

## INVITED MEDICAL REVIEW

## Traditional Chinese medicine and oral diseases: today and tomorrow

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With a history of over 2000 years, traditional Chinese medicine (TCM) evolves into a unique system of diagnosing and treating illnesses. It is a challenge to convey the fundamentals of this traditional medicine to our Western colleagues because of the differences in language, philosophy and concept of diagnosis and treatment. This review attempts to tackle these barriers by introducing several widely used Chinese medicines for treating oral diseases. China Journals Full-text Database and Pubmed were used as the searching engines. Although many studies have demonstrated that the Chinese medicines are effective in treating oral diseases including recurrent aphthous stomatitis, oral lichen planus, leukoplakia, and Sjögren's syndrome, most of them lacked standard criteria of post-treatment assessment and laboratory evidence. Randomized controlled clinical trials with specific assessment criteria are required to close the gap between TCM and evidenced-based medicine.

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**Keywords:** Chinese medicine; oral disease; treatment; herbology

### Introduction

With a history of more than 2000 years, Traditional Chinese Medicine (TCM) has formed a unique system to diagnose and treat a variety of diseases. The therapeutic approaches in typical TCM include herbal therapy, acupuncture, dietary therapy, and qigong exercises. Herbology is one of the most important treatment modalities utilized in TCM. Each herbal medicine

prescription is a cocktail of several herbs. The Chinese pharmacopoeia lists over 6000 medicinal substances and their properties. Among these substances around 600 herbs are commonly used today (Unschuld, 1986, Fratkin and Dharmananda, 2001).

Chinese patent medicine (zhōng chéng yào) refers to the drugs made according to a standardized formula (even though the word “patent” is used none of the manufactures have exclusive rights over these formulae). Several herbs and other ingredients are dried, ground and mixed according to the formulae. These drugs are available in pharmacies as condensed pills, oral liquids, granules or capsules. Thus all Chinese patent medicines with the same name are expected to have the same proportions of ingredients. Most Chinese medicines with natural ingredients can be taken as a long-term treatment with fewer side effects. Chinese medicines are not indicated for the treatment of acute illness but are best suited for managing non-severe chronic diseases.

Although TCM has been used for treating oral diseases for a very long time, it is barely known and understood by clinicians and scientists outside China. It is a challenge to make this traditional medicine understood by our Western colleagues because of the huge differences in language, philosophy and concept of diagnosis and treatment. This review attempts to tackle this difficulty by introducing five Chinese medicines widely used in the treatment of some common oral diseases, such as recurrent aphthous stomatitis (RAS), oral lichen planus (OLP), leukoplakia and Sjögren's syndrome (SS) (Table 1). Totally 128 clinical reports were retrieved from the China Journals Full-text Database and Pubmed. However, most of the articles were case reports or case series without standard criteria for evaluating the effectiveness of treatment. Therefore only reports using the standard criteria issued by Society of Oral Mucosal Disease of Chinese Stomatological Association (2001, 2005) were selected.

### Liuwei Dihuang (liù wèi dì huáng)

Liuwei Dihuang is consists of six ingredients extracted from natural herbs including: radix rehmanniae, fructus

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**Table 1** Application of Chinese medicines in oral diseases

Chinese medicine	Oral mucosal diseases
Liuwei Dihuang	Recurrent aphthous stomatitis Sjögren's syndrome Oral lichen planus
Tripterygium glycosides	Recurrent aphthous stomatitis Oral lichen planus Sjögren's syndrome
Stomatitis-healing granule	Recurrent aphthous stomatitis
Composite Taixian tablet	Oral lichen planus
Zengshenping	Oral lichen planus Oral leukoplakia

corni officinalis, radix dioscoreae oppositae, alismatis rhizoma, sclerotium poriae cocos and cortex moutan radicis. It is one of the most commonly used Chinese medicines in the treatment of various local and systemic chronic diseases.

Several reports demonstrated that long-term administration of LiuWei DiHuang could modulate the cell-mediated immune response of RAS patients by correcting the imbalance of T-lymphocyte subsets (Zou and Zhang, 2003, Sun, 2004). Following the investigation of 30 RAS patients and 30 healthy volunteers, Sun (2004) reported that the RAS patients had depressed CD3<sup>+</sup>, CD4<sup>+</sup> cell counts and elevated CD8<sup>+</sup> cell counts. The CD4<sup>+</sup>/CD8<sup>+</sup> ratio was also depressed. Six months after oral administration of Liuwei Dihuang, the CD3<sup>+</sup>, CD4<sup>+</sup> cell counts and CD4<sup>+</sup>/CD8<sup>+</sup> ratio became elevated significantly. All these values were not statistically different from the healthy volunteers. Clinical studies in different centers showed a varied response of the RAS patients to Liuwei Dihuang: 13.3–70.0% healed, 10.0–76.9% improved, and 3.3–20.0% patients had no positive response to this medication (Table 2) (Zhou, 1995, Lü, 2001, Sun, 2003, Xie, 2004, Jia and Luo, 2006, Tong and Feng, 2008, Wang, 2009).

Shen (2002) used Liuwei Dihuang to treat 30 SS patients. Three months after the treatment, Schimer test, tear break-up time test, rose-bengal score dye test and salivary flow test demonstrated a reduction of dryness of the mouth and eyes in all the patients. The rheumatoid factor became negative in 10/16 (62.5%) patients. Six

months after the treatment, antinuclear antibodies of 10/23 (43.5%) patients and anti-SSA/anti-SSB antibodies of 13/28 (46.4%) patients became negative. Zhao (2006) reported the outcome of a long-term administration (1–3 years) of Liuwei Dihuang for patients with SS. At the 6-month follow-up after stopping the mediation, two patients (6.7%) had complete remission and 15 patients (50%) had reduced dryness without recurrence. Nine patients (30%) had alleviated symptoms while taking the medication but recurred after stopping it. Four patients (13.3%) did not respond to the treatment.

Xuan (1997) investigated the combined administration of Liuwei Dihuang and retinoic acid cream in treatment of 43 patients with OLP. They found that the combined medications were more effective than retinoic acid cream alone, particularly for treating the patients with a history of OLP less than 3 years.

### Tripterygium glycosides (léi gōng téng duō dài)

*Tripterygium wilfordii* is a native plant that grows in many parts of China and Burma. It has been commonly used in the treatment of a wide spectrum of autoimmune and inflammatory diseases (Tao et al, 2001, 2002, Qiu and Kao, 2003, Kumar et al, 2005, Canter et al 2006). Studies have demonstrated that *T. wilfordii* was capable of reducing the serum levels of IgG and correcting the imbalanced T-lymphocyte subsets (Li et al, 1996, Wong et al, 1998, Fang et al, 2006). A recent study also showed that *T. wilfordii* inhibited tumor progression by its anti-angiogenic activity (He et al, 2009). However, it is notable that *T. wilfordii* is the most toxic among all the Chinese herbs. Its adverse effects mainly include gastrointestinal disturbance, infertility and suppression of immune system (Wang, 1993). Tripterygium glycosides are extracted from the peeled roots of *T. wilfordii*. This is effective at a much lower dosage and has less adverse effects compared to other preparations of *T. wilfordii*.

Li et al (1996) treated 27 RAS patients with oral Tripterygium glycosides for 3 months. The plasma soluble interleukin-2 receptor levels reduced from 601.5 ± 225.2 U ml<sup>-1</sup> to 380.8 ± 94.2 U ml<sup>-1</sup> which was not significantly different from the healthy volunteers (302.0 ± 105.3 U ml<sup>-1</sup>). Studies also reported that

	Number of cases	Prognosis			
		Heal (%)	Marked improvement	Moderate improvement	No improvement (%)
Lü, 2001	30	13.3	36.7%	43.3%	6.7
Xie, 2004	50	18.0	38.0%	34.0%	10.0
Sun, 2003	40	25.0	50.0%	17.5%	7.5
Tong, 2008	30	70.0	10.0%	20.0	
Zhou, 1995	52	19.2	76.9%	3.9	
Wang, 2009	80	55.0	32.5%	12.5	
Jia, 2006	120	52.5	26.7%	17.5%	3.3

**Table 2** Effect of Liuwei Dihuang for treating RAS

Heal: complete remission of the pain and lesions, no recurrence within 1 year; Marked improvement: complete remission of the pain and lesions, no recurrence within 6 months; Moderate improvement: reduction of pain, size and number of lesions, interval of recurrence is prolonged; No improvement: no reduction/worsening in the pain, size and number of lesions (Society of Oral Mucosal Disease of Chinese Stomatological Association 2001).

Tripterygium glycosides reduced the serum nitric oxide of RAS patients to normal levels (Bu *et al*, 2006, Ma *et al*, 2006). Zhang (2003) compared the effectiveness of Tripterygium glycosides and hydrocortisone for treating RAS patients. Thirty patients received oral hydrocortisone (started at 60 mg day<sup>-1</sup> and gradually reduced to 10 mg day<sup>-1</sup> for 10 days), and 30 patients were treated with oral Tripterygium glycosides (60 mg day<sup>-1</sup> for 10 days). Results showed that Tripterygium glycosides was as effective as hydrocortisone.

Many studies have demonstrated the effectiveness of Tripterygium glycosides in the treatment of OLP patients (Table 3). In all these reports, an overall 20.0–84.0% of the patients markedly improved, 12.0–45.8% moderately improved, and 4.0–50.0% had no improvement after treatment (Zheng, 1988, Yin *et al*, 1996, Jiang and Wang, 2000, Xu, 2001, Han *et al*, 2007). Zheng (1988) investigated 100 OLP patients, 66 without erosive lesions and 34 with erosive lesions. All patients with reticular OLP showed improvement after 1 month treatment with Tripterygium glycosides, while plaque-like lesion required longer treatment and improvement was found after 2–3 months. However, effectiveness of Tripterygium glycosides for treating erosive lesions was less. Tripterygium glycosides also demonstrated promising results in the treatment of OLP while being used in combination with other therapies such as Nd-YAG laser, triamcinolone and chloroquine (Yin *et al*, 1996, Guan and Zhu, 2003, Zhang *et al*, 2008).

Huang and Chen (1996) reported a clinical trial where *T. wilfordii* were used to treat 18 patients with SS. Three months after treatment, 16 patients showed increased salivary and tear flow and reduced symptoms of dry mouth and dry eye. The increased erythrocyte sedimentation rate in 7/11 (63.6%) and IgG in 10/13 (76.9%) patients returned to normal levels. The circulatory immune complex in 12/15 (80%) and antinuclear antibody in 7/11 (63.6%) patients became negative.

### Stomatitis-healing granule (kǒu yán qīng chōng jì)

Stomatitis-healing granule is made of cochinchinese asparagus root, tuber ophiopogonis japonici, radix scrophulariae ningpoensis, flos Lonicerae japonicae

**Table 3** Effect of Tripterygium glycosides for treating OLP

	Number of cases	Prognosis (%)		
		Marked improvement	Moderate improvement	No improvement
Zheng, 1998	100	84.0	12.0	4.0
Yin, 1996	30	23.3	30.0	46.7
Xu, 2001	30	20.0	30.0	50.0
Jiang, 2000	24	41.7	45.8	12.5
Han, 2007	30	66.7	13.3	20.0

Marked improvement: complete remission of erosion and pain, no/mild white streak; Moderate improvement: reduction of pain, white streak, and size of erosion; No improvement: no reduction/worsening of pain, white streak, and size of erosion (Society of Oral Mucosal Disease of Chinese Stomatological Association 2005).

**Table 4** Effect of Stomatitis-healing granule for treating RAS

	Number of cases	Prognosis (%)			
		Heal	Marked improvement	Moderate improvement	No improvement
Meng, 2006b	32	56.3	28.1	12.5	3.1
Huang, 2007	70	60.0	17.1	14.3	8.6
Wang, 2004	32	0	62.5	34.4	3.1
Huang, 2007	70	60.0	17.1	14.3	8.6
Meng, 2006a	116	19.2	23.9	44.8	12.1
Zhen, 2002	86	48.8	29.1	11.6	10.5

and radix glycyrrhizae uralensis. An animal study using a mice model showed that Stomatitis-healing granule reduced the permeability of capillaries, inhibited delayed-type hypersensitivity and decelerated granuloma growth. *In vitro* assessment demonstrated inhibition of *Staphylococcus aureus*, *Streptococcus pneumoniae* and hemolytic streptococcus A and B (Li *et al*, 1999). Clinically Stomatitis-healing granule is mainly used for treating RAS. In all these studies an overall 0–60% patients healed, 17.1–62.5% improved markedly, 11.6–44.8% improved moderately after treatment. 3.1–12.1% patients had no positive response to this medication (Table 4) (Zhen *et al*, 2002, Wang and Wang, 2004, Meng, 2006a, 2006b, Huang, 2007).

### Composite Taixian tablet (fù fāng tái xiǎn piàn)

Composite Taixian tablet contains radix ligustici chuanxiong, radix ginseng, radix paeoniae lactiflorae, semen persicae and radix et caulis jixueteng. It is mainly used for the treatment of OLP. An *in vitro* study showed that Composite Taixian tablet reduced the platelet adhesion of OLP patients without affecting platelet aggregation, which suggested its ability for improving blood viscosity and microcirculation (Lin and Zhou, 1992, Lin *et al*, 1992).

Studies demonstrated that after being treated with Composite Taixian tablet, the overall rates of marked improvement were 23.3–36.9%, moderate improvement were 35–46.7%. Around 16.4–41.7% patients had no positive response (Table 5) (Zeng *et al*, 1993, Pan and Yi, 1997, Zhang *et al*, 2001). A clinical trial by Pan and Yi (1997) recruited 30 patients (26 with non-erosive and 4 with erosive OLP). The 26 patients with non-erosive OLP were randomly assigned to an experimental group (composite Taixian tablet) and a control group (placebo). The four patients with erosive OLP were evenly

**Table 5** Effect of Composite Taixian tablet for treating OLP

	Number of cases	Prognosis (%)		
		Marked improvement	Moderate improvement	No improvement
Pan, 1997	15	36.9	46.7	16.4
Zeng, 1993	139	26.6	54.7	18.7
Zhang, 2001	60	23.3	35.0	41.7



assigned to the experimental and control groups. After 3 months of treatment, six patients in the experiment group improved markedly (40%), seven patients improved moderately (47%) and two patients did not respond to the medication (13%). In the control group, none of the patients showed marked improvement, five patients improved moderately (33%) and 10 patients did not improve (67%). However, the study did not specifically state the prognosis of the four patients with erosive lesions.

### Zengshengping (zēng shēng píng)

Zengshengping is composed of vietnamese sophora root, bistort rhizome, north valerianaceae, cortex dictamni, *Prunella vulgaris* L and *Dioscorea bulbifera*. Zengshengping is known to modulate immune reactions, inhibit production of inflammatory cytokines, suppress tumor cell proliferation and reduce the incidence of squamous cell carcinoma (Cai *et al*, 1980, Lin, 1990, Fan, 1993, Wang *et al*, 1994).

Zengshengping has been used to treat patients with precancerous lesions of the esophagus successfully since 1980s. Lin *et al* (1998) reported after giving Zengshengping for 3 years, the cancer incidence reduced from 5.3% (102/1922) to 2.79% (28/1054). Hou and colleagues (2002) reported that after 3 years blocking treatment of esophageal epithelia dysplasia with the same medication, cancer incidence reduced from 3.85% (102/2649) to 2.01% (28/1396). A randomized controlled clinical trial by Sun *et al* (2010) showed that Zengshengping significantly reduced the size of the oral lesion in 67.8% (40/59) patients with leukoplakia, which was significantly higher than that in the control group (17% (9/53)) using placebo. The chemopreventive effect of Zengshengping was significantly associated with the decrease of two cell proliferation biomarkers, silver stained nucleoli organizer region and proliferating cell nuclear antigen-labeling index. Shang *et al* (2004) reported that after treatment with Zengshengping, the size of oral leukoplakia reduced significantly in 74.6% (47/63) patients. Zengshengping has been also used for treating OLP, with a 79.4% (50/63) (Sun *et al*, 2004) and 90% (90/100) (Cao *et al*, 2001) patients positively responding to this medication.

### Conclusion

Although TCM has been used for over 2000 years in the treatment of various diseases, it is not fully understood and accepted by the clinicians outside China. Even in China, not all the practitioners believe its effectiveness. The major barrier between the TCM and contemporary medicine is not only the language, but the basic concepts in diagnosis and management of the disease. While the contemporary medicine developed from an evidence-based system, the TCM is basically experience-based. It was a challenge to search and select high quality reports from hundreds of papers related to this topic. Most of the clinical studies were case reports or case series without good controls.

Standard criteria for post-treatment assessment and laboratory evidence supporting the findings and conclusions were lacking in most of the reports. Many Chinese clinicians and scientists have been making a great effort to build the missing link between the 1000-year-experience based knowledge and the evidence-based medical sciences. Even though the authors planned a systematic review at the beginning, we were compelled to perform a general review giving a glimpse of TCM in oral diseases because of the lack of high quality animal and clinical studies. The effective chemical components, optimal ratios of the herb “cocktail” and the mechanisms of the medicines on different diseases need to be explored by high quality laboratory and animal experiments, as well as randomized controlled clinical trials.

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### Author contributions

All authors contribute to this manuscript.

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