ADA CE Program ARTICLE 2

Efficacy and safety of Chinese patent medicines in the treatment of recurrent aphthous stomatitis

A systematic review

Peiru Zhou, DDS; Qinghua Mao, DDS; Hong Hua, DDS, PhD; Xiaosong Liu, DDS, PhD; Zhimin Yan, DDS, PhD

ABSTRACT

Background. Recurrent aphthous stomatitis (RAS) is the most common chronic oral mucosal condition of the oral cavity. Investigators in clinical trials have evaluated the effectiveness of Chinese patent medicines in the treatment of RAS. However, the results are conflicting rather than conclusive. To evaluate the efficacy and safety of Chinese patent medicines for the treatment of RAS, the authors conducted a systematic review.

Types of Studies Reviewed. The authors searched 9 electronic databases to identify randomized controlled trials (RCTs) or potential clinical controlled trials (CCTs), published in any language, in which the investigators compared Chinese patent medicines with vitamin tablets or placebos for the treatment of RAS.

Results. The authors included 11 RCTs and 1 CCT in the review. Results showed that Chinese patent medicines were beneficial for patients with RAS in relieving ulcer pain and reducing the duration and frequency of attacks. The reported adverse effects of Chinese patent medicines included stomachache, abdominal distention, diarrhea, mild nausea, and gastrointestinal discomfort, which were either self-limiting or could be relieved by treatment cessation.

Conclusions and Practical Implications. Chinese patent medicines may be effective for treatment of RAS by means of relieving pain and reducing ulcer size and episode duration and frequency.

Key Words. Recurrent aphthous stomatitis; Chinese patent medicine; systematic review; efficacy; safety.
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Recurrent aphthous stomatitis (RAS), also called *recurrent aphthous ulcer*, is the most common chronic oral mucosal condition of the oral cavity, which affects 5% to 25% of the population.[1-3] The age of onset of RAS is usually between 10 and 19 years, with no sex predilection,[4] but it can persist into adulthood and throughout life.[4] The underlying cause is not clear,[5] although several factors are known to predispose a person to RAS, including local, systemic, immunologic, genetic, allergic, nutritional, and microbial factors,[1] as well as local trauma.[6]

The typical minor type of RAS lesion is most common and manifests with a painful, rounded or oval ulcer less than 1 centimeter in diameter with a gray-white pseudomembrane and an erythematous halo, which heals within 7 to 14 days. Although minor RAS is common, major RAS also can occur in 10% of patients with RAS.[1] It is more severe, with a diameter greater than 1 cm. Major RAS ulcers can last from weeks to months. Herpeslike RAS is characterized by numerous small ulcers that coalesce, and it is the rarest form of the condition.[7,8] Diagnosis of RAS usually is based on previous or current history of RAS and clinical manifestations; however, it should be differentiated carefully from manifestations of systemic diseases such as Behçet

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syndrome, Reiter syndrome, Crohn disease, celiac disease, ulcerative colitis, inflammatory bowel disease, erythema multiforme major, vitamin and mineral deficiencies, hematologic disorders, gastrointestinal diseases, and cyclic neutropenia immune deficiencies.[9]

The primary aim of treatment is to reduce pain and promote healing, as well as to reduce RAS episode duration and recurrence rate. For severe RAS cases that are characterized by major type or frequent recurrence, immunosuppressants (for example, colchicines, pentoxifylline, dapsone, azathioprine, hydroxychloroquine, and cyclosporine) might be necessary; however, the widespread use of such agents is limited because of potential adverse events. No satisfactory curative treatment exists for RAS.[10] Traditional Chinese herbs are becoming increasingly popular and accepted worldwide. In China, topical and systemic patent medicines made of traditional Chinese herbs commonly are prescribed—for example, Liuwei Dihuang pills generally are considered safe and can be effective. However, to our knowledge, no meta-analyses or systemic reviews have been published on the effects of Chinese herbal medicines for treatment of RAS. Therefore, we conducted a systematic review to assess the existing randomized controlled trials (RCTs) and clinical controlled trials (CCTs) that included Chinese patent medicines for the treatment of RAS and to provide an up-to-date evidence-based evaluation of the effectiveness and safety of Chinese patent medicines for RAS treatment.

METHODS

Databases and search strategies. We searched 9 electronic databases for RCTs or CCTs focusing on Chinese patent medicines for treatment of RAS: China National Knowledge Infrastructure database (1979-2015), VIP China Science and Technology Journal Database (1989-2015), Chinese Biomedical Literature Database (1977-2015), Wanfang Data (1985-2015), Embase (1966-2015), PubMed (1949-2015), Science Citation Index (1900-2015), and current controlled trials and the Cochrane Central Register of Controlled Trials in the Cochrane Library (search date: March 15, 2015). We used hand searching as a complement. We used no restrictions for language or type of publication. All the searches ended in March 2015. We included in this review all clinical trials in which the investigators compared the use of Chinese patent medicines with vitamin tablets or placebos for RAS treatment. The search terms used individually or combined included "Chinese patent medicine," "Chinese patent drugs," "traditional Chinese medicine," "Chinese herbology," "Chinese medicine," "Chinese material medica," "Chinese herbs," "Chinese herbal medicine," "herbal medicine," "Chin Tradit Pat Med," "recurrent aphthous ulcer," "recurrent aphthous stomatitis," "recurrent oral ulcer," and "recurrent oral ulceration."

Inclusion and exclusion criteria and outcomes. We included in this review studies that met the following inclusion criteria:

- Participants had to be patients with a confirmed diagnosis based on previous or current history of RAS or clinical examination who sought care for RAS-like lesions. Exceptions were patients with Behçet syndrome, Reiter syndrome, erythema multiforme, viral infections, celiac disease, Crohn disease, ulcerative colitis, vitamin- and mineral-deficiency anemia (vitamin B_{12}, folic acid, and serum iron), and other systemic diseases.
- Interventions in the treatment group were orally administered Chinese patent medicines with or without vitamin tablets, with no restrictions on the types or doses.
- Control groups received placebos or vitamin tablets.
- Investigators had to report at least 1 of the primary or secondary outcomes. Primary outcomes included ulcer pain, ulcer size, episode duration, and episode frequency associated with RAS; secondary outcomes included patients' quality of life.
- The studies had to be RCTs or CCTs.

We excluded the following types of studies:

- duplicate publications reporting the same groups of participants;
- studies that lacked basic information regarding the participants or interventions;
- studies with inconsistencies in the duration or frequency of interventions between the treatment and control groups;
- studies in which the investigators used only topical formulations of Chinese patent medicines;
- case reports, reviews, workshop summaries, and studies about clinical observations.

Data collection and analysis. Two of the authors (P.Z., Q.M.) performed the literature searches independently. In addition, both authors were responsible for selection of studies and data collection. We conducted the literature search by using the following criteria from the *Cochrane Handbook for Systemic Reviews of Interventions*, Version 5.1.0.[11] We imported the search results from the 9 databases into reference management software (NoteExpress 3.0.4, Beijing Aegean Sea

ABBREVIATION KEY. bid: Twice a day. **CBM:** Chinese Biomedical Literature Database. **CCT:** Clinical controlled trial. **CD:** Cluster of differentiation. **CNKI:** China National Knowledge Infrastructure. **Cochrane:** Cochrane Central Register of Controlled Trials in the Cochrane Library. **qd:** Once a day. **RAS:** Recurrent aphthous stomatitis. **RCT:** Randomized controlled trial. **SCI:** Science Citation Index. **TCM:** Traditional Chinese medicine. **tid:** 3 times a day. **VIP:** VIP China Science and Technology Journal Database. **Wanfang:** Wanfang Data.

Software). We removed duplicate reports by means of the software, and we removed irrelevant studies by screening the titles and abstracts. We obtained full articles for all possibly relevant trials. We identified studies meeting the inclusion criteria. We collected various data, including the title of the study, article source, year of publication, authors, study size, sample size, methodological details, diagnostic criteria, methods of intervention for the treatment and control groups, treatment course, complications, follow-up, and adverse effects. We resolved disagreements by means of discussion and achieved consensus through additional reviewers (X.L., Z.Y.).

Assessment of the risk of bias in the included studies. We evaluated the risk of bias in the included RCTs and CCTs by using the *Cochrane Handbook for Systemic Reviews of Interventions*, Version 5.1.0 and software (RevMan 5.3.3; Cochrane Informatics and Knowledge Management Department).[11] The assessment criteria included 7 domains: random sequence generation (selection bias), allocation concealment (selection bias), masking of participants and personnel (performance bias), masking of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. We graded studies as having a low risk of bias if we found that they had a low risk of bias for all key domains and as having an unclear risk of bias if 1 or more of the key domains was unclear; we graded all other studies as having a high risk of bias.

Data synthesis. We performed a meta-analysis for trials with good homogeneity of study design, participants, interventions, control, and outcome measures by using software (RevMan 5.3.3). Otherwise, we conducted a descriptive analysis.

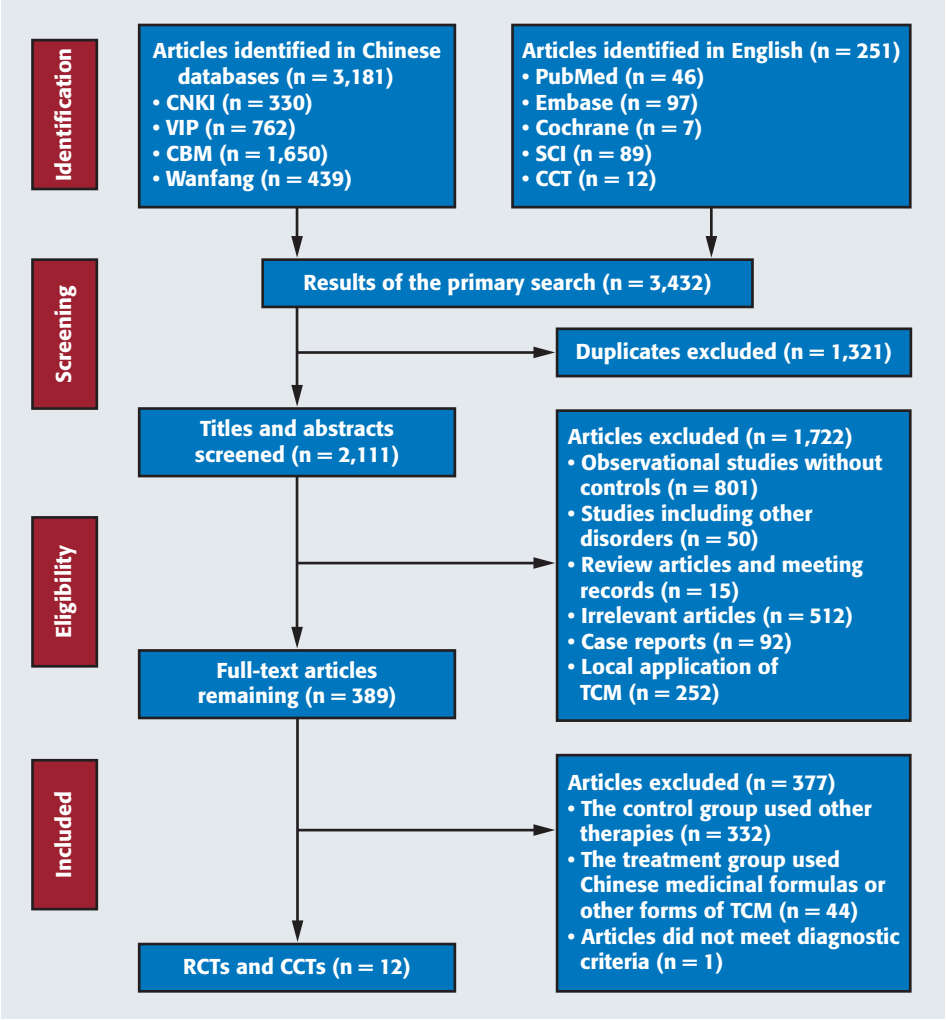

Figure 1. Study selection process. CBM: Chinese Biomedical Literature Database. CCT: Clinical controlled trial. CNKI: China National Knowledge Infrastructure. Cochrane: Cochrane Central Register of Controlled Trials in the Cochrane Library. RCT: Randomized controlled trial. SCI: Science Citation Index. TCM: Traditional Chinese medicine. VIP: VIP China Science and Technology Journal Database. Wanfang: Wanfang Data. *Source: Moher and colleagues.*[12]

RESULTS

Basic information. ***Search strategy and description of the included studies.*** After an initial search through the 9 electronic databases, we identified 3,432 citations (3,181 in Chinese and 251 in English: none were found in languages other than English and Chinese). We excluded 1,321 studies that were duplicates. Among the remaining 2,111 potentially relevant abstracts identified, 1,722 were not RCTs or CCTs. We read the remaining 389 full-text articles and excluded 332 because the control groups were treated with therapies other than a placebo or vitamin tablet, 44 because the

TABLE 1

Characteristics of the included studies.*

STUDY	STUDY TYPE	SAMPLE SIZE (TREATMENT/ CONTROL)
Cheng and Zhuang,[13] 1998	RCT†	70/52
Hao and Li,[14] 2001	CCT‡	70/70
Li,[15] 2001	RCT	80/35
Lv,[16] 2002	RCT	30/22
Sun,[17] 2003	RCT	40/40
Yan and Colleagues,[18] 2006	RCT	70/40
Zheng and Colleagues,[19] 2007	RCT	60/44
Meng and Colleagues,[20] 2010	RCT	90/88
Yu,[21] 2011	RCT	30/30
Duan and Colleagues,[22] 2012	RCT	31/30
Peng and Colleagues,[23] 2012	RCT	96/48
Xu and Colleagues,[24] 2013	RCT	40/40

* The diagnosis standard was clinical manifestation recurrence history for all studies.
† RCT: Randomized controlled trial.
‡ CCT: Clinical controlled trial.

TABLE 2

Interventions used in the included studies.

STUDY	INTERVENTION	
	Treatment	Control
Cheng and Zhuang,[13] 1998	Liuwei Dihuang pills, 9 grams, tid* for 45 d	Vitamin C tablets, 0.2 g, tid + vitamin B1 tablets, 20 milligrams, tid + vitamin B2 tablets, 10 mg, tid for 45 d
Hao and Li,[14] 2001	Chaihu oral liquid, 10 milliliters, tid for 14 d, then bid† for 14 d, and finally qd‡ for 14 d	Compound vitamin B tablets, 2 tablets, tid for 42 d
Li,[15] 2001	Red pills and black pills, 10 of each, bid for 30 d	Compound vitamin B tablets, 2 tablets, tid + vitamin B1 tablets, 10 mg, tid + vitamin B2 tablets, 5 mg, tid for 30 d
Lv,[16] 2002	Liuwei Dihuang pills, 3 g, tid for 90 d	Compound vitamin B tablets, 2 tablets, tid for 90 d
Sun,[17] 2003	Liuwei Dihuang pills, 6 pills, tid for 90 d	Vitamin C tablets, 0.1 g, tid + vitamin B2 tablets, 5 mg, tid for 90 d
Yan and Colleagues,[18] 2006	Licorzinc, 0.25 g, tid for 60 d	Vitamin B2 tablets, 5 mg, tid for 60 d
Zheng and Colleagues,[19] 2007	Licorzinc, 0.25 g, tid for 60 d	Vitamin B2 tablets, 5 mg, tid for 60 d
Meng and Colleagues,[20] 2010	Zhibai dihuang pills, 9 g, bid + vitamin B2 tablets, 0.2 g, tid for 14 d	Vitamin B2 tablets, 20 mg, tid for 14 d
Yu,[21] 2011	Pearl dropping pills, 0.2 g, qid for 5 d	Placebo (dropping pills), 0.2 g, qid for 5 d
Duan and Colleagues,[22] 2012	Bergamot ulcer particles, 5 g, tid for 7 d	Placebo (starch tablets), 5 g, tid for 7 d
Peng and Colleagues,[23] 2012	Yiqing capsules, 1 g, tid for 7 d	Placebo (capsules), 1 g, tid for 7 d
Xu and Colleagues,[24] 2013	Qingwei powder, 20 g, tid for 6 d	Placebo (granules), 20 g, tid for 6 d

* tid: 3 times a day.
† bid: Twice a day.
‡ qd: Once a day.

treatment groups were treated with Chinese medicinal formulas or other forms of traditional Chinese medicine (TCM), and 1 because it did not meet the diagnostic criteria. We included 12 trials that met the inclusion criteria in the review. All included studies were published in Chinese. Figure 1 depicts the process from identification to final study inclusion, which we have presented according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses format.[12]

Study characteristics. Tables 1 through 3[13-24] summarize the characteristics of the 12 clinical trials included in this review. Overall, 1,246 patients with RAS were included in these trials. Of these patients, 707 were treated with an oral Chinese patent medicine with or without vitamin tablets, and 539 patients were treated with vitamin tablets or a placebo. The sample size of each single group in these trials ranged from 22 to 96 (Tables 1-3).[13-24]

Risk of bias and quality assessment of the studies. The quality of most of these trials was low according to the Cochrane quality assessment criteria (Table 4).[13-24] Figures 2 and 3 depict the risk of bias. Information about random sequence generation, allocation concealment, and selective reporting were either unclear or deemed high risk. Investigators in only 1 trial[23] reported the assessment index extensively. We conducted a descriptive analysis owing to the limitations of statistical heterogeneity.

Effectiveness of interventions. ***Chinese patent medicines versus placebos (n = 4).*** Investigators in 4 studies[21-24] compared the effects of Chinese patent medicines, including bergamot ulcer particles, Qingwei powder, Yiqing capsules, and pearl dropping pills, with a placebo (Tables 1-3).[13-24] Investigators in 2 placebo-controlled trials[21,22] reported that Chinese patent medicines were effective in reducing pain and ulcer size in RAS (t test, $P < .05$). Investigators in the remaining 2 of the 4 studies[23,24] reported no difference between Chinese patent medicines and placebo in terms of pain score and ulcer size (t test, $P > .05$). Investigators in 1 study[22] reported that treatment with Chinese patent medicines reduced the frequency of RAS episodes (χ^2 test, $P < .01$). Investigators in 2 studies[21,23] measured the improvement of TCM symptoms (*Zheng* in Chinese, which for RAS symptoms is a burning sensation of the ulcer), and investigators in 1 study[21] reported marked improvements in the treatment group compared with the control group (t test, $P < .01$). In the other study,[23] the treatment group

showed a trend toward greater improvement of TCM symptoms compared with that of the control group, but there were no significant differences between the 2 groups (χ^2 test, $P > .05$).

Chinese patent medicines versus vitamin tablets (n = 8). Investigators in the remaining 8 studies compared the effects of Chinese patent medicines with those of vitamin tablets (Tables 1-3).[13-24] Investigators in 4 of the 8 studies reported significant improvements in pain scores (χ^2 test, $P < .05$).[14,18-20] Investigators in 7 studies reported changes in RAS episode frequency and significant differences favoring Chinese patent medicines over vitamins ($P < .05$).[13-19] Investigators in 2 studies compared the episode duration of RAS, and both reported significant improvement in the Chinese patent medicine group (χ^2 test, $P < .05$) compared with the control group.[14,15] Investigators in 2 studies reported that Chinese patent medicines may be effective in reducing ulcer size during an RAS episode (χ^2 test, $P < .05$).[14,20] Investigators in 3 studies reported marked differences between Chinese patent medicines and vitamin tablets in terms of reduction of the number of ulcers (χ^2 test, $P < .05$).[17-19]

In addition to clinical observations, investigators in 1 of the 8 studies compared the titers of T lymphocyte subpopulations before and after treatment with a Chinese patent medicine.[17] Before treatment, the levels of cluster of differentiation (CD) 3, CD4, and CD4:CD8 ratio were significantly lower than normal (*t* test, $P < .01$), and CD8 levels were higher than normal (*t* test, $P < .01$). After treatment, the levels of CD3, CD4, and CD4:CD8 ratio were significantly increased (*t* test, $P < .01$) and close to normal (*t* test, $P > .05$), which might indicate the possible underlying mechanisms.

TABLE 3

Outcomes and follow-up used in included studies.

STUDY	TREATMENT COURSE, DAYS	OUTCOME MEASURE	COMPLICATIONS	FOLLOW-UP	ADVERSE EVENT
Cheng and Zhuang,[13] 1998	45	Episode duration Episode frequency Ulcer number	No	Not mentioned	Not mentioned
Hao and Li,[14] 2001	42	Pain degree Episode frequency Ulcer number Ulcer size Episode duration	No	1 y	Not mentioned
Li,[15] 2001	30	Pain degree Episode frequency Ulcer number Ulcer size Episode duration	No	Not mentioned	Not mentioned
Lv,[16] 2002	90	Ulcer number Episode frequency	No	12-18 mo	Not mentioned
Sun,[17] 2003	90	Pain degree Episode frequency Ulcer number Episode duration	No	2 y	Not mentioned
Yan and Colleagues,[18] 2006	60	Pain degree Ulcer number Episode frequency	No	12-18 mo	Not mentioned
Zheng and Colleagues,[19] 2007	60	Pain degree Ulcer number Episode frequency	No	12-18 mo	Not mentioned
Meng and Colleagues,[20] 2010	14	Pain degree Ulcer size	No	3 mo	Not mentioned
Yu,[21] 2011	5	Pain degree Ulcer size Ulcer number Traditional Chinese medicine syndromes (burning sensation of the ulcer, dry mouth, constipation, scanty dark urine)	No	Not mentioned	None
Duan and Colleagues,[22] 2012	7	Pain degree Episode frequency Ulcer number Ulcer size	No	1 y	2 patients with mild nausea and 3 patients with gastrointestinal discomfort
Peng and Colleagues,[23] 2012	7	Pain degree Traditional Chinese medicine syndromes (burning sensation of the ulcer, fever, dysphoria, hot eyes, dry mouth, halitosis, constipation, scanty dark urine)	No	Not mentioned	Stomachache, abdominal distention, and diarrhea
Xu and Colleagues,[24] 2013	6	Pain degree Ulcer size	No	Not mentioned	None

Adverse events and adverse reactions. Investigators in 2 trials reported adverse events or adverse reactions.[22,23] Investigators in 1 study monitored general physical

TABLE 4

Quality assessment of included randomized controlled trials.

STUDY	RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	MASKING OF PARTICIPANTS AND PERSONNEL	MASKING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	OTHER BIAS	SUMMARY
Cheng and Zhuang,[13] 1998	High bias	High bias	Low bias	Low bias	Low bias	Uncertain	Uncertain	High risk of bias
Hao and Li,[14] 2001	Uncertain	High bias	Low bias	Low bias	Low bias	Uncertain	Uncertain	Unclear risk of bias
Li,[15] 2001	Uncertain	High bias	Low bias	Low bias	Uncertain	Uncertain	Uncertain	High risk of bias
Lv,[16] 2002	High bias	High bias	Low bias	Low bias	Uncertain	Uncertain	Uncertain	High risk of bias
Sun,[17] 2003	Uncertain	High bias	Low bias	Low bias	Low bias	Uncertain	Uncertain	High risk of bias
Yan and Colleagues,[18] 2006	High bias	High bias	Low bias	Low bias	Uncertain	Uncertain	Uncertain	High risk of bias
Zheng and Colleagues,[19] 2007	High bias	High bias	Low bias	Low bias	Uncertain	Uncertain	Uncertain	High risk of bias
Meng and Colleagues,[20] 2010	Low bias	High bias	Low bias	Low bias	Uncertain	Uncertain	Uncertain	High risk of bias
Yu,[21] 2011	High bias	High bias	Low bias	Low bias	Low bias	Low bias	Low bias	High risk of bias
Duan and Colleagues,[22] 2012	Uncertain	High bias	Low bias	Low bias	Low bias	Uncertain	Uncertain	High risk of bias
Peng and Colleagues,[23] 2012	Low bias	Low bias	Low bias	Low bias	Low bias	Uncertain	Low bias	Low risk of bias
Xu and Colleagues,[24] 2013	High bias	Low bias	Low bias	Low bias	Low bias	Uncertain	Uncertain	Unclear risk of bias

signs (body temperature, breathing rate, heart rate, blood pressure, and weight), conducted laboratory examinations (whole blood cell testing, urinalysis, stool examination, liver and kidney function testing, and electrocardiography), and recorded any adverse drug reactions and adverse events.[23] They reported no severe adverse events, and the adverse reactions were primarily gastrointestinal reactions such as stomachache, abdominal distention, and diarrhea, which were related to the medicine itself and were resolved either spontaneously or on cessation of the medicine. Safety analysis showed that the incidences of adverse events in the Chinese patent medicine group and placebo group were 11.58% and 6.25%, respectively, and those of adverse reactions were 5.26% and 2.08%, respectively. Results of χ^2 and Fisher exact probability tests demonstrated no significant difference between the treatment group (Chinese patent medicine) and the control group (placebo) ($P > .05$). In the other study, the investigators reported mild nausea and gastrointestinal discomfort in the Chinese patent medicine group, which was considered related to individual sensitivity or the pungent smell of Chinese patent medicines.[22] The investigators reported no other adverse events or adverse reactions. Statistical heterogeneity limited the analysis of subgroups and publication bias.

DISCUSSION

RAS is the most common chronic oral mucosal condition of the oral cavity, with an incidence of 5% to 25% in the general population.[3] The underlying cause of RAS is multifactorial and not entirely clear. To our knowledge, no known cure exists, and various interventions are being used for the treatment of RAS in clinical settings. The interventions are segregated sequentially according to the treatment ladder on the basis of the patient's response. In general, systemic interventions such as immunosuppressants are used after ineffective topical therapy. However, because no single treatment has been found to be effective, results with regard to the best systemic intervention for RAS remain inconclusive.

In 2012, results from a systematic review of studies on RAS treatments published in the *Cochrane Database of Systematic Reviews* indicated insufficient support for the use of any intervention because there was almost no evidence for any treatment to be considered first-line therapy.[25] Nevertheless, the review did not include

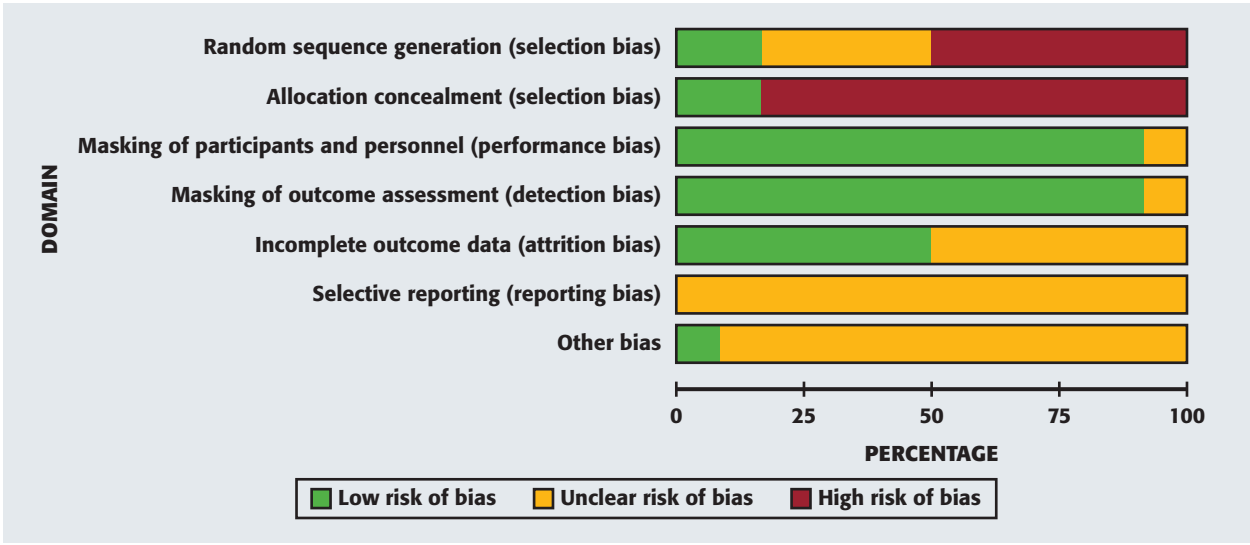

Figure 2. Risk of bias graph reviewing authors' judgments about each risk of bias item presented as percentages across all included studies. *Source: Higgins and Green.*[11]

Chinese databases and did not evaluate the effect of Chinese patent medicines as 1 of the interventions. In addition, the authors of the 2012 Cochrane review failed to stratify therapies on the basis of different clinical types, which is a common limitation. In our review, we could not stratify the interventions owing to the varying designs of the included studies.

Liuwei Dihuang pills are a popular patent TCM used clinically for treating RAS, as described in this study. This medicine is sourced from the book *Key to Therapeutics of Children's Diseases* written by Qian Yi of the Song dynasty, published in 1119 CE. Essentially, Liuwei Dihuang pills consist of 6 ingredients: *Cornus officinalis*, *Rehmannia glutinosa*, Rhizoma dioscoreae, *Cortex moutan radicis*, *Poria cocos*, and *Alisma plantago-aquatica*. Research on Liuwei Dihuang pills has become a hot topic, including pharmacologic function, clinical application, and disease prevention.[26] Investigators in several studies have reported that Liuwei Dihuang pills can improve immune function to reduce the incidence of tumors and induced liver or colorectal cancers in animal models. In addition, these pills have been reported to protect the liver by recovering or improving its detoxification and excretion functions, as well as playing a role in antiaging by scavenging free radicals.[26,27] In the field of oral medicine, Liuwei Dihuang pills are used widely to treat RAS in China. Study results have demonstrated that Liuwei Dihuang pills could correct the imbalance of T lymphocyte subsets and modulate cell-mediated immune responses in patients with RAS.[28] Sun[17] reported that patients with RAS had depressed $CD4^+$ and $CD3^+$ T-cell counts and a low $CD4^+$:$CD8^+$ ratio. After 6 months of oral treatment with Liuwei Dihuang pills, the $CD3^+$ and $CD4^+$ T-cell counts and the $CD4^+$:$CD8^+$ ratio elevated significantly and were close to the normal ranges; this finding is in accord with the etiopathogenesis of RAS.

Topical medications are often effective in treating minor RAS. However, for major RAS, systemic use of immunosuppressants (steroids and thalidomide) and adjunctive immunosuppressants (colchicines, pentoxifylline, dapsone, azathioprine, hydroxychloroquine, and cyclosporine) may be necessary. However, this solution remains unsatisfactory because almost all topical therapies simply relieve pain and promote healing but are not helpful in reducing the frequency of RAS episodes. Moreover, the adverse events of systemic immunosuppressants limit long-term use, and the curative effects cannot be maintained with treatment discontinuation.[29]

In our analysis, we evaluated 12 clinical trials consisting of 1,246 patients. Compared with placebo, vitamin tablets or Chinese patent medicines were beneficial for patients with RAS in terms of relieving pain and promoting healing, as well as reducing the duration and frequency of RAS events. More importantly, the incidence of adverse effects was lower. The adverse effects were mild and could either be alleviated spontaneously or disappear after cessation of the medicine.[22,23] In addition to the lower incidence of adverse events, some studies involved evaluation of long-term side effects. According to Duan and colleagues,[22] there were no obvious adverse effects with these medications. Only 2 participants reported mild nausea, and 3 reported intestinal discomfort, which may be associated with individual sensitivity. Furthermore, there was 1 study in which the investigators used laboratory testing to evaluate adverse events. Xu and colleagues[24] investigated the

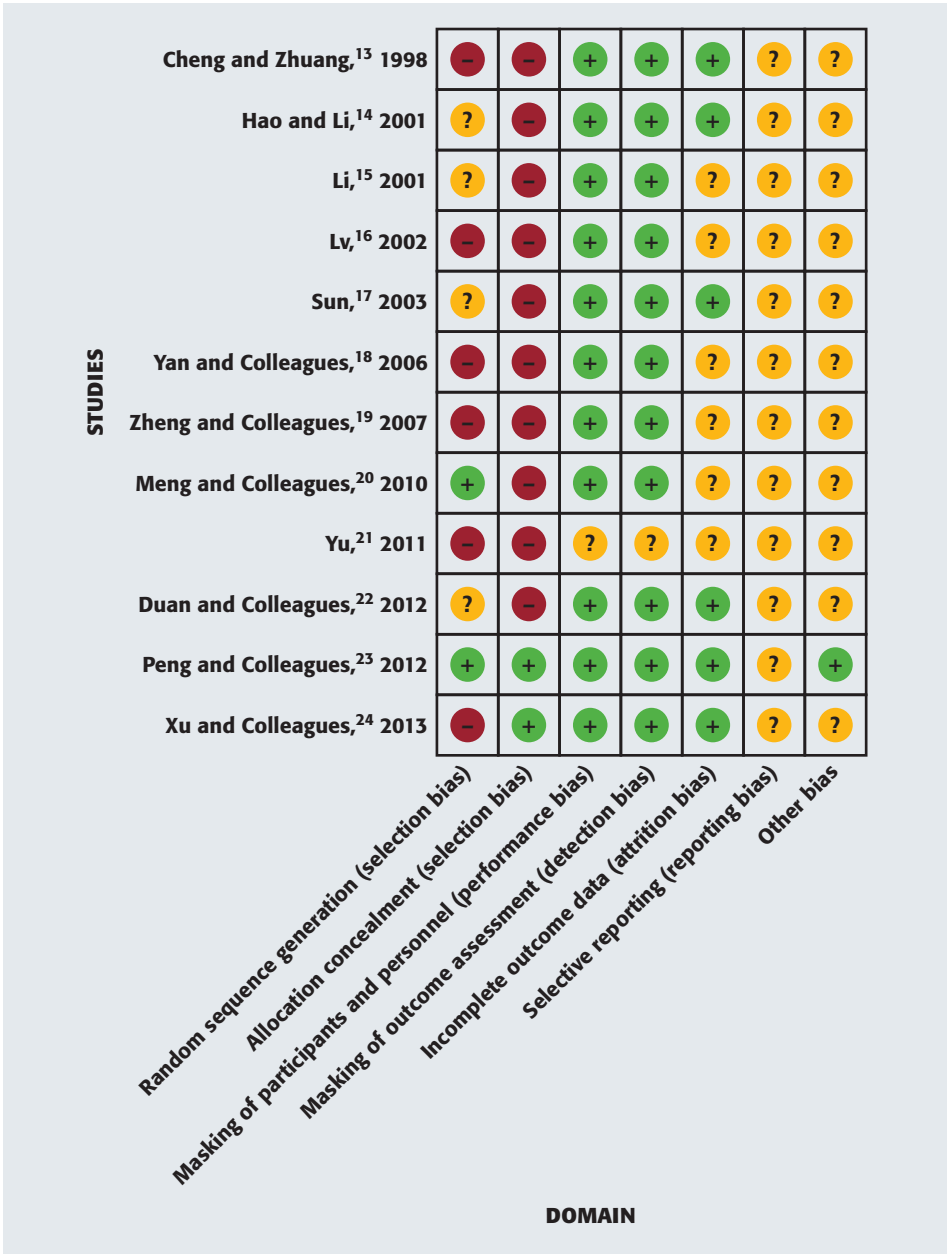

Figure 3. Risk of bias summary reviewing authors' judgments about each risk of bias item for each included study. +: Low risk of bias. –: High risk of bias. ?: Unclear risk of bias. *Source: Higgins and Green.*[11]

adverse effects of medications, which showed that there was no abnormality in electrocardiographic, blood pressure, and routine blood examination results. Consequently, this review provides some evidence that Chinese patent medicines may be a promising and safe intervention for managing long-term RAS.

However, there are limitations that weaken the recommendation of Chinese patent medicines for clinical use. First, we could not perform a meta-analysis because of statistical heterogeneity, and challenges in publishing negative results may have resulted in publication bias. Second, although TCM has been used for several years in the treatment of RAS, both topically and systemically, it is not fully understood and accepted by clinicians outside China. It is a challenge for Chinese clinicians to convey this concept to Western colleagues because of marked differences in language and philosophy. Third, it was a challenge to select high-quality reports from hundreds of articles related to this topic. Most clinical studies were case reports or case series without good controls.

In summary, the development of TCM should change from experience based to evidence based. Herbal medicine–oriented models or disease-oriented models may be used to validate the strength of clinical trials. The rationale of study designs may affect the inclusion and exclusion criteria of future meta-analyses. Because the number of well-designed and high-quality RCTs on the efficacy and safety of Chinese patent medicines for the treatment of RAS is limited, high-quality RCTs are essential to investigate the effectiveness of Chinese patent medicines in treating RAS.

CONCLUSIONS

Findings of this review suggest that Chinese patent medicines may be effective for treating RAS in terms of relieving pain and reducing ulcer size as well as episode

duration and frequency. However, well-designed, double-masked, placebo-controlled RCTs and comparative trials are required to investigate further the effectiveness of Chinese patent medicines for treatment of RAS. ■

Dr. Zhou is a doctoral candidate, Department of Oral Medicine, Peking University School and Hospital of Stomatology, Beijing, China.
Dr. Mao is a doctoral candidate, Department of Oral Medicine, Peking University School and Hospital of Stomatology, Beijing, China.
Dr. Hua is a professor, Department of Oral Medicine, Peking University School and Hospital of Stomatology, Beijing, China.
Dr. Liu is an associate professor, Department of Oral Medicine, Peking University School and Hospital of Stomatology, Beijing, China.
Dr. Yan is an associate professor, Department of Oral Medicine, Peking University School and Hospital of Stomatology, National Engineering Laboratory for Digital and Material Technology of Stomatology, No. 22, Zhongguancun South St., Haidian District, Beijing 100081, China, e-mail yzhimin96@163.com. Address correspondence to Dr. Yan.

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Drs. Zhou and Mao equally contributed as co-first authors.

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