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ORIGINAL RESEARCH

Efficacy and safety of topical herbal medicine treatment on recurrent aphthous stomatitis: a systemic review

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Abstract: This study aimed to evaluate the efficacy and safety of topical treatment with natural herbal medicines on recurrent aphthous stomatitis (RAS). Nine electronic databases were searched to identify the randomized controlled trials and clinical controlled trials that reported the potential effect of natural herbal medicines on RAS published in Chinese or English. Ulcer size and duration, and remission of pain were assessed as main outcome measures. The methodological quality of the studies was evaluated using the *Cochrane Handbook for Systemic Review of Interventions* and Rev Man software. Thirteen trials with a total of 1,515 patients were included in the present analysis, which showed that topical treatment with natural herbal medicines seemed to benefit RAS patients by reducing ulcer size, shortening ulcer duration, and relieving pain without severe side effects. In conclusion, there is some evidence of the efficacy of topically applied natural herbal medicines with regards to improved RAS outcome measures and fewer side effects. However, given the limitations of this study, the evidence remains insufficient. Well-designed and high-quality randomized controlled trials are required for further exploration.

Keywords: recurrent aphthous stomatitis, herbal medicine, systemic review, randomized controlled trial, clinical controlled trials, oral disease

Introduction

Recurrent aphthous stomatitis (RAS), or recurrent aphthous ulcer (RAU), is one of the most common oral diseases, with an estimated prevalence of 25%.[1] Many factors may be involved in its progression, such as genetic predisposition, immunological abnormalities, microbial infection, psychological stress, and hormonal state.[2] Since the etiology and pathogenesis of RAS remains unclear, there is currently no consensus regarding a definitive curative therapy. The commonly accepted treatment strategy is to lessen the pain and duration of lesions.[3] Topical corticosteroids, antibiotics, and analgesics are highly recommended for patients with RAS.[4] However, longer treatment and frequent exposure to these medications may cause fungal infection and drug resistance, which may further lead to more severe adverse effects or even life-threatening complications.[5]

Natural herbal medicines as an alternative therapy for RAS have been widely used in many countries for decades.[6–8] Clinical studies on the use of such remedies have reported favorable benefits to patients by reducing the discomfort and duration of ulcers.[8–11] However, no evidence-based reviews regarding the efficacy and safety of the topical application of these medicines on RAS have been available in the literature to date. Therefore, we conducted this analysis to evaluate the efficacy and safety of topical treatment with natural herbal medicines on RAS.

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Materials and methods

Database and search strategy

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.[12] All clinical trials that reported the effect of topical treatment with natural herbal medicines on RAS were selected in the Chinese National Knowledge Infrastructure, the Chinese Biomedical Literature Database, the Chinese Scientific Journal Database (VIP), WANFANG data (WANFANG), PubMed, Excerpta Medica dataBASE (EMBASE), Science Citation Index (SCI), Current Controlled Trials (CCT), and the Cochrane Central Register of Controlled Trials in the Cochrane Library (up to April 2015). Publication language was confined to Chinese and English. The following terms were searched individually or combined: "Chinese patent medicine", "Chinese patent drugs", "traditional Chinese medicine", "Chinese herbology", "Chinese medicine", "Chinese material medica", "Chinese herbs", "Chinese herbal medicine", "natural herbal medicine", "Chin Tradit Pat Med", "herbal medicine", "recurrent aphthous ulcer", "recurrent aphthous stomatitis", "recurrent oral ulcer", and "recurrent oral ulceration". Manual searching was used as a complementation.

Inclusion and exclusion criteria

Inclusion criteria

Randomized controlled trials (RCTs) and clinical controlled trials (CCTs) that evaluated the efficacy and safety of topical treatment with natural herbal medicines on RAS were collected. In accordance with "The diagnosis and management of recurrent aphthous stomatitis: a consensus approach",[13] patients meeting the diagnostic criteria for RAS were included, with no restrictions on age, sex, or race. Patients in the experimental group received natural herbal medicines locally, without combined topical Western medications or systemic administration. Patients in the control group had to receive placebo treatment, chlorhexidine rinse. The outcome measures included the assessment of ulcer size, lesion duration, and remission of pain.

Exclusion criteria

Studies which there was duplication of study subjects were excluded, as were case reports or clinical observations without control groups, reviews, workshop summaries, translated papers or abstracts, animal studies, research reports without relevant or adequate information on participants, and interventions.

Data extraction and quality assessment

Two independent reviewers (CL Li and HL Huang) identified studies using the search strategy. If the eligibility of a study was not unanimous, a third reviewer party (H Hua and WC Wang) was consulted. Data were extracted from the included studies as follows: journal citation, author, year of publication, title, sample size, mediations, methodological details, therapeutic duration, and clinical outcomes.

The quality of the enrolled publications was assessed according to the *Cochrane Handbook for Systemic Review of Interventions*, Version 5.1.0, and Rev Man 5.3 software.[14] The assessment criteria were random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias.

Data analysis

Due to the poor homogeneity of the included publications, only descriptive analysis was conducted in the present study.

Results

Description of the assessed publications

A total of 3,231 abstracts (2,953 in Chinese and 278 in English) were selected from nine databases; 1,154 studies were excluded for duplication. According to the exclusion criteria, screening of the titles and abstracts resulted in the removal of 1,948 articles. Full-text review of the remaining 129 publications indicated that 13 studies met the inclusion criteria and they were enrolled into the final analysis.[8–11,15–23] The flowchart displayed in Figure 1 shows the detailed selection process.

To share more information with regard to this topic, part of excluded articles were provided as Supplementary material.

Characteristics of the studies

The characteristics of the 13 studies are summarized in Table 1. A total of 1,515 RAS patients were studied in this review. The sample size ranged from 15 to 150 patients in each study. Twelve different types of herbal medicine, in the form of gargles, membranes, powders, tablets, toothpastes, and gelatin preparations, were used, among which eight were traditional Chinese medicines and four were Iranian herbal medicines. The experimental period in these trials ranged from 3 to 10 days, with an average time of 5.92±2.21 days.

Risk of bias and quality assessment of the studies

Among the included studies, 12 were RCTs and one was self-controlled. The quality of over 50% of enrolled studies was

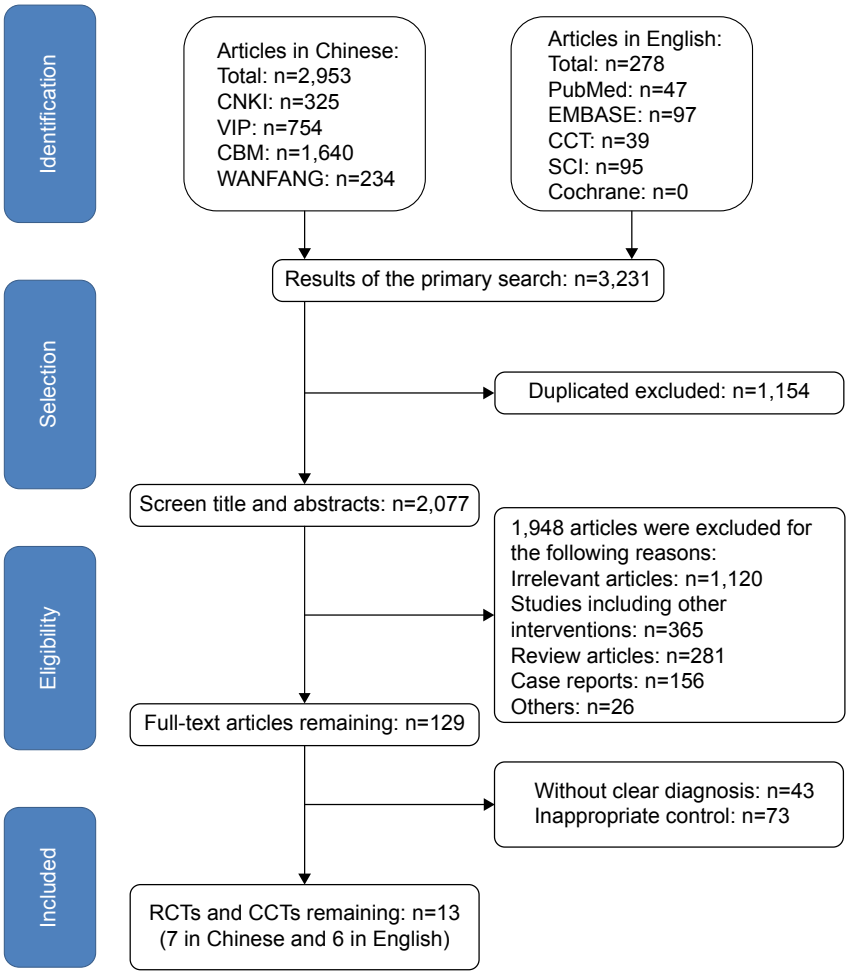

Figure 1 Study selection process.
Abbreviations: CBM, Chinese Biomedical Literature Database; CCTs, clinical controlled trials; CNKI, Chinese National Knowledge Infrastructure; EMBASE, Excerpta Medica database; RCTs, randomized controlled trials; VIP, the Chinese Scientific Journal Database; WANFANG, WANFANG data; SCI, Science Citation Index.

rated as poor, according to the Cochrane quality assessment criteria (Table 2 and Figure 2).

Effects of the interventions

Due to the heterogeneity of the enrolled trials, only descriptive analysis was conducted in this study.

Main outcome measure

The main outcome measures assessed in this study were ulcer size, lesion duration, and remission of pain.

Size of ulcer

Four out of 13 trials reported a change in ulcer size, which was measured by different methods. Haghpanah et al[11] evaluated the average diameter of all ulcers; however, Jiang et al[10] and Liu[23] evaluated the maximum diameter of the ulcer, while Liu et al[8] determined the size of the ulcer by the maximum diameter and its vertical diameter. Nevertheless, all the studies reported a statistically significant reduction of the ulcer size in patients receiving herbal medicine therapy compared with the controls, with the exception of the study by Haghpanah et al,[11] who reported that a significant difference between the herbal medicine group and the control group was only observed in the first day of the intervention, with no statistically significant differences between the groups for the remaining time points.

Duration of ulcer

Four trials reported data on the duration of the ulcer. Ghalayani et al[16] reported a significant difference in the mean healing time between 8.6±0.99 days of placebo treatment and 5.3±0.81 days of treatment with *Punica granatum* extract ($P<0.001$). In the study by Liu et al,[22] it was found that Tian-zhu aerosol oral rinse remarkably reduced the duration of the ulcer compared with chlorhexidine rinse ($P<0.05$); however, no detailed information was described. In the study by Amanlou et al,[15] the average time for complete healing of the lesions in patients receiving *Satureja khuzestanica* extract

Table 1 Characteristics of the enrolled studies

Study	Authors	Year	Article source	Type of study	Sample size (treatment/control)	Medications/formula
8	Liu et al	2012	*Evidence-based Complementary Alternative Medicine*, 2012;2012:284620	RCT	33/28	Yunnan Baiyao/toothpaste
9	Gavanji et al	2014	*Integrative Medicine Research*, 2014;3(2):83–90	RCT	210 patients in 7 groups, 30 in each	Alcoholic and water extracts of *Punica granatum*
10	Jiang et al	2013	*Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, 2013;115(2):212–217	RCT	42/42	Berberine/gelatin
11	Haghpanah et al	2015	*Caspian Journal of Internal Medicine*, 2015;6(1):3–8	Self-controlled	15/15	*Zingiber officinale* extract/mucoadhesives
15	Amanlou et al	2007	*Daru*, 2007;15(4):231–235	RCT	20/20	*Satureja khuzestanica* extract and its oil preparation/solution
16	Ghalayani et al	2013	*Journal of Research Pharmacy Practice*, 2013;2(2):88–92	RCT	20/20	*P. granatum* extract/gelatin
17	Wu	2000	*Journal of Clinical Stomatology*, 2000;16(3):172–173	RCT	150/130	Nourishing Yin and promoting granulation membrane formula
18	Han and Zhang	2003	*Journal of Zhengzhou University* (*Medical Sciences*), 2003;38(5):810–811	RCT	88/88	Qingmei ulcer membrane
19	Huang et al	1996	*Jin Ling Yi Yuan Xue Bao*, 1996;9(2):173–174	RCT	33/28	Nourishing Yin and promoting granulation membrane formula
20	Liu et al	2006	*Journal of TCM University of Human*, 2006;26(3):36–37	RCT	58/58	KouChuangNing tablets
21	Wei and Li	2003	*Shan Xi Zhong Yi*, 2003;23(8):714–725	RCT	63/58	Fufangjiaolianzhiji/membrane
22	Liu et al	2013	*Journal of Chengdu University of TCM*, 2013;36(4):80–82	RCT	43/40	Tian-zhu aerosol oral rinse
23	Liu	2010	*Chinese Journal of Misdiagnosis*, 2010;10(28):6826	RCT	36/36	Kangfuxinye/gargle

	Interventions	
	Treatment	**Control**
8	Teeth brushed with Yunnan Baiyao toothpaste twice daily; 1 g toothpaste for 3 minutes, for 5 days	Same procedure with placebo toothpaste
9	Mouth rinsed with alcoholic and water extracts of *P. granatum* var Pleni-flora, *P. granatum* var Sweet Alak, and *P. granatum* var Saveh Black for 10 minutes, four times daily, for 10 days	Negative control received no treatment
10	Berberine gelatin dabbed onto the ulcer for 30 minutes, four times daily, for 5 days	Same procedure with placebo gelatin
11	Stage 1: patients received placebo mucoadhesive, applied for 20 minutes, four times daily, for 7 days; stage 2: delayed until next RAS episode, then patients received mucoadhesive containing *Z. officinale* alcoholic extract, which was applied for 20 minutes, four times daily, for 7 days	
15	A small, sterile cotton pad impregnated with five drops of hydroalcoholic extracts (25%) of *S. khuzestanica* solution or its essential oil preparation was applied to the lesions for 1 minute and patients then fasted for at least 30 minutes; procedure repeated four times daily, for 7 days	Same procedure with hydroalcoholic solution in the absence of any active material
16	A small, sterile cotton pad impregnated with a hydroalcoholic extract of *P. granatum* flowers was applied to the lesions for 1 minute and the patients then fasted for at least 30 minutes; procedure repeated three times daily, for 7 days	Same procedure with placebo gel
17	Nourishing Yin and promoting granulation membrane formula was applied to the lesions four times daily, for 5 days	Same procedure with chlorhexidine membrane
18	Qingmei ulcer membrane was applied to the lesions four times daily, for 5 days	Oral administration of vitamin B2 (10 mg) and vitamin C (300 mg) three times daily
19	Qingmei ulcer membrane was applied to the lesions four times daily, for 5 days	Same procedure with chlorhexidine membrane
20	KouChuangNing tablets (1.0 g) were held in the mouth until dissolved every 2 hours, six times per day, for 5 days	Same procedure with placebo tablets
21	Fufangjiaolianzhiji membrane was applied to the lesions, for 3 days	Same procedure with chlorhexidine membrane

22		Mouth rinsed with natural saline twice; 10 minutes later, Tian-zhu aerosol oral rinse was used for 5 minutes; procedure repeated four times daily, for 10 days	Same procedure with chlorhexidine rinse	
23		Mouth rinsed with Kangfuxinye for 1–2 minutes, three times daily, for 3 days	Same procedure with natural saline	
	Treatment course	**Outcome measurement**	**Complication**	**Follow-up**
8	5 days	Ulcer size (maximum diameter × vertical diameter) and pain level (VAS)	Two patients in the placebo group complained of lingual numbness, which spontaneously resolved	Not mentioned
9	10 days	Pain level and the degree of the participants' satisfaction (VAS)	Not mentioned	Not mentioned
10	5 days	Ulcer size (maximum diameter) and pain level (VAS)	None	Not mentioned
11	7 days	Ulcer size (average diameter), the diameter of lesions and the inflammatory zone, and pain level (VAS)	None	Not mentioned
15	7 days	Duration for complete healing and duration of elimination of pain	Two participants reported a slight burning sensation after receiving *S. khuzestanica* essential oil	7 days
16	7 days	Pain level (VAS), duration for complete healing, and duration of elimination of pain	Not mentioned	Until complete healing
17	5 days	Healing rate	None	Not mentioned
18	5 days	Healing rate	Not mentioned	Not mentioned
19	5 days	Healing rate	None	Not mentioned
20	5 days	Healing rate	One case in the experimental group and one case in the control group reported side effects, but no detailed information was provided	Not mentioned
21	3 days	Healing rate	Not mentioned	Yes, but without detailed information
22	10 days	Healing rate, recurrence rate within 1 year, and duration for complete healing	Not mentioned	1 year
23	3 days	Level of pain, ulcer size (maximum diameter), degree of erythema, and healing rate	None	Not mentioned

Abbreviations: RAS, recurrent aphthous stomatitis; RCT, randomized controlled trial; VAS, visual analog scale.

Table 2 Quality assessment of included studies

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
8	Low bias	Low bias	Low bias	Low bias	Low bias	Low bias	Uncertain
9	Uncertain	Low bias	Low bias	Low bias	Low bias	Low bias	Uncertain
10	Uncertain	Low bias	Low bias	Low bias	Low bias	Low bias	Uncertain
11	Uncertain	Low bias	Low bias	Low bias	Low bias	Low bias	Uncertain
15	Uncertain	Uncertain	Low bias	Low bias	Low bias	Low bias	Uncertain
16	Uncertain	Low bias	Low bias	Low bias	Low bias	Low bias	Uncertain
17	Low bias	Uncertain	Low bias	Low bias	High bias	High bias	Uncertain
18	Low bias	Uncertain	High bias	High bias	Low bias	Low bias	Uncertain
19	Uncertain	Uncertain	High bias	High bias	High bias	High bias	Uncertain
20	Low bias	Low bias	Low bias	Low bias	High bias	High bias	Uncertain
21	Low bias	Uncertain	High bias	High bias	Low bias	Low bias	Uncertain
22	Uncertain	Uncertain	High bias	High bias	Low bias	Low bias	Uncertain
23	Uncertain	Uncertain	High bias	High bias	High bias	High bias	Uncertain

or its essential oil was 5.90±1.24 days and 6.85±1.3 days, respectively, which were both significantly less than those receiving placebo treatment (10.40±1.66 days, P=0.0001). Moreover, there was no significant difference between the experimental groups. In the study by Wei and Li,[21] the healing time of the lesions in patients receiving Fufangjiaolianzhiji (2.79±0.30 days) was significantly shorter than when patients received a chlorhexidine rinse (6.02±1.45 days, $P<0.05$).

Remission of pain

Remission of pain was described in all the trials included in this literature review and it was described as the main outcome index in six studies. In addition, a visual analog scale (VAS) was applied in five out of the six studies to record the level of pain. In these studies, the visual analog scale score was significantly decreased in the herbal medicine groups than in the control groups.[8–11,16] In addition, two trials reported the average period of pain elimination, which was significantly shorter in patients receiving herbal medicine than placebo treatment.[15,16]

Side effects

Five trials did not report side effects,[9,16,18,21,22] while five trials reported that there were no side effects[10,11,17,19,23] and three trials reported slight side effects.[8,15,20] In the study by Liu et al,[20] one patient receiving herbal medicine and one patient in the control group reported side effects, but no detailed information was provided. In the study by Amanlou et al,[15] two participants reported a slight burning sensation after receiving *S. khuzestanica* essential oil (prepared in an ethanol/water mixture: 50% v/v) on the first application. Liu et al[8] noted that two patients in the placebo group complained of slight lingual numbness, which spontaneously remedied.

Discussion

RAS is one of the most common oral disorders and its etiology is not well understood. Its management is mainly directed toward symptomatic, supportive treatment.[3] Therefore, corticosteroids and analgesics serve as the first choice for RAS patients.[4] However, longer treatment times and frequent exposure to such drugs may induce severe complications, such as secondary fungal infections and drug resistance.[5] There has been a long history of the use of natural herbal medicines for various disorders, including RAS, worldwide and such remedies have been studied both in clinic trials and experimental studies.[8,9,24,25] In this study, we focused on the efficacy and safety of the topical application of natural herbal medicines for the treatment of RAS.

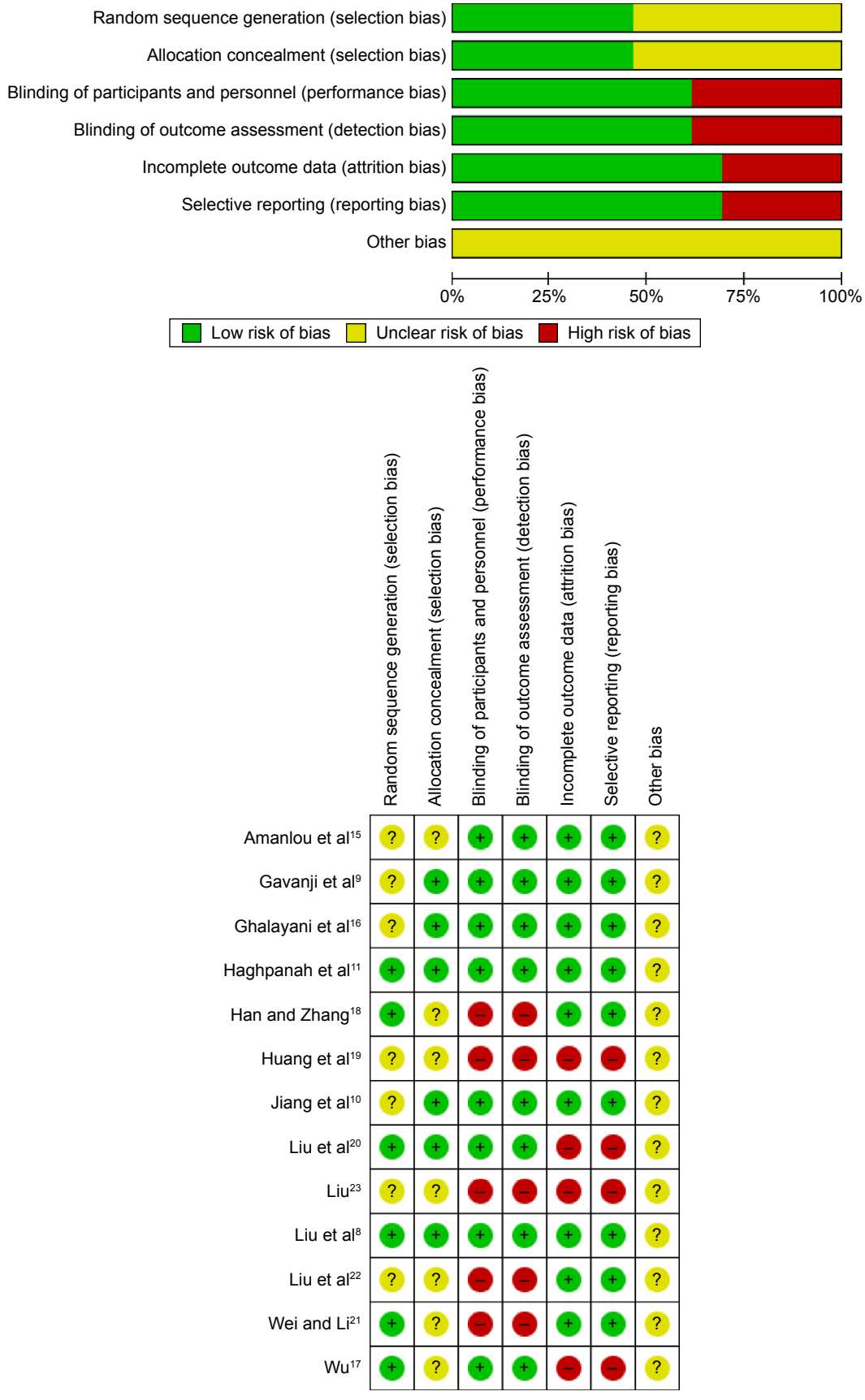

Figure 2 The Cochrane Collaboration's tool for assessing risk of bias.
Note: +, low bias; ?, uncertain; –, high bias.

A total of 1,515 subjects in 13 clinical trials were analyzed in the present analysis. Compared with controls, topical natural herbal medicines greatly improved the patients' symptoms by reducing ulcer size, shortening ulcer duration, and relieving pain without severe complications. However, only a weak conclusion can be drawn due to several limitations. First, the homogeneity of the studies was quite poor, with variables such as the various types of treatment, dosage, formula, application method, sample size, and experiment duration. Second, the quality of the studies was not sufficient because of poor study design and high risks in the performance, detection, attrition, and reporting bias. Therefore, a meta-analysis could not be conducted based on the current data. Consequently, this analysis unveiled the need for well-designed multicenter RCTs, which are of paramount importance for further exploration. Furthermore, precise criteria and standard methodologies should be established to ensure high-quality data.

The rationale of study designs can be a guarantee of strong clinical trials. The herbal medicine–oriental model or disease–oriental model may greatly affect the inclusion and exclusion criteria of future meta-analyses.

Detailed information of the herbal medicine used in future studies, including the formula, dosage, therapy duration, application protocols, and control intervention, should be provided. If possible, the dosage and application protocol should be homogenized for different forms of the same medicine.

In the studies included in this review, the therapy duration ranged from 3 to 10 days. However, we found that the natural course of an untreated ulcer was 9.5±1.3 days[15,16] and the duration of herbal medicine treatment was 5.21±1.73 days.[15,16,21,22] It is therefore suggested that the experimental period should exceed 7 days to avoid missing valuable data. Moreover, follow-up is highly recommended.

In addition to the above, the index and measurement of outcomes should be described clearly and consistently in future studies. According to the current data, ulcer size, lesion duration, and level of pain are commonly considered as the main outcome indicators. However, researchers often failed to assess them in a standard way, especially with regards to the ulcer size. Actually, manifestation of RAS may be a single ulcer or several round or elliptic recurrent ulcers in the oral mucosa.[4] Therefore, measurement of the maximum diameter may not be suitable to determine the ulcer size accurately. Theoretically, evaluation of the ulcer area may be better in describing the lesion size; however, the precise calculation may restrict its application in clinic. We suggest that measurement of the maximum diameter and its vertical diameter should be made, as described in the study by Liu et al,[8] as it is a precise and convenient way to determine the size of lesions. Finally, appropriate statistical methods also represent an important part of study protocols and can allow sample size calculation and data analysis.

In summary, the current data show favorable benefits of the topical treatment of RAS with natural herbal medicines and only three of the included studies reported slight and/or transient side effects during the clinical trial period. Thus, there is some evidence to suggest that topical herbal medicine therapy is an effective and safe alternative option to current Western medicine-based treatments for RAS.

Conclusion

There is weak evidence with regards to the efficacy of the topical application of natural herbal medicines for the treatment of RAS patients' conditions, with few side effects reported. However, given the limitations of the trials included in this assessment and the methodologies employed in the current data, a definitive conclusion cannot be drawn. Well-designed and high-quality RCTs are required for further exploration.

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Disclosure

The authors report no conflicts of interest in this work.

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