaluate the effectiveness of alternative interventions [9].

The use of natural products represents an alternative that should be investigated due to their anti-inflammatory action

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with less possibility of adverse side effects [10], less toxicity, and more affordable costs [11]. The search for such products is increasing in the face of the limitations of conventional medicine [12] and the appreciation of healthier lifestyle habits associated with the use of natural products [13].

The therapeutic activities of medicinal plants are validated through ethnopharmacological surveys, laboratory tests, and clinical trials, which are considered the gold standard for the analysis of therapeutic interventions [14]. By grouping, organising, and evaluating the results of clinical trials through systematic review, it is possible to evaluate the natural products used to treat OM.

The systematic analysis of publications makes it possible to recognise the natural products with the best results and, with this, to indicate their clinical use as well as to direct future research [15].

## Materials and methods

### Study design

A systematic review was carried out following the PRISMA protocol under registration number CRD 42,019,118,673 (PROSPERO).

### Clinical question

The clinical question based on the PICO strategy (Table 1) was the following: “Which medicinal plants are effective in the treatment of OM induced by cancer treatment?”.

### Search strategy

The searches in the databases were carried out on 10/27/2018 and followed the strategy described in (Table 2).

### Inclusion criteria

The inclusion criteria were the following: randomised clinical trials or non-randomised clinical trials; patients with OM induced by cancer treatment; and treatments performed with medicinal plants.

### Exclusion criteria

The exclusion criteria were the following: literature reviews; clinical trials without a control group; in vitro studies; and in vivo animal studies.

### Article selection and data extraction

The selection of articles was independently carried out by two reviewers. The Kappa index was calculated after reading 10% of the papers (0.82). The inclusion criteria were applied to select the titles and abstracts, which were included based on the eligibility criteria. The differences were resolved by consensus between the two researchers.

### Bias risk assessment

The risk of bias assessment was performed in randomised clinical trials using the Cochrane manual (Review Manager) [16]. The evaluated items were the following:

- Selection bias: the generation of random sequence and allocation hiding
- Performance bias: the blinding of participants and professionals
- Detection bias: the blinding of outcome evaluators
- Friction bias: incomplete outcomes
- Reporting bias: the reporting of selective outcomes
- Other biases

### Analysis of the results

The results were analysed using the Cochrane manual evaluation method [17] for randomised clinical trials.

## Results

The search strategy illustrated in the PRISMA flowchart (Fig. 1) identified 1064 studies whose titles and abstracts were evaluated according to the inclusion criteria. Of this

**Table 1** Description of the PICO strategy used in the development of the clinical question

Acronym	Definition	Description
P	Participants	Patients with oral mucositis induced by cancer treatment
I	Intervention	Treatment with medicinal plants
C	Control or comparison	Without treatment/placebo, anti-inflammatories, and chlorhexidine
O	Outcome	Reduction of the incidence of mucositis, healing time, degree of severity, and symptomatology

**Table 2** Database search strategy

Databases	Keywords
PubMed/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 mucosities OR stomatitis OR stomatitides OR “oral ulcer”) AND (chemotherapy OR radiotherapy OR immunotherapy OR cancer OR neoplasia OR neoplasm OR tumor OR tumour)
Medline/Lilacs/Web of Science/SciELO	(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 mucosities OR stomatitis OR stomatitides OR oral ulcer) AND (chemotherapy OR radiotherapy OR immunotherapy OR cancer OR neoplasia OR neoplasm OR tumor OR tumour)

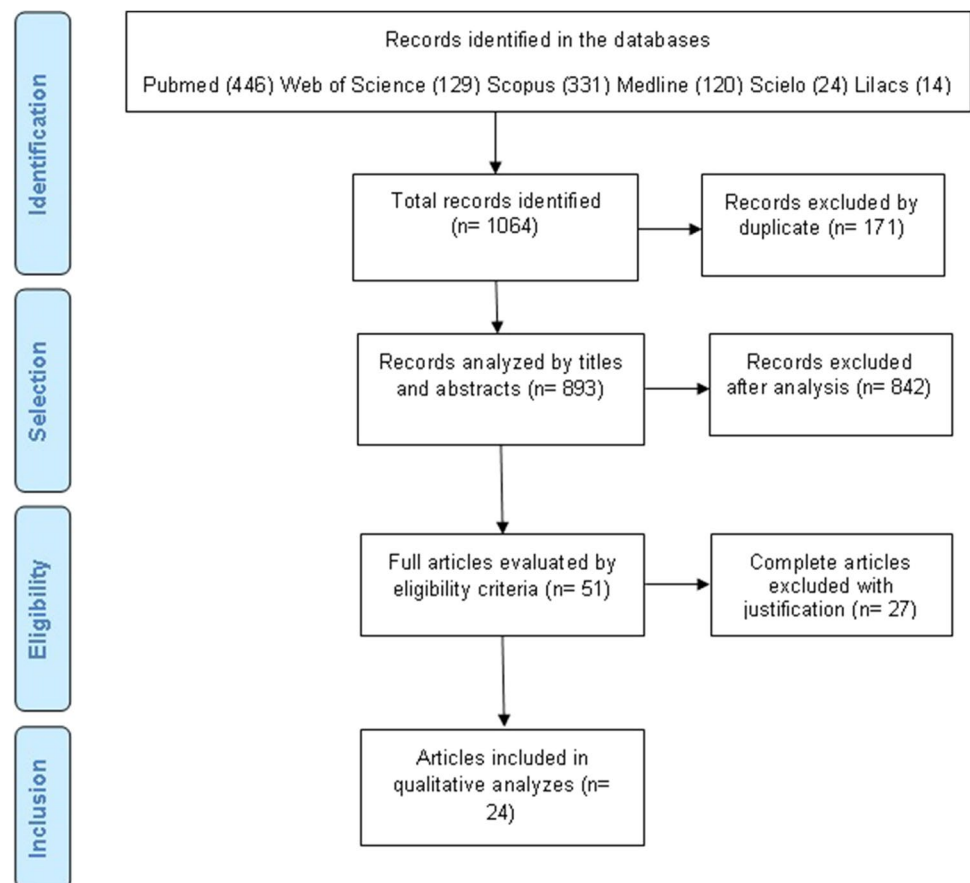
total, 51 works were pre-selected and read in full. After the complete reading, 27 studies were excluded after applying the exclusion criteria, such as the absence of a control group, literature reviews, and design of the study conducted in vivo (animals) and in vitro.

For qualitative analysis, 24 articles were selected and included in this systematic review. The articles included are described in chronological order in Table 3. The total sample consisted of 1296 patients undergoing treatment for OM with medicinal plants. Fourteen clinical trials evaluated only one plant species. The most widely used plant extracts

were *Matricaria chamomilla* [18–20], *Aloe vera* [21, 22], *Isatis indigotica* Fort [23], *Olea europaea* [24], *Calendula officinalis* [25], *Curcuma longa* [26], *Glycyrrhiza glabra* [27], *Achillea millefolium* [28], *Morus nigra* L. [29], *Zataria multiflora* [30], and *Plantago major* [31].

The action of herbal medicines on mucositis lesions was evaluated in 6 clinical trials that used the following products: Mucotrol™ [32], Qingre liyan [33], SAMITAL® [34], Mucosyte biopharm [35], CHIN [36], and Faringel [37]. The other studies (4) used the following plant compounds to treat oral mucositis: essential oils of manuka and kanuka [38],

**Fig. 1** PRISMA flowchart for inclusion of articles in the systematic review



**Table 3** Clinical trials included in the systematic review in chronological order of publication

Origin and author	Comparison groups	Plant extract (popular name)	Initial (final) sample	Variables analysed	Results
USA Fidler et al. [18]	TG: 30 min; cryotherapy and rinse with chamomile CG: 30 min; cryotherapy and rinse with placebo	<i>Matricaria chamomilla</i> (chamomile)	164 (163)	OM degree following toxicity criteria (NCT) to assess mucositis induced by 5-FU	TG: 60% did not present OM while CG 55% presented OM ( $p = 0.43$ ) Cryotherapy with chamomile did not present a statistically significant action in OM induced by 5-FU
USA Su et al. [21]	TG: <i>Aloe vera</i> gel CG: Placebo	<i>Aloe vera</i> (aloe)	58 (58)	Incidence, duration, and degree of OM; weight loss; need for hospitalisation; assessment of pain intensity (VAS); use of analgesics	TG presented lower degrees of mucositis (II and III) compared to CG ( $p = 0.39$ ) Groups TG and CG showed similar results in the degree of OM, weight loss, and use of analgesics, without statistical significance
India Naidu et al. [32]	TG: Mucotrol™ CG: Placebo	MF5232 Mucotrol™ C. <i>tetragonolobus</i> , <i>A. stearic</i> , magnesium, <i>Aloe vera</i> , <i>Centella asiatica</i> , <i>E. glycyrrhizin</i> , <i>Y.cuspidatum</i> , <i>Angelica</i> sp., <i>Camelia sinensis</i>	30 (30)	Epidermal growth factor (EGF), OM degree (WHO and RTOG), objective scoring system for ulceration (OSSU), and erythema (OSSE)	Pilot study, where TG showed a reduction in the OM degree (WHO and RTOG). Did not show differences between the groups (both results without statistical significance) CG showed an increase in the OM degree (31.45% in OSSU and 63.63% in OSSE), with $p < 0.05$ More studies with a larger sample are needed because it was a pilot study
China Wu et al. [33]	TG: Rinse with QRLYD (200 ml) CG: Rinse with Dobell solution	Qingre Liyan Decoction (QRLYD)	60 (60)	OM degree (RTOG), incidence, ability to feed (days 0, 14, and 28), EGF, TCD4/TCD8 count	TG: Reduction in the OM incidence ( $p < 0.05$ ), EGF increase in saliva ( $p < 0.05$ ), and higher concentration of TCD4 and TCD8 ( $p < 0.05$ ). QRLYD has healing and preventive action for OM
New Zealand Maddocks-Jennings et al. [38]	TG: Essential oil based rinse (manuka and kanuka) PG: Placebo (sterile water) CG: Standard rinse	Essential oils of <i>leptospermum scoparium</i> (manuka) and <i>Kunzea ericoides</i> (kanuka)	23 (19)	Development of OM, assessment of pain intensity (VAS), and nutritional status of the patient	Later manifestation of OM in the TG (15.6 days) than PG (7 days) and CG (10.8 days), with $p < 0.05$ TG reported less pain and less weight loss than the PG and CG groups. Despite the positive results, the study limitation was the reduced sample size

Table 3 (continued)

Origin and author	Comparison groups	Plant extract (popular name)	Initial (final) sample	Variables analysed	Results
Taiwan You et al. [23]	TG: 0.5 g/30 ml lIF in water CG: Placebo (saline solution)	<i>Isatis indigoica</i> Fort (indigowood root)	20 (20)	OM degree (NCI), nutritional status and dysphagia, IL-1 $\beta$ , and IL-6 (ELISA) in periods (weeks 1, 3, 5, and 7)	TG had less difficulty swallowing ( $p=0.002$ ), reduced presence of anorexia ( $p=0.002$ ), less weight loss ( $p=0.006$ ), less white blood cells ( $p=0.046$ ), and lower IL-6 production in all evaluated periods ( $p<0.05$ ) compared to CG. TG showed higher levels of IL-1 $\beta$ in the entire period evaluated, without statistical significance, except for week 3 ( $p=0.0039$ )
Iraq Ahmed [24]	TG: Olive leaf extract rinse G1: Benzidamine hydrochloride rinse CG: Placebo (saline solution rinse)	<i>Olea europaea</i> L. (olive leaf extract)	31 (25)	OM degree (WHO and OMAS) at days 1, 8, and 15. Levels of salivary cytokines (IL-1 $\beta$ and TNF- $\alpha$ )	TG and G1 showed lower degrees of OM compared to CG ( $p<0.005$ ). TG showed lower levels of IL-1 $\beta$ and TNF- $\alpha$ compared to G1 and CG ( $p<0.005$ ). CG showed higher OM degrees (OMAS) on days 8 and 15 ( $p<0.005$ )
Iran Babae et al. [25]	TG: <i>C. officinalis</i> extract rinse CG: Placebo rinse	<i>Calendula officinalis</i> (daisy)	40 (38)	OM degree (OMAS) for weeks 1–7	TG showed lower degrees of OM compared to CG at weeks 2, 3 and 6. OM intensity was reduced in TG compared to CG ( $p<0.005$ )
Italy Pawar et al. [34]	TG: SAMITAL® CG: Placebo	SAMITAL® ( <i>Vaccinium myrtillus</i> , <i>Macleaya cordata</i> , and <i>Echinacea angustifolia</i> ) Indena SpA, Milão Itália	30 (30)	OM degree (WHO), assessment of pain intensity (VAS), and quality of life	TG presented a reduction (day 31 to the end of treatment) in the degree of OM ( $p<0.05$ ) and presented pain reduction (day 4 to the end of treatment, $p<0.05$ ). CG presented pain reduction (day 7 to day 21 of treatment, $p<0.05$ )
India Rao et al. [26]	TG: <i>C. longa</i> CG: Povidone-iodine	<i>Curcuma longa</i> (saffron)	80 (79)	OM degree (RTOG) for weeks 1–7. Interrupted treatment days and weight loss	TG presented a reduction in the degree of OM ( $p<0.0001$ ), a reduction in interruptions of the first treatment cycle (up to 4 weeks) ( $p<0.0001$ ), and showed less weight loss than CG ( $p<0.0001$ )

Table 3 (continued)

Origin and author	Comparison groups	Plant extract (popular name)	Initial (final) sample	Variables analysed	Results
Iran Chalayani et al. [27]	TAMF: Triamcinolone acetone mucoadhesive film LMF: Licorice mucoadhesive film	<i>Glycyrrhiza glabra</i> (licorice or regaliz)	60 (60)	OM degree (WHO), duration of lesions, and assessment of pain intensity (VAS)	TAMF and LMF showed significant pain reduction ( $p < 0.05$ ), notable effects on the degree of mucositis ( $p < 0.05$ ), and similar effects in pain relief and/or anti-inflammatory action, without statistical significance TG showed lower OM degrees on days 7 and 14 ( $p < 0.001$ ). The severity degree was reduced after treatment with plant extract
Iran Miranzadeh et al. [28]	TG: <i>Achillea millefolium</i> distilled solution for mouthwash CG: Routine solution	<i>Achillea millefolium</i> (yarrow or thousand leaves)	56 (56)	OM degree (WHO) on days 0, 7, and 14	TG had a lower incidence of OM (3.3%) when compared to the CG (9.0%) ( $p = 0.01$ ). G2 had a shorter duration of OM (1.9 days) when compared to CG (5.7 days) ( $p = 0.01$ ). G2 had the lowest incidence of oral ulcerations (30%) and CG had the highest (90%) ( $p < 0.05$ ) TG and CG showed no differences in OM degrees and in healing time. There were no patients with grade IV OM There was no difference in the intensity of OM
Brazil Braga et al. [19]	G1: Chamomile 0.5% G2: Chamomile 1% G3: Chamomile 2% CG: Control (0.12% chlorhexidine)	<i>Matricaria chamomilla</i> (camomila)	40 (40)	Incidence and intensity of OM (WHO): symptoms (pain), signs (erythema and ulceration), oral function (ability to swallow)	G2 had a lower incidence of OM (3.3%) when compared to the CG (9.0%) ( $p = 0.01$ ). G2 had a shorter duration of OM (1.9 days) when compared to CG (5.7 days) ( $p = 0.01$ ). G2 had the lowest incidence of oral ulcerations (30%) and CG had the highest (90%) ( $p < 0.05$ ) TG and CG showed no differences in OM degrees and in healing time. There were no patients with grade IV OM There was no difference in the intensity of OM
Iran Sahebamee et al. [22]	TG: <i>Aloe vera</i> rinse CG: zidamine rinse	<i>Aloe vera</i>	26 (26)	OM degree (WHO), presence of erythema, and report of dysphagia	TG showed a reduction in OM degree after 8 days ( $p = 0.0038$ ) and used less analgesics than CG ( $p < 0.05$ ). TG and CG maintained similar degrees of hygiene TG had a lower level of pain (VAS) ( $p < 0.05$ ), had smaller areas of ulceration ( $p < 0.05$ ), and had a lower incidence of mucositis compared to CG ( $p < 0.05$ ) TG did not present OM in 70% of the patients, while CG did not present MB in 40% of the patients (D5, $p < 0.05$ )
Italy Bardellini et al. [35]	TG: Mucosyde Biopharm (verbascoside, polyvinylpyrrolidone and sodium hyaluronate) CG: Placebo (water-based solution)	Mucosyde Biopharm (verbascoside, polyvinylpyrrolidone and sodium hyaluronate)	56 (56)	OM degree (WHO), pain intensity assessment (VAS), and oral hygiene level	TG showed a reduction in OM degree after 8 days ( $p = 0.0038$ ) and used less analgesics than CG ( $p < 0.05$ ). TG and CG maintained similar degrees of hygiene TG had a lower level of pain (VAS) ( $p < 0.05$ ), had smaller areas of ulceration ( $p < 0.05$ ), and had a lower incidence of mucositis compared to CG ( $p < 0.05$ ) TG did not present OM in 70% of the patients, while CG did not present MB in 40% of the patients (D5, $p < 0.05$ )
Brazil Dos Reis et al. [20]	TG: Chamomile ice cryotherapy CG: Control (ice)	<i>Matricaria chamomilla</i> (chamomile)	38 (38)	Assessment of oral mucosa 8, 15, and 22 days after chemotherapy. OM degree (WHO) and pain intensity assessment (VAS)	TG showed a reduction in OM degree after 8 days ( $p = 0.0038$ ) and used less analgesics than CG ( $p < 0.05$ ). TG and CG maintained similar degrees of hygiene TG had a lower level of pain (VAS) ( $p < 0.05$ ), had smaller areas of ulceration ( $p < 0.05$ ), and had a lower incidence of mucositis compared to CG ( $p < 0.05$ ) TG did not present OM in 70% of the patients, while CG did not present MB in 40% of the patients (D5, $p < 0.05$ )
Turkey Mutluay Yayla et al. [39]	TG: <i>Sage tea-thyme-peppermint hydrosol</i> CG: No use of extract and/or placebo	<i>Sage tea-thyme-peppermint hydrosol</i>	78 (60)	OM degree (WHO) evaluated clinically and by photography on days 5 (D5) and 14 (D14)	TG showed a reduction in OM degree after 8 days ( $p = 0.0038$ ) and used less analgesics than CG ( $p < 0.05$ ). TG and CG maintained similar degrees of hygiene TG had a lower level of pain (VAS) ( $p < 0.05$ ), had smaller areas of ulceration ( $p < 0.05$ ), and had a lower incidence of mucositis compared to CG ( $p < 0.05$ ) TG did not present OM in 70% of the patients, while CG did not present MB in 40% of the patients (D5, $p < 0.05$ )

Table 3 (continued)

Origin and author	Comparison groups	Plant extract (popular name)	Initial (final) sample	Variables analysed	Results
Iran Tavakoli Ardakani et al. [40]	TG: <i>Matricaria recutita</i> and <i>Mentha piperita</i> rinse CG: Placebo (distilled water)	<i>Matricaria chamomilla</i> and <i>Mentha piperita</i> (chamomile and mint)	70 (60)	Degree of OM; MB (NCT), assessment of pain inten- sity, (VAS) xerostomia and dysphagia	TG had a shorter duration of OM compared to CG ( $p < 0.05$ ). TG presented a lower degree of severity of OM ( $p = 0.006$ ), less xerosto- mia ( $p = 0.04$ ), and dysphagia ( $p = 0.009$ ). Reduced need for complementary medications ( $p = 0.03$ ), narcotic analgesics ( $p = 0.047$ ), total parenteral nutrition (TPN) ( $p = 0.02$ ), and the duration of TPN ( $p = 0.03$ ) TG showed a higher incidence of OM at weeks 3, 4, and 7 ( $p = 0.005$ ). TG showed a higher degree (severity) of OM at weeks 4 and 6 ( $p = 0.005$ ). CG presented more reports of pain compared to TG ( $p = 0.005$ ) and had lower scores when answering the quality of life questionnaire compared to TG ( $p < 0.000$ )
Turkey Demir Dogan et al. [29]	TG: Blackberry molasses CG: Placebo	<i>Morus nigra</i> L. (blackberry molasses)	83 (80)	OM incidence, degree, assess- ment of pain intensity, and quality of life	TG showed objective mucositis in grade 1 (1), grade 2 (22), and grade 3 (30), while CG showed objective mucositis in grade 1 (3), grade 2 (17), and grade 3 (31) $p = 0.665$ . TG and CG also showed similar degrees of functional mucositis without statistical significance ( $p = 0.442$ ), dysphagia, and pain control ( $p = 0.866$ ) TG showed a lower degree of OM ( $p < 0.005$ ) and showed a lower incidence and less pain compared to CG ( $p < 0.005$ ) TG showed a lower OM degree at week 7 ( $p < 0.01$ ) and significant reduction in pain ( $p < 0.01$ ). TG and CG showed no significant differences in the degree of xerostomia
Italy Marucci et al. [37]	TG: Faringel solution CG: Placebo	Faringel; composed of propolis 6%, <i>Aloe vera</i> 30%, marigold 2%, chamomile 0.3%, and honey	107 (104)	Degree of objective and func- tional mucositis (CTCAE v3.0), dysphagia, pain control	
Iran Rezaeipour et al. [41]	TG: <i>A. digitatae</i> Alef and <i>M.</i> <i>syhvestris</i> extract CG: Placebo	<i>Alcea digitata</i> Alef and <i>Malva</i> <i>syhvestris</i> L. (mauve)	23 (22)	Treatment effectiveness: assess- ment of pain intensity (VAS) and OM degree (WHO)	
China Wang et al. [36]	TG: CHIN CG: Recombinant human epi- dermal growth factor (rh EGF)	CHIN (Chinese decoction; com- posed of Rhubarb, licorice, mint, scutellaria, Radix Liriope, red peony root, lumbrius)	70 (70)	OM degree (NCT), pain intensity (VAS), xerostomia, and body mass index	

Table 3 (continued)

Origin and author	Comparison groups	Plant extract (popular name)	Initial (final) sample	Variables analysed	Results
Iran Aghamohammadi et al. [30]	TG: Mouthwash with extract of <i>Zataria multiflora</i> GP; Placebo	<i>Zataria multiflora</i> (zataria)	63 (52)	OM degree (WHO and OMAS) at weeks 1–7	TG showed a lower degree of mucositis (OMAS and WHO) compared to the GP ( $p < 0.005$ ). TG showed lower incidence and less pain compared to GP ( $p < 0.005$ )
Spain Cabrera-Jaime et al. [31]	TG: Plantago major extract CLX: Chlorhexidine SB: 5% sodium bicarbonate	Plantago major (plantain or taioba)	60 (50)	Product efficacy: healing time, pain intensity (VAS), swal- lowing capacity, and quality of life	TG, CLX, and SB showed no significant difference in heal- ing time, pain intensity, or the ability to swallow (liquids and solids) ( $p > 0.05$ )

CTCAE v.3.0, Common Terminology Criteria for Adverse Events version 3.0; CG, control group; ELISA, enzyme-linked immunosorbent assay; EGF, epidermal growth factor; IL-1 $\beta$ , Interleukin 1 beta; IL-6, Interleukin-6; IIF, *Isatis indigotica* Fort; LMF, Licorice mucoadhesive film; NCI, National Cancer Institute; OM, oral mucositis; OMAS, Oral Mucositis Assessment Scale; PG, placebo group; QRLYD, Qingre Lijian Decoction; RTOG, Radiation Therapy Oncology Group; TCDA/TCDS, T lymphocytes CD4 and CD8; TG, treatment group; TAMF, triamcinolone acetate mucoadhesive film; TNF- $\alpha$ , Tumour Necrosis Factor-Alpha; VAS, Visual Analogical Scale; WHO, World Health Organization; 5-FU, 5-fluorouracil.

thyme tea with mint (sage tea thyme peppermint hydrosol) [39], *Matricaria chamomilla* with *Mentha peperita* [40], and *Alcea digitata* Alef with *Malva sylvestris* [41].

The countries that presented the largest number of publications on the use of plant extracts in the treatment of mucositis were Iran [22, 25, 27, 28, 30, 40, 41] and Italy [34, 35, 37]. Other countries that carried out works with natural products were Brazil [19, 20], the USA [18, 21], India [26, 32], China [33, 36], Turkey [29, 39], New Zealand [38], Taiwan [23], Iraq [24], and Spain [31].

In the present study, there were limitations regarding the evaluation of the data analysis of the primary studies. As for the existence of publication bias, one of the great limitations of systematic reviews, there is the possibility that studies with negative results, mainly of small size, have not been published. The high heterogeneity among the studies, mainly regarding the plant species, did not allow for the realisation of the meta-analysis; thus, the qualitative analysis was carried out.

### Bias risk assessment

Bias risk assessment was performed in clinical trials following the criteria of the Cochrane manual [17]. The risk of selection bias has not been identified in the studies. The performance bias resulting from the blinding of participants and professionals was identified as a limiting factor and was reported in the study by Wang et al. [36]. The blinding of outcome evaluators was described in 82.14% (23/24) of the studies evaluated. The evaluation of incomplete outcomes was considered uncertain in all studies analysed. Figure 2 presents the assessment of the risk of bias performed by the Review Manager program (RevMan 5.3).

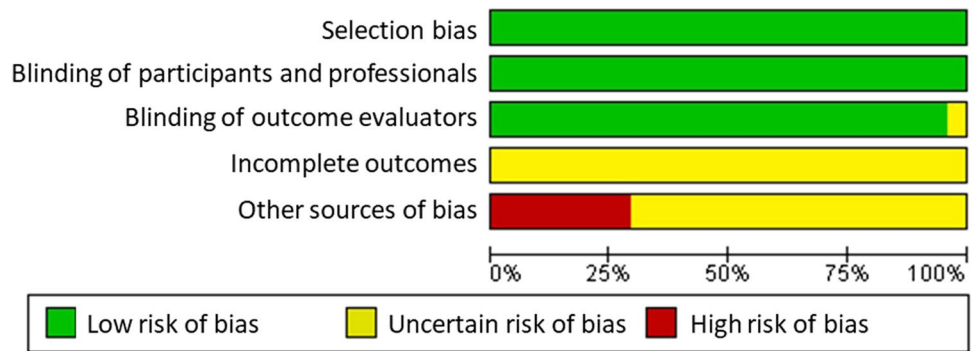
### Discussion

OM, commonly manifested in patients undergoing cancer treatment, is considered the most severe non-haematological complication of cancer therapy [5, 42] and can become a limiting factor in cancer treatment [4, 5]. Its treatment consists of relieving painful symptoms and preventing the spread of infections since the lesions are a gateway for pathogenic microorganisms [8].

The search for products of plant origin to treat OM has been carried out in several countries, mainly in Iran and Italy. There are several factors that propagate the practice of phytotherapy, such as the high cost of allopathic drugs, the search for less aggressive products, and the appreciation of healthier lifestyle habits [13].

Among the 893 works identified in the electronic databases, only 24 met the inclusion criteria and underwent qualitative analysis. Most of the studies ( $n = 14$ , 58.3%)



**Fig. 2** Assessment of the risk of bias in clinical trials

evaluated the action of treatments carried out with a single plant species. The plant species found were the following: *Matricaria chamomilla* [18–20], *Aloe vera* [21, 22], *Isatis indigotica* Fort [23], *Olea europaea* L. [24], *Calendula officinalis* [25], *Curcuma longa* [26], *Glycyrrhiza glabra* [27], *Achillea millefolium* [28], *Morus nigra* L. [29], *Zatarra multiflora* [30], and *Plantago major* [31].

Vegetable compounds were evaluated in four clinical trials that used the combination of essential oils of manuka and kanuka [38], salvia, thyme and mint tea [39], chamomile with mint [40], and *Alcea digitata* Alef with *Malva sylvestris* [41].

Herbal medicines were evaluated in 6 (25%) of the 24 articles included Mucotrol™ [32], Qingre liyan [33], SAMITAL® [34], Mucosyte biopharm [35], CHIN [36], and Faringel [37].

The pioneering study on the use of medicinal plants in the treatment of mucositis was carried out in the USA with *Matricaria chamomilla* (chamomile) by Fidler et al. [18]. Chamomile, whose action initially did not show favourable and significant results [18], currently shows its beneficial action on mucositis lesions [43]. The incidence and duration of OM were lower in patients who underwent treatment with a mouthwash manipulated with 1% chamomile extract [19], and the treatment performed with cryotherapy made with chamomile infusion reduced the duration and severity of the lesions [20].

The use of the mouthwash manipulated with the combination of chamomile and mint resulted in a shorter duration of lesions and a lower degree of severity of OM, according to the National Cancer Institute scale [40]. Chamomile is considered a promising alternative treatment for OM [43].

*Aloe vera* has antibacterial, antifungal, anti-inflammatory, antioxidant, and anti-tumour pharmacological action [44]. Its beneficial effects are attributed to the polysaccharides present in its pulp, which is widely used as a medicine and cosmetic [45]. The action of *Aloe vera* in the treatment of OM has presented divergent results between studies [21, 22]; therefore, its indication is still questionable.

The species *Isatis indigotica* Fort, a plant of traditional Chinese medicine, has as main components indigo, indirubin, organic acids, nucleosides, glucosinolates, lignans, ceramides, steroids, and polysaccharides [46]. It has multiple pharmacological properties, such as antiviral, anti-cancer, and antibacterial properties [47]. When carrying out an analysis of the degree of severity of OM, patients undergoing treatment with *Isatis indigotica* Fort extract had less severe lesions and less difficulty swallowing [23].

The extract of *Olea europaea* L., manipulated from the olive leaf, is marketed as a natural supplement for its multiple benefits, such as its antioxidant activity and antimicrobial action, which helps in the treatment of various infectious diseases [48], and its anti-inflammatory action [49]. Its use reduced the severity of OM lesions (Oral Mucositis Assessment Scale scale) and reduced the levels of Interleukin 1 beta (IL-1 $\beta$ ) and Tumour Necrosis Factor-Alpha (TNF- $\alpha$ ) [24].

*Calendula officinalis*, popularly known as daisy, is used in folk medicine for its anti-inflammatory action in the treatment of wounds, minor burns, bruises, skin rashes and stomach ulcers, or inflammation of the oral and pharyngeal mucosa [50]. Other important pharmacological activities are its antioxidant, antimicrobial, and healing activities. The biological activity of each extract is due to its constituents, including terpenoids, flavonoids, phenolic acids, carotenoids, coumarins, quinones, volatile oils, amino acids, and lipids [51]. Its use reduced the intensity and degree of OM [25].

*Curcuma longa* (curcumin), also called saffron, has anti-inflammatory, antimicrobial, antioxidant, and antineoplastic properties [52]. It is used to treat a variety of diseases because of its actions related to wound healing and the increase in the amount of collagen [53]. The treatment performed for OM reduced its degree of severity [26].

*Glycyrrhiza glabra*, popularly known as licorice or regaliz, is a species of flowering plant belonging to the *Fabaceae* family. It has sweet roots rich in glycyrrhizin, from which syrup is extracted. It is used in herbal medicine in many Asian and European countries, with effectiveness in

the treatment of cough, peptic ulcer, constipation, and other viral infections [54]. The constituents of the *Glycyrrhiza* extracts have anti-inflammatory effects that result in the inhibition of inflammatory cytokines, such as IL-6, IL-1 $\beta$ , and TNF- $\alpha$ . [55]. In the treatment of OM, patients showed an improvement in painful symptoms [27], but *Glycyrrhiza glabra* should be used with caution since it can present important side effects, such as hypertension and secondary disorders induced by hypokalaemia [56].

*Achillea millefolium*, popularly known as yarrow or thousand leaves, is an important species in the *Asteraceae* family and is used in the treatment of gastrointestinal disorders, hepatobiliary disorders, gynaecological disorders, inflammation, and wound healing [57]. Treatment with milefolium extract reduced the degree of severity of OM after 7 and 14 days [28].

The species *Morus nigra* L. (blackberry) is rich in secondary metabolites, such as flavonoids, and is associated with important biological activities with antioxidant and anti-inflammatory actions [58]. Blackberry molasses did not reduce the incidence or severity of OM [29].

The *Zataria multiflora* plant belongs to the *Laminaceae* family and is found in Iran, Pakistan, and Afghanistan. Traditionally, it is used as an antiseptic, anaesthetic, and antispasmodic because it has phenolic constituents, such as carvacrol, thymol, and eugenol [59]. Treatment with *Zataria multiflora* extract reduced the severity of OM on the OMAS and World Health Organization (WHO) scales [30].

The therapeutic plant *Plantago major*, popularly known as plantain, is a species of plantago of the *Plantaginaceae* family. They present bioactive flavonoid compounds, alkaloids, phenolics, glycosides, polysaccharides, and vitamins with healing, antiulcerative, anti-inflammatory, antioxidant, and anticancer effects [60]. In the treatment of OM, the *Plantago major* extract did not reduce the healing time or pain intensity [31].

The association of *Alcea digitata* Alef and *Malva sylvestris*, described in Persian medicine as mucilage plants, can be used for its anti-inflammatory and analgesic properties [61]. *A. digitata* and *M. sylvestris* reduced the degree of OM intensity (WHO scale) and promoted an improvement in the level of pain [41].

The essential oils of manuka (*Leptospermum scoparium*) and kanuka (*kunzea ericoides*), found in New Zealand, have anti-inflammatory, analgesic, and antimicrobial properties. Its treatment postponed the onset of the appearance of the first mucositis lesions [38]. The preventive action of thyme tea and pepper hydrosol reduced the incidence of OM [39].

Herbal medicines composed of more than one plant species and obtained by the pharmaceutical industry were part of the methodology of some studies included in the systematic review.

Mucotrol™ (Belker Pharmaceuticals, Geo Pharma, USA), an herbal medicine composed of sorbitol, magnesium stearate, *Aloe vera* sp., Acesulfame K, glycyrrhizin extract, and centella asiatica, promoted a reduction in the degree of severity of mucositis on the WHO scale. However, there was no significant difference in the Radiation Therapy Oncology Group (RTOG) scale [32].

The Chinese medicine by decoction Qinre liyan—QRLYD (Puji Pharmacy, Shaanxi, China) consists of *los Loniceræ*, *Rhizoma belamcandae*, *Lasiosphaera seu calvatia*, *Radix astragali*, *Radix glehniae*, *Radix ophiopogonis*, *Radix trichosanthes*, *Radix scrophulariae*, *Rhizoma ligusticum wallichii*, *Herba agrimoniae*, *Rhizoma imperatae*, and *Radix glycyrrhizae*. The QRLYD rinse did not improve the degree of severity of OM lesions [33].

The herbal medicine SAMITAL® (Indena SpA, Milan, Italy), whose botanical formulation contains multiple components (*Vaccinium myrtillus*, *Macleaya cordata*, and *Echinacea angustifolia*), was produced for the treatment of OM induced by chemotherapy and/or radiation therapy. SAMITAL® was analysed in two clinical phases by Bertoglio et al. [62] and Pawar et al. [34]. SAMITAL® reduced the degree of mucositis (WHO scale) and the number of lesions, as well as decreased the intensity of pain from the fourth day of treatment [34, 62].

Mucosyte (BIOPHARM, Milan, Italy) is a solution composed of verbascoside, polyvinylpyrrolidone, and sodium hyaluronate. In its formulation, it has anti-inflammatory and analgesic properties. Treatment with the herbal medicine Mucosyte reduced the degree of severity of the lesions and decreased the need for analgesics [35].

The herbal medicine Faringel® (Ca Di Group, Italy), composed of propolis, *Aloe vera*, calendula, chamomile, and honey, did not reduce the degree of severity of OM nor did it promote pain control [37].

The typical Chinese medicine plant compound, CHIN (modified Liangge San), promoted the protection of the mucosa by regulating the nuclear factor kappa B (NF- $\kappa$ B) signalling pathway and regulating the oral flora. It showed important anti-inflammatory activity, with a reduction in the degree of severity of OM lesions, and it improved the level of pain [36].

The risk of bias assessment followed the Cochrane Collaboration criteria for the development of systematic intervention reviews [17]. No risks were identified in controlled clinical trials in relation to the selection of participants as the groups were formed by cancer patients undergoing treatment. In 82.14% of the studies, the outcome evaluators were blind. The evaluation of incomplete outcomes was considered uncertain in all articles analysed.

The systematic review can have limitations like any other type of study. Possible sources of bias are mentioned, such as publication bias, where the published results are different

from reality due to the non-publication of unfavourable findings or negative results [16]. Another limitation for this method is the impossibility to better detail each research since the papers lacked specific information described in the systematic review. The meta-analysis could not be carried out due to the high heterogeneity between the studies since several natural products were identified in different designs.

Evidence-based medicine assists healthcare professionals in treating and making clinical decisions for the most appropriate procedure, besides collaborating with future work [63]. In this systematic review, controlled clinical trials, considered the gold standard for the development of research in humans [64], were included in the qualitative analysis and provided the main natural products used to treat OM.

## Final considerations

*Matricaria chamomilla* is a good alternative for complementary treatment of OM since the species has proven anti-inflammatory effects, and, despite the few clinical trials in humans, they do not point out any harmful effects to anyone using it.

*Isatis indigóitico* [23], the rinse with olive leaf extract [24], *Calendula officinalis* [25], *A. digitatae*, and *M. sylvestris* [41] promoted improvement in mucositis lesions, but further studies are necessary since these plant species were analysed in small samples.

The herbal medicines Mucotrol™ [32] and QRLYD [33] promoted improvement in the degree of severity of mucositis. SAMITAL® [34] and MUCOSYTE [35] promoted a reduction in the degree of mucositis and better pain control. The Chinese decoction CHIN [36] promoted good pain control.

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## Declarations

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