

# Meta-analysis on the Effectiveness and Safety of propolis preparation in the Treatment of aphthous ulcers

## **Abstract:**

Objective: To systematically evaluate the effectiveness and safety of propolis preparation in the treatment of aphthous ulcers in order to provide evidence-based references for its clinical treatment. Methods: Databases, such as CNKI, VIP, Wanfang, CBM, PubMed, EMBASE, Cochrane Library, and so on, were searched to collect the randomized controlled trials (RCT) on the propolis preparation (the treatment group) with the conventional treatments (the control group) in the treatment of aphthous ulcers. After the data of clinical studies that met the inclusion criteria were extracted by two researchers, the Cochrane risk-of-bias tool was used to evaluate the methodology quality, and RevMan 5.4 was used for Meta-analysis. Results: A total of 23 studies were included, involving 2467 participants with 1356 in the treatment group and 1111 in the control group. The overall quality of the RCTs was relatively low. Meta-analysis showed that propolis preparation for aphthous ulcers, compared with conventional Western medicines could improve the total efficacy rate (RR= 1.40, 95%CI[1.33, 1.46],  $P<0.00001$ ), no incidence of adverse reactions. Conclusion: Propolis preparation has demonstrated promising therapeutic efficiency and safety in treatment of aphthous ulcers. However, this study has certain limitations since the overall quality of included RCTs is relatively low, affecting the reliability of the results, and further high-quality studies are required for verification.

Keywords: propolis preparation; aphthous ulcers; randomized controlled trials; systematic reviews; Meta-analysis

## **Introduction**

Oral ulcer is a very common clinical oral mucosal disease. Its incidence rate is high and it can reach about 20% in people<sup>(1)</sup>. The incidence of oral mucosa disease is the highest in oral mucosa disease, which seriously affects the patients' speech, eating and living mood. The etiology of the disease is complex, and many factors can cause the disease<sup>(2)</sup>. The oral ulcers may be lead by such as the common cold, gastrointestinal dyspepsia, depressed mood, nervous and other reasons. The disease is more in the population of 10 ~ 30 years old, and the female incidence is higher, it occurs in all seasons of the year. Most patients show heavy mental burden and even fear of oral cancer. As the etiology of the disease is unknown, it is difficult to find a specific cure, the current treatment measures are mainly to improve the symptoms<sup>(3)</sup>. Clinical can not determine the specific cause of oral

ulcer, to cure this disease for the current medical level is still difficult to do. Until now, the causes of canker ulcers have not been clearly studied<sup>(4)</sup>. But with the VB12, iron, zinc, folic acid, trace element lack of patients at ordinary times, malnutrition. aphthous ulcer occur when progesterone levels increase and progesterone levels decrease during menstruation. Because labor intensity of a few jobs is big, work study is in high tension, bring about nervous function disorder, can accompany constipation, diarrhoea digestive system disease at the same time, still have the heredity that concerns with parental medical history. About 80% of oral ulcers are light ulcers. When most patients first develop oral ulcers, there are corn-like red dots, round or irregular ellipses, which are superficial ulcers with a diameter less than 5mm. They often occur on non-keratinized oral mucosa such as lips and cheeks, and have obvious pain feeling. Clinically, symptomatic treatment is generally adopted. It is mainly to relieve pain and pain in patients, eliminate inflammation and shorten the course of disease. There are many treatment methods for oral ulcer, but the curative effect is not ideal<sup>(5-9)</sup>.

Propolis is a kind of sticky brown aromatic gelatinous solid substance which is mixed and processed by the secretions of the superior glands of bees and beeswax and the resin materials collected in the honeycomb. It contains various substances such as lipid aromatic oil, beeswax, pollen, trace elements, vitamins, flavonoids, plant antibiotics and a concentration of a large number of active components similar to those of rubber plants. With anti-inflammatory, antibacterial, analgesic, promote wound healing, reduce blood viscosity and other functions; As an immune factor activator, can promote antibody production, enhance macrophage phagocytosis ability, improve the activity of enzymes in the body: propolis solution after local coating of the unique film, can form a thin film layer on the mucosal surface of the disease, play the role of mechanical isolation of external stimulation. At present, propolis has been used in internal medicine, surgery, gynecology, dermatology, otorhinolaryngology, treatment of hyperlipidemia, diabetes, gastrointestinal ulcer and other diseases. Propolis has been used for oral diseases since 1953. Propolis ointment and propolis patch are widely used in the clinical practice of Odessa Stomatological College in the treatment of recurrent aphthous ulcer, oral erosion ulcer and mold damage. In 1972, Kurjahn reported that propolis ether ethanol solution was used as a new drug adhesive "stomapin" in the treatment of oral mucous membrane diseases. Cafar et al believed that local application of propolis preparation for the treatment of recurrent oral sores could form protective film on the ulcer surface, inhibit the growth of pathogenic microorganisms, relieve pain under anesthesia and relieve vasospasm, which not only had symptomatic analgesic effect, but also promoted tissue metabolism and ulcer healing<sup>(10-15)</sup>.

In this paper, the effectiveness and safety of propolis in the treatment of oral ulcer were systematically evaluated by searching relevant literature and adopting Meta analysis method, in order to provide evidence-based medical evidence for propolis treatment of oral ulcer and further provide reference for clinical application of propolis.

## **1. Data and methods**

## *1.1. Inclusion Criteria*

### *1.1.1 Type of literature*

Published randomized controlled study on propolis combined with Conventional Western medicine in the treatment of oral ulcer.

### *1.1.2 Patients*

Patients with oral ulcer who met the diagnostic criteria of Traditional Chinese medicine or Western medicine were not limited in age, gender, race and region.

### *1.1.3 Intervention measures*

The treatment group was treated with propolis or combined with western medicine. Propolis could be used according to the patient's symptoms, dosage, dosage form, and so on. The control group received conventional treatment with western medicine.

### *1.1.4 Indicators*

Indicators included total response rate (including cured, effective and effective) and adverse reactions, and so on.

## *1.2. Exclusion Criteria*

- 1) Non-randomized Controlled trials (RCTS), such as self-controlled, blank, or placebo Controlled trials;
- 2) Review, expert experience sharing, case reports and systematic evaluation;
- 3) Cell test, animal test and tissue study test;
- 4) Duplicate published studies;
- 5) Study on missing efficacy indicators.

## *1.3. Retrieval strategy*

Computer retrieval of CNKI, VIP, Wanfang, CBM, PubMed, EMBASE, Cochrane Library and other databases. The retrieval time is from the database construction to August 2021, and the retrieval method is the combination of subject words and free words. Chinese search terms included "propolis" and "canker ulcer""aphthous ulcers""Oral ulcer"; English search words included "Propolis", "aphthous ulcers" and "Oral ulcer""canker ulcer". There is no limitation on the type and language of publication.

## *1.4. Literature screening and data extraction*

According to the inclusion and exclusion criteria, two researchers independently screened the literatures

and developed a literature information extraction table, which included the name of the first author, publication time, research method, intervention and control measures, corresponding indicators and data, course of treatment, sample size, results, and so on. The extracted data will be evaluated independently by 2 researchers. If there is any difference, it will be solved through discussion with the third party evaluator.

### *1.5. Literature quality evaluation*

The included studies were evaluated for the risk of bias using the literature evaluation criteria provided by the Cochrane Collaboration, including randomization, randomization hiding, blindness, data integrity, withdrawal/withdrawal, selective reporting results, and others. Each item was judged by three risk levels of bias: "high risk", "low risk" or "uncertain risk". The data were evaluated independently by two researchers. If there was any difference, it could be solved through discussion with the third party evaluator.

### *1.6. Statistical Analysis*

Meta-analysis was performed using RevMan 5.4 software. Relative Risk (RR) was taken as the effect size of dichotomy variable, Standardised Mean Difference (SMD) was taken as the effect size of continuous variable, and 95% confidence interval (CI) was used to represent the interval estimation as the significance standard. Heterogeneity test was carried out for the included literatures. When there was no statistical heterogeneity among the studies participating in the systematic evaluation ( $I^2 < 50\%$ ), fixed-mode analysis should be selected. When statistical heterogeneity was present ( $I^2 \geq 50\%$ ), random-effect analysis or subgroup analysis was performed based on possible heterogeneous factors. Funnel plot was drawn to observe whether there was publication bias in the included literature.

## **2. The results**

### *2.1 Basic information was included in the study*

A preliminary search was made for 51 related literatures. After the "NoteE Xpress" literature management software was used to remove duplicate literatures, 23 literatures<sup>(16-38)</sup> were included according to inclusion and exclusion criteria, including one foreign literature, and the rest were Chinese literatures. A total of 2467 patients were enrolled, including 1356 in the experimental group and 1111 in the control group. The treatment group was treated with propolis, plus or minus formula combined with western medicine, and the control group was treated with western medicine. The specific literature screening process is shown in Figure 1. See Table 1 for the basic characteristics of the literature.

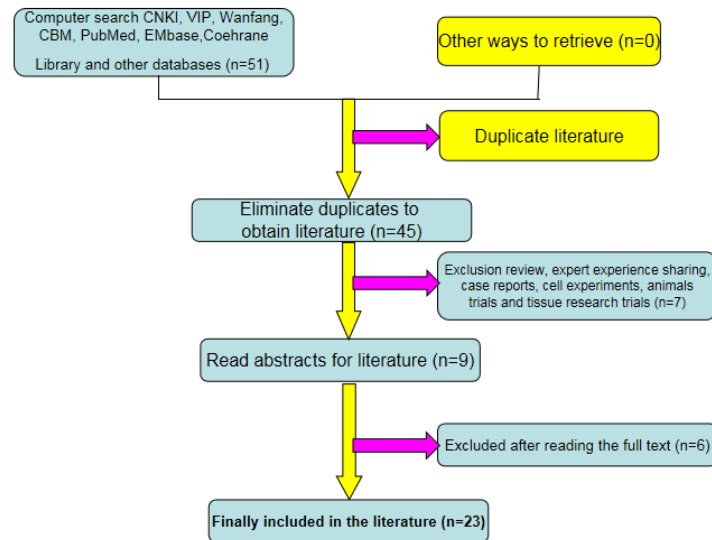


Figure 1. The literature screening process

Table 1 Basic features of the included literature

Included in the study	Sample size/case		Treatment group	Treatment intervention measures	Period of treatment /d	Outcome indicators
	Treatment group	The control group				
WeiGuangZhi2013	22	22	Propolis+control group	Propolis+control group	7d	①
LiuYanHui2015	60	60	Propolis+control group	Propolis+control group	7d	①
ZhaoXinKe2011	43	43	Propolis+control group	Propolis+control group	180d	①
WeiShiGang2010	120	120	Propolis+control group	Propolis+control group	7d	①
LiuChunHong2014	80	80	Propolis+control group	Propolis+control group	10d	①
ChenJun2013	78	78	Propolis+control group	Propolis+control group	5d	①+②
XieBaiLan2012	44	44	Propolis+control group	Propolis+control group	5d	①
ChenJinLiang2009	38	38	Propolis+control group	Propolis+control group	7d	①
WangJie2010	24	24	Propolis+control group	Propolis+control group	5d	①
DuRuYu2009	28	14	Propolis+control group	Propolis+control group	7d	①
QiuWei2002	150	30	Propolis+control group	Propolis+control group	10d	①+②
HuFang2002	38	40	Propolis+control group	Propolis+control group	6d	①
QiuWei2003	45	30	Propolis+control group	Propolis+control group	7d	①
WeiWenQing2003	63	58	Propolis+control group	Propolis+control group	3d	①
LiWanDong2009	108	105	Propolis+control group	Propolis+control group	5d	①
YangXue2014	30	30	Propolis+control group	Propolis+control group	6d	①
CaiPing2015	33	33	Propolis+control group	Propolis+control group	7d	①
HuHuiMin2016	54	54	Propolis+control group	Propolis+control group	14d	①
GuoXin2017	60	60	Propolis+control group	Propolis+control group	3d	①
ZhangJun2017	46	46	Propolis+control group	Propolis+control group	240d	①

JiPing2004	120	30	Propolis+control group	3-4d	①
HuangLiMei2013	60	60	Propolis+control group	30d	①
Mona G Arafat2018	12	12	Propolis+control group	10d	①

Note: ① is the total effective rate; ② is the incidence of adverse reactions.

## 2.2 Bias risk assessment

Cochrane bias risk assessment tool was used to evaluate the quality of the included literatures. Among the 23 RCTs included, 3 literatures described specific randomized methods and processes and were rated as having low bias risk. The 15 literatures only mentioned the word "random" without describing specific methods, and the risk of bias was not clear. Three literatures did not mention the word "random", one was grouped according to the order of occurrence of oral ulcer in chemotherapy, and the other was grouped according to the order of visit. The above five literatures were rated as high risk of bias. All literature data are complete and all pre-designed indicators are reported. The evaluation of bias risk is shown in Figure 2, and the summary of bias risk is shown in Figure 3.

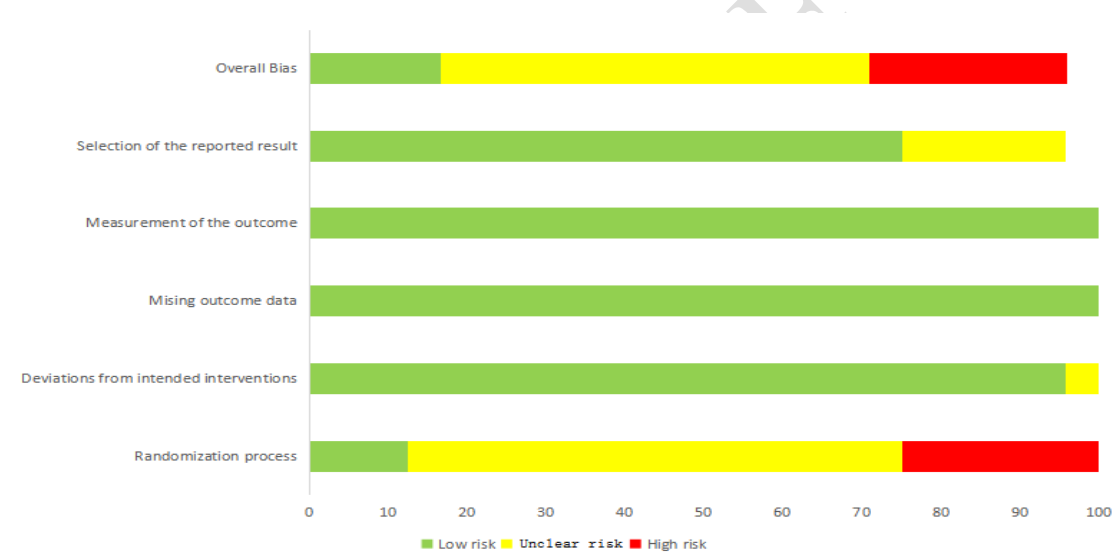


Figure 2. Bias Risk Assessment

	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
WeiGuangZhi2013	?	+	+	+	?	?
LiuYanHui2015	?	+	+	+	+	!

ZhaoXinKe2011	?	+	+	+	+	!
WeiShiGang2010	?	+	+	+	+	!
LiuChunHong2014	?	+	+	+	+	!
ChenJun2013	?	+	+	+	+	!
XieBaiLan2012	?	+	+	+	+	!
ChenJinLiang2009	?	+	+	+	+	?
WangJie2010	?	+	+	+	?	!
DuRuYu2009	?	+	+	+	+	?
QiuWei2002	?	?	+	+	?	?
HuFang2002	?	+	+	+	?	!
QiuWei2003	?	+	+	+	?	!
WeiWenQing2003	+	+	+	+	+	+
LiWanDong2009	?	+	+	+	+	!
YangXue2014	?	+	+	+	+	!
CaiPing2015	?	+	+	+	+	!
HuHuiMin2016	?	+	+	+	+	!
GuoXin2017	?	+	+	+	+	!
ZhangJun2017	?	+	+	+	+	!
JiPing2004	+	+	+	+	+	+
HuangLiMei2013	+	+	+	+	+	+
Mona G Arafa2018	?	+	+	+	?	?

Figure 3 summary of bias risk

## 2.3 Meta analysis

### 2.3.1 Total effective rate

Twenty-three papers <sup>(16-38)</sup> introduced the effective rate of treating oral ulcer in 2467 patients, including 1356 cases in test group and 1111 cases in control group. Heterogeneity test showed no statistical heterogeneity ( $P=0.001$ ,  $I^2=53\%$ ), so the fixed effect model was used for Meta-analysis. The

results showed that the treatment effect of the experimental group was better than that of the control group, the difference was statistically significant ( $rr = 1.40, 95\% \text{ CI } [1.33, 1.46]$ ,  $p < 0.00001$ ), as shown in Fig 4.

In this meta-analysis, risk bias analysis was conducted on the total effective rate, and it was found that the funnel plots were all asymmetrically distributed, suggesting that publication bias might exist, as shown in Figure 5.

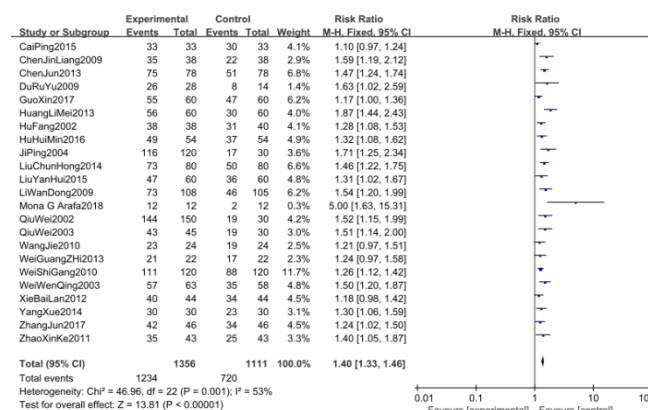


Figure 4. Meta-analysis of total effective rate

### 2.3.2 Incidence rate of adverse reaction

Incidence of adverse reactions of 23 only 1 piece of paper to record the treatment of oral cavity ulcer incidence of adverse reactions,, but did not have adverse reaction was observed, and the remaining 22 articles didn't explain the observed whether the occurrence of adverse reactions, but didn't explain the occurrence of adverse reactions, suggest two groups had no adverse reaction, It is indicated that propolis is safe to treat oral ulcer.

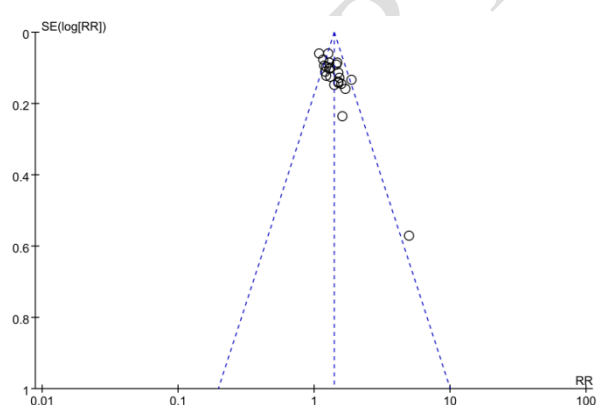


Fig. 5 Funnel plot of the total effective rate of the two groups

## 3. Discussion and Conclusion

Oral cavity ulcer is recrudescence oral cavity ulcer is to point to reason unknown, break out repeatedly, have



its self-limited isolated circle or elliptic ulcer. Another name is recurrent mouth sores<sup>(39)</sup>.

Its etiology and pathogenesis are not clear, and may be related to infection, endocrine, immune dysfunction, nutritional deficiency, mental, microcirculation disorders and other factors. The disease has a high incidence and is highly recurrent, with severe pain. It affects eating and speaking. Bring great pain and inconvenience to patients. Clinical treatment is mainly local, supplemented by systemic treatment. Its treatment principle is to eliminate pathogenic inducement, improve body health, alleviate local symptoms, promote ulcer healing.

Propolis is a kind of gelatinous solid substance with aromatic smell, which is made by mixing the resin collected from the buds and trunks of plants with the secretions of the palatine gland and beeswax. The effect of propolis on *Staphylococcus aureus*, green streptococcus, hemolytic streptococcus and *Proteus* is stronger than penicillin and tetracycline. At the same time, propolis can promote tissue regeneration, promote the shedding of necrotic tissue.

Propolis is yellowish brown, brown or green, taste slightly bitter, contains a variety of physiological active substances, chemical composition is more complex, pharmacological action is also very wide. Among them, flavonoids are considered as the main active ingredients, clinically used for the treatment of colds, skin diseases, ulcers, burns, tumors and diabetes, and so on, is a potential medicine and natural health food<sup>(40)</sup>.

Local application of propolis preparation for the treatment of recurrent aphthous ulcer can form a protective film on the ulcer surface. Inhibit the growth of pathogenic microorganisms, analgesia and relieve vasospasm, both symptomatic analgesic effect, and promote tissue metabolism and ulcer healing. The ethanol solution of propolis and some of its components have a local anesthetic effect that can quickly relieve pain and symptoms. Propolis is applied directly to aphthous ulcer. Can immediately form a thin layer of propolis film, not easy to be spit off, and protect the damaged mucosa, promote wound healing.

As an immune factor activator, it can promote the production of antibodies, enhance the phagocytosis of macrophages, and improve the activity of enzymes in the body. Its unique propolis solution after local coating film, can form a film layer on the mucosal surface of the disease, play the role of mechanical isolation of external stimulation. At present, it has been applied in internal medicine, surgery, gynecology, dermatology, ear, nose and throat, treating diseases such as hyperlipidemia, diabetes, gastrointestinal ulcer and so on(41,42).

A meta-analysis was conducted on 23 RCTs included in this study. The results showed that propolis combined with conventional treatment of western medicine could improve the efficacy of oral ulcer patients compared with conventional treatment of western medicine (RR=1.40, 95%CI[1.33, 1.46],  $P < 0.00001$ ), without adverse reactions.

The limitations of this study: The overall quality of the literature included was low, only 3 articles described the specific random method, 15 articles only mentioned the random grouping, but did not describe the specific method, 3 articles did not mention the word "Random", one literature was grouped according to the order of occurrence of oral ulcer in chemotherapy, one literature was grouped according to the order of treatment, only one literature was studied by single-blind method. The intervention measures and treatment duration were different in the literature, and there was no reference to follow-up after treatment. Only one article reported "Observed adverse reaction", and no adverse reaction was recorded in the literature, it may have some influence on the safety evaluation; 22 of the 23 articles included were in Chinese, and the subjects were all Chinese, and there were some differences in age, sex and disease severity, which increased the heterogeneous sources. Supplements, conference papers and Grey literature are not available and may affect the evaluation results. Therefore, in order to improve the evidence-based medicine, a large sample, multi-center, high-quality randomized controlled study is needed to further verify the effectiveness and safety of propolis application.

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