Scientific Research Publishing

Open Journal of Stomatology, 2023, 13, 233-242
https://www.scirp.org/journal/ojst
ISSN Online: 2160-8717
ISSN Print: 2160-8709

Experimental Study of *Emilia Sonchifolia* Combined with *Coptidis Rhizoma* for the Prevention and Treatment of Oral Ulcer

Qiaomei Deng[1], Chunying Wei[1], Jieling Luo[1], Xiaowei Wen[1], Mingbo Su[1], Zhuofei Ma[1,2*]

[1]School of Stomatology, Youjiang Medical University for Nationalities, Baise, China
[2]Graduate School, Guangxi University of Chinese Medicine, Nanning, China
Email: *mazhuofei@126.com

How to cite this paper: Deng, Q.M., Wei, C.Y., Luo, J.L., Wen, X.W., Su, M.B. and Ma, Z.F. (2023) Experimental Study of *Emilia Sonchifolia* Combined with *Coptidis Rhizoma* for the Prevention and Treatment of Oral Ulcer. *Open Journal of Stomatology*, **13**, 233-242.
https://doi.org/10.4236/ojst.2023.138020

Received: July 17, 2023
Accepted: August 19, 2023
Published: August 22, 2023

Abstract

Objective: This paper aims to investigate the therapeutic effect of the combination of *Emilia Sonchifolia* and *Coptidis Rhizoma* on oral ulcer rats. **Methods:** 36 SD rats of half male and half female were kept for 7 days, and 6 rats among them were selected as normal group by random sampling method, and the rest rats were randomly divided into model group, positive control group, *Emilia Sonchifolia* group, *Coptidis Rhizoma* group and combined group after the establishment of oral ulcer model. The normal group and model group were given blank film, the positive control group was given Guilin Watermelon Frost, and the *Emilia Sonchifolia* group, *Coptidis Rhizoma* group and combined group were given the corresponding oral film, which was administered to the ulcer for 7 days continuously, 2 times per day. The healing of oral ulcer was assessed at the end of the last day of administration, and the ulcer area was calculated on the 1st, 3rd, 5th and 7th days after successful modeling, and the serum levels of IL-2 and TNF-α in rats were detected by *Emilia Sonchifolia*. **Results:** The grading of ulcer healing in the positive control group and the combined group was better than the other groups, and the difference was statistically significant when compared with the model group ($p < 0.05$). On the 3rd, 5th and 7th days, the ulcer area in the *Coptidis Rhizoma* group, *Emilia Sonchifolia* group, combined group and positive control group was smaller than that in the model group, and the difference was statistically significant ($p < 0.05$), indicating that the *Emilia Sonchifolia* group, *Coptidis Rhizoma* group and combined group were all effective in reducing the area of oral ulcer, among which the combined group was more effective. The level of pro-inflammatory factor TNF-α was reduced and the level of anti-inflammatory factor IL-2 was increased in the *Emilia Sonchifolia* group,

Coptidis Rhizoma group and combined group, and the difference was statistically significant ($p < 0.05$) when compared with the model group, with the positive control group and combined group having better effects than the other groups. **Conclusion:** The combination of *Coptidis Rhizoma* and *Emilia Sonchifolia* is effective in the treatment of oral ulcer in rats, and the effect of the combination is better than that of the drug alone.

Keywords

Emilia Sonchifolia, *Coptidis Rhizoma*, Oral Ulcer, IL-2, TNF-α

1. Introduction

Oral ulcer is ulcerative lesions that occur on the oral mucosa and are characterized by redness, swelling, heat and pain, and their incidence is high and on the rise [1]. It is characterized by periodic recurrent attacks, which seriously affect the quality of life of patients and can even lead to malignant changes [2]. At present, there is no ideal drug for the treatment of Recurrent Oral Ulceration (ROU) in clinical practice, and most of them are based on symptomatic supportive treatment such as elimination of causes, pain relief, and anti-infection. Commonly, it used medications include oral ulcer bulk, watermelon cream, cidadex iodine tablets, metronidazole tablets, cotrimoxazole dexamethasone film, vitamin B complex, etc, despite the variety, the therapeutic effect is still poor [3] [4]. Traditional Chinese medicine has obvious advantages in the treatment of recurrent oral ulceration and can effectively prevent distant episodes of oral ulceration [5]. *Emilia Sonchifolia* has anti-inflammatory, analgesic, and immune-enhancing effects, and it is commonly used in folklore for the treatment of upper respiratory tract infections, cough suppression, and anti-rheumatism [6]. Wang Y found that *Emilia Sonchifolia* flavonoid had a significant bacteriostatic effect on Staphylococcus aureus through in vitro bacteriostatic study [7]. Zhang Y found that *Emilia Sonchifolia* has pain-relieving and analgesic effects [8]. *Coptidis Rhizoma* is a common clinical Sonchifolia that has been studied in the treatment of oral ulcer. Li J found that *Coptidis Rhizoma* promoted the reduction of inflammatory edema caused by chemical burn oral ulcer, and at the same time reduced the infiltration of inflammatory cells in the ulcerated tissue [9]. Zhang Sli found that *Coptidis Rhizoma* and *Licorice Tang* Plus Therapy helped to alleviate ulcer pain symptoms in patients with ROU and was able to regulate the level of inflammatory factors in patients. [10] Both medicinal materials have anti-inflammatory effects and have shown promise in the treatment of recurrent oral ulcer. In this project, the combination of *Emilia Sonchifolia* and *Coptidis Rhizoma* was used to make an oral film, and the method of topical application was used to study the therapeutic effect on oral ulcer using rats as experimental subjects.

2. Methods

2.1. Experimental Animals

Animal protocols were approved by the Institutional Animal Ethics Committee of Youjiang Medical University for Nationalities. Typically, 10 - 12-week-old rats with similar body weight were used for oral ulcer healing. In our research, SD rat with (200 g ± 20 g, half male and half female), were provided by Changsha Tianqin Biotechnology Co. Ltd (license number SCXK (Hunan) 2022-0011), to be quarantined and ready for use. The rats were housed under room temperature of 18˚C - 24˚C and humidity of 40% - 50% for 7 d. During the experiment, the rats were free to eat and drink in normal circadian rhythm.

2.2. Drugs and Reagents

Emilia Sonchifolia (Liuzhou Guizhong Pharmacy Chain Co., Ltd., Lot No. 20220318); *Coptidis Rhizoma* (Guangxi Xianju Traditional Chinese Medicine Technology Co., Ltd.); Film-forming materials: HPC (Shaanxi Zhengyi Pharmaceutical Accessories Co., Ltd., lot No. 20220517), Polyvinyl alcohol (Jiangxi Alpha Hi-Tech Pharmaceutical Co., Ltd., lot No. 20220503), Parbomer (Beijing Guoren Yikang Ltd., Lot No. 20220902); Guilin Watermelon Frost (Guilin Sanjin Pharmaceutical Co., Ltd.); Defoamer (Guangzhou New Materials Co., Ltd., Lot No. 20220929); Rat tumor necrosis factor TNF-α enzyme-linked immunosorbent assay kit (Elabscience Biotechnology Co., Ltd., Lot No. DP02HHP09247); Rat interleukin IL-2 Emilia Sonchifolia kit (Elabscience Biotechnology Co., Ltd., Lot No. DP0468641125); 40% Glacial acetic acid (Guangdong Guanghua Sci-Tech Co., Ltd., Lot No. 20200922); 20% Uratan (Sinopharm Chemical Reagent Co., Ltd., Lot No. 20201030).

2.3. Instruments

MB-530 *Emilia Sonchifolia* analyzer (Shenzhen Huisong Technology Development Co., Ltd.), TGL-16 tabletop high-speed frozen centrifuge (Hunan Xiangyi Laboratory Instrument Development Co., Ltd.), HH-ZK600 thermostatic water bath (Gongyi Yingyu Gaoke Instrument Factory), Maigao M3 vortex mixer (Shanghai Maigao Scientific Instruments Co., Ltd.), Eppendorf pipette (Germany), Scicntz-12N vacuum freeze dryer (Ningbo Scientz Biotechnology Co., Ltd.).

2.4. Drug Preparation

2.4.1. Preparation of *Coptidis Rhizoma* Oral Film

Add 150 ml of water to 50 g of *Coptidis Rhizoma*, boil for 30 min, separate the liquid, add 150 ml of water to the dregs, boil for 20 min and filter to get the liquid, mix the liquid twice, concentrate to 100 ml, then put the medicinal soup into the freeze dryer equipment for lyophilisation to produce lyophilised powder, and finally combine the lyophilized powder with the film-forming material to prepare the oral film agent [11].

2.4.2. Preparation of *Emilia Sonchifolia* Oral Film

Add 300 ml of water to 100 g of *Emilia Sonchifolia*, boil for 12 min, separate the liquid, add 300 ml of water to the dregs, boil for 10 min and filter to get the liquid, mix the liquid twice, concentrate to 100 ml, then put the medicinal soup into the freeze dryer equipment for lyophilisation to produce lyophilised powder, and finally combine the lyophilized powder with the film-forming material to prepare the oral film.

2.4.3. Preparation of Combined Oral Film

Add 450 ml of water to 50 g of *Coptidis Rhizoma*, boil for 20 min, add 100 g of *Coptidis Rhizoma*, boil for 12 min, separate the liquid, add 450 ml of water to the dregs, filter the liquid after boiling for 15 min, mix the liquid twice, concentrate to 100 ml, then put the medicinal soup into the freeze dryer equipment for lyophilisation to produce lyophilised powder, and finally combine the freeze-dried powder with the film-forming material. The lyophilized powder is finally combined with the film-forming material to prepare the oral film.

2.5. Animal Experiment

2.5.1. Establishment of Oral Ulcer Rat Model

The rats were anesthetized with 20% *uratan* (0.5 ml/100g), and after anesthesia, the upper and lower jaws were separated with hemostatic forceps to expose the buccal mucosa of the oral cavity and fixed on the operating table, and the lower left buccal mucosa of rats was dried with sterile cotton balls, isolated from moisture, and a 3 mm × 3 mm square filter paper containing 40% glacial acetic acid was placed on the dried left buccal mucosa and remove the filter paper sheet after 30 s. The rat oral ulcer model was established [12].

2.5.2. Animals Administration and Grouping

The rats were divided into 6 groups: normal group, Model group, *Emilia Sonchifolia* group, *Coptidis Rhizoma* group, Combined group, Positive control group, each group was consisted of 6 rats. *Emilia Sonchifolia* group: after the induction of ROU, *Emilia Sonchifolia* oral film was applied to the ulcer; *Coptidis Rhizoma* group: after the induction of ROU, a *Coptidis Rhizoma* oral film was applied to the ulcer. Combined group: after the induction of ROU, the ulcer was coated with combined oral film; Model group: after the induction of ROU, the normal oral film was applied to the ulcer; Positive control group: after the induction of ROU, the Guilin Watermelon Frost was sprayed on the ulcer; Normal group: normal diet feeding, no induction of ROU; the drug was administered on the 1st day after modeling, and the drug was administered 2 times per day for 7 days respectively according to the group.

2.6. Oral Ulcer Healing Assay

2.6.1. Surface Healing of Ulcer

Assess the grading of oral ulcer degree and ulcer repair score. The grading standards for the degree of oral ulcer and ulcer healing are as follows:

Grade 0: no ulcer, normal mucous membrane, ulcer damage repair score of 100; Grade I: ulcer, no obvious pseudomembrane on the ulcer surface, no tissue necrosis, ulcer damage repair score of 80; Grade II: ulcer, a thin layer of yellow-white pseudomembrane on the ulcer surface, a small amount of tissue necrosis, ulcer damage repair score of 60; Grade III: ulcer The surface pseudomembrane is thick, and there is inflammatory edema and more tissue necrosis around the ulcer, the ulcer damage repair score is 40; Grade IV: the ulcer surface pseudomembrane is thick, there is obvious inflammatory edema around the ulcer and a lot of tissue necrosis, the ulcer damage repair score is 20 [13].

2.6.2. Area of Oral Ulcer

The maximum transverse diameter (d1) and maximum longitudinal diameter (d2) of oral ulcer in each group of rats before and on the 1st, 3rd, 5th and 7th day after administration were measured using vernier calipers, and the ulcer area was calculated (ulcer area = $\pi \times d1 \times d2 \times 1/4$, π was taken as 3.14) [14].

2.6.3. Determination of Inflammatory Factors

Rats were executed rapidly after the last administration, blood was taken from the heart of the rats and the specimens were left to stand for 20 min, centrifuged at 3500 r/min for 15 min and the supernatant was extracted. The content of *IL-2* and *TNF-α* in rat serum was determined using *Emilia Sonchifolia* kits [15].

2.7. Statistics

Results and expressed were expressed as mean ± s.d., and statistical analysis was performed by one-way ANOVA was used for the degree of ulcer healing, ulcer area, and inflammatory factor content, and two-by-two comparisons between the means of multiple groups were performed, and the LSD was used when the variance was the same, and the Tamheni test was used when the variance was not the same. A $p < 0.05$ was considered significant.

3. Results

3.1. Effect of the Degree of Healing of Oral Ulcer in Rats

The ulcer healing degree of the positive control group (83.33) and the combined group (83.33) was better than that of the other groups, and compared with the model group (70.00), the difference was statistically significant ($p < 0.05$). The ulcer recovery of the *Coptidis Rhizoma* group (76.67) and *Emilia Sonchifolia* (73.33) group was somewhat improved compared with the model group (70.00), but the difference was not statistically significant ($p > 0.05$). There was no significant difference between *Emilia Sonchifolia* group, *Coptidis Rhizoma* group and Combined group ($p > 0.05$) (**Table 1**).

3.2. Effect of the Area Change of Oral Ulcer in Rats

There was no statistically significant difference in ulcer area between *Emilia Sonchifolia* group (20.48), *Coptidis Rhizoma group* (20.37), and combined group

Table 1. Effect on the degree of healing of oral ulcer of rats ($\bar{x}$ ± s, n = 6).

Groups	N	Mouth ulcer degree grading (piece)					Ulcer repair score
		0	I	II	III	IV	
Normal group	6	6	-	-	-	-	100.00 ± 0.00
Model group	6	0	3	3	0	0	70.00 ± 10.95
Emilia Sonchifolia group	6	0	4	2	0	0	73.33 ± 10.33[#]
Coptidis Rhizoma group	6	1	3	2	0	0	76.67 ± 15.06[#]
Combined group	6	1	5	0	0	0	83.33 ± 8.17*
Positive control group	6	1	5	0	0	0	83.33 ± 8.17*

Note: *, compared with the model group, $p < 0.05$; [#]compared with the combined group, $p > 0.05$.

(20.26), positive control group (20.22) and model group (20.57) on the first day ($p > 0.05$), indicating that there was no significant difference in modeling area between groups. On the 3rd, 5th and 7th day after administration, the ulcer area of *Coptidis Rhizoma*, *Emilia Sonchifolia*, combined, positive control and model group was smaller than that of the model group, and the ulcer area of the positive control group was the smallest, followed by the combined group, with statistically significant differences ($p < 0.05$). The ulcer area of *Emilia Sonchifolia* group was not significantly different from that of the combined group on the 3rd and 7th day after administration ($p > 0.05$). On the 5th day after administration, the ulcer area of *Emilia Sonchifolia* (10.12) was larger than that of the combined group (7.26), with statistically significant differences ($p < 0.05$). On the 3rd, 5th, and 7th day of administration, the ulcer area of the *Coptidis Rhizoma* group was larger than that of the combined group, and the difference was statistically significant ($p < 0.05$) (**Table 2**).

3.3. Effect of Inflammatory Factors in the Serum of Rats

Compared with the model group, the *Emilia Sonchifolia group* (73.78), *Coptidis Rhizoma* group (72.97), combined group (72.18) and positive control group (62.36) could reduce the level of *TNF-α* and increase the level of *IL-2*, and the difference was statistically significant ($p < 0.05$). The differences were not statistically significant when comparing *TNF-α* in the *Emilia Sonchifolia* group and *Coptidis Rhizoma* group with the combined group ($p > 0.05$). The difference was statistically significant when comparing *IL-2* in the *Emilia Sonchifolia* group and *Coptidis Rhizoma* group with the combined group ($p < 0.05$) (**Table 3**).

4. Discussion

As a common and frequent oral mucosal disease, oral ulcer has a complex pathogenesis and its etiology is still unclear, so it is difficult to be eradicated by existing treatment methods because of its recurrent nature. In this experiment, we

Table 2. Changes in the area of oral ulcer of rats ($\bar{x}$ ± s, n = 6).

Groups	Day 1/mm^2	Day 3/mm^2	Day 5/mm^2	Day 7/mm^2
Normal group	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Model group	20.57 ± 0.53	15.04 ± 0.68	13.08 ± 0.68	9.08 ± 0.89
Emilia Sonchifolia group	20.48 ± 0.67	13.51 ± 0.83*	10.12 ± 0.60*#	6.09 ± 0.66*
Coptidis Rhizoma group	20.37 ± 0.49	12.40 ± 0.75*#	8.71 ± 0.99*#	5.37 ± 0.68*#
Combined group	20.26 ± 0.42	11.79 ± 0.87*	7.26 ± 0.42*	4.32 ± 0.36*
Positive control group	20.22 ± 0.35	11.00 ± 0.86*	5.46 ± 0.40*	2.82 ± 1.45*

Note: *, compared with the model group, $p < 0.05$; #compared with the combined group, $p > 0.05$.

Table 3. Inflammatory factor concentrations in serum of rats ($\bar{x}$ ± s, n = 6).

Groups	*TNF-α*/pg·mL^{-1}	*IL-2*/pg·mL^{-1}
Normal group	48.22 ± 1.14	52.24 ± 1.19
Model group	83.42 ± 1.83	33.20 ± 0.85
Emilia Sonchifolia group	73.78 ± 0.81*	39.73 ± 0.46*#
Coptidis Rhizoma group	72.97 ± 0.50*	42.34 ± 0.78*#
Combined group	72.18 ± 0.67*	44.26 ± 0.91*
Positive control group	62.36 ± 1.70*	47.18 ± 0.34*

Note: *, compared with the model group, $p < 0.05$; #, compared with the combined group, $p > 0.05$.

studied the effect of combining *Coptidis Rhizoma* with *Emilia Sonchifolia* to prevent and treat oral ulcer, and found that the oral film made of *Emilia Sonchifolia* combined with *Coptidis Rhizoma* had improved the clinical symptoms and oral mucosal pathological damage in rats with oral ulcer, and the overall effect of the combined medicine was better than that of the medicine alone.

In this experiment, the oral ulcer model was established by chemical cautery method, and the mucosa showed more serious inflammatory edema reaction due to the stimulating effect of glacial acetic acid on the mucosa. *Berberine*, the main active ingredient contained in *Coptidis Rhizoma*, has a good antibacterial and anti-inflammatory effect [16]. The extract of *Emilia Sonchifolia* is rich in flavonoids, alkaloids, terpenoids, sterols, polysaccharides and other chemical components, and the pharmacological study proved that *Emilia Sonchifolia* extract has inhibitory effect on *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *S. typhi* [17]. The application of the Zhuang medicine *Emilia Sonchifolia* combined with *Coptidis Rhizoma* topical treatment achieved anti-inflammatory and antibacterial effects, reduced inflammatory reaction, eliminated inflammatory edema, and promoted ulcer healing. In the present experiment, the results of oral ulcer healing assay in rats showed that *Emilia Sonchifolia* combined with *Copti-*

dis Rhizoma could effectively promote the healing of oral ulcer in rats, especially the change of ulcer area was significantly greater than that of the model group.

Abundant clinical and experimental studies have confirmed that during the progression of oral ulcer disease, the abnormally activated macrophages in the oral mucosa secrete a large amount of pro-inflammatory factors (such as *TNF-α*, *IL-6*, etc.) that directly damage the mucosa and surrounding tissues, and macrophages can also promote the expression of genes of pro-inflammatory factors such as *TNF-α* and inhibit the expression of genes of anti-inflammatory factors such as *IL-2*, thus making the synthesis and secretion of *TNF-α* and etc genes increase, causing an imbalance between anti-inflammatory and pro-inflammatory factors, making oral mucosal damage more severe and leading to difficult healing of oral ulcer [18]. In the study, the results of cytokines measured in *Emilia Sonchifolia* experiments in the model group showed a significant increase in the level of TNF-a, which proved the success of modeling. The results of this experiment showed that the combination group could significantly reduce TNF-a levels, suggesting that *Emilia Sonchifolia* combined with *Coptidis Rhizoma* probably inhibit the inflammatory response of oral ulcer by reducing serum levels of the pro-inflammatory factor TNF-a, thus accelerating healing.

IL-2 has a role in promoting the proliferation and differentiation of *B cells*, and also regulates the function of *NK cells*, which can strongly resist oral mucosal pathogens, thus improving the cellular immunity of ROU patients. *IL-2* increases the molecular level on the surface of mononuclear macrophages in the process of clearing inflammation and tissue healing in the body, which then increases the ability of macrophages to clear damaged cells and pathogens. The ability of macrophages to clear damaged cells and pathogens is enhanced, and the healing of oral ulcer is accelerated by the stimulation of the inflammatory response, which leads to the repair of damaged tissues [19]. It has been reported that exogenous *IL-2* supplementation is a simple and practical immunotherapy in the treatment of ROU and some tumor immunity, and it is non-toxic, efficient, and improves resistance, which facilitates the repair of ROU ulcer surface, and *IL-2* shows a trend of reduced levels in patients with recurrent oral ulcer [20]. In the present experiment, the combination of *Emilia Sonchifolia* and *Coptidis Rhizoma* significantly increased the level of *IL-2* in the serum of rats with oral ulcer, and the effect was better than that of the drug alone, suggesting that the combination of *Emilia Sonchifolia* and *Coptidis Rhizoma* may achieve the effect of inhibiting inflammation by increasing the level of anti-inflammatory factors, which may be related to the combined effect of the two drugs.

In summary, *Coptidis Rhizoma* and *Emilia Sonchifolia* combined with film agent has a promoting effect on the healing of oral ulcer, the combined drug effect is better than that of drugs alone, providing a new treatment for oral ulcer. Its mechanism of action may be related to lowering the level of *TNF-α*, increasing the level of *IL-2*, suppressing inflammatory response, and regulating the immune function of rats with oral ulcer, which should be further studied.

The present study is limited to the evaluation of the therapeutic efficacy of oral ulcer in rats in the short term, without the observation and evaluation of the recurrence and long-term efficacy, and lacks of clinical collaborative research, and the sample size is relatively small, so we will further increase the sample size in the future to validate the results of this experiment, so as to systematically and comprehensively evaluate the therapeutic efficacy and safety of the combination of the *Emilia Sonchifolia* and *Coptidis Rhizoma* on oral ulcer.

Fund Program

College Student Innovation and Entrepreneurship Project Training Program (Project No.: S202210599112).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Luo, M., Liu, Y.P., Li, Y.C., *et al.* (2020) Clinical and TCM Treatment Analysis of 4435 Cases of Oral Mucosal Disease. *Chinese Medical Science*, **10**, 3-6.

[2] Chen, Q.M. (2012) Oral Mucosal Pathology. 4th Edition, People's Health Publishing House, Beijing, 64-71.

[3] Suter, V.G.A., Sjölund, S. and Bornstein, M.M. (2017) Effect of Laser on Pain Relief and Wound Healing of Recurrent Aphthous Stomatitis: A Systematic Review. *Lasers in Medical Science*, **32**, 953-963. https://doi.org/10.1007/s10103-017-2184-z

[4] Lin, S.T., Peng, S., Hu, J., *et al.* (2020) Analysis of the Effect of Self-Administered Oral Ulcer Dispersion in the Treatment of Oral Ulcer. *China Continuing Medical Education*, **12**, 148-151.

[5] Zhang, Y., Ng, K.H., Kuo, C.Y. and Wu, D.J. (2018) Chinese Herbal Medicine for Recurrent Aphthous Stomatitis: A Protocol for Systematic Review and Meta-Analysis. *Medicine*, **97**, e13681. https://doi.org/10.1097/MD.0000000000013681

[6] Liang, L.Q., Chen, S.F., Lu, W. and Su, H.Z. (2021) Research Progress on the Chemical Composition, Pharmacological Effects and Clinical Application of the Zhuang Medicine, Diaozhong. *Chinese Journal of Ethnic Medicine*, **27**, 75-78.

[7] Wang, Y.N., Liu, B.R., Dang, X.M. and Wang, D.C. (2013) Inhibitory Effect of Rutin on Sortase A of *Staphylococcus aureus*. *Journal of Jilin Agricultural University*, **35**, 303-307.

[8] Zhang, Y.J., Zheng, Z.X., Chen, J.M., Li, K.S., Li, Y.D. and Li, C.H. (2011) Observations on the General Pharmacological Effects of *Emilia sonchifolia* Extract. *Chinese Patent Medicine*, **33**, 1238-1241.

[9] Zhang, S.L. (2021) Clinical Observation on the Treatment of Recurrent Oral Ulcer with the Addition and Subtraction of *Coptidis Rhizoma* Gan Cao Tang. *Guangming TCM*, **36**, 2486-2488.

[10] Li, J., Su, X.L., Yang, H.F. and Mu, X.Q. (2020) Observation on the Anti-Inflammatory Effect of Chuan *Coptidis Rhizoma* on Chemical Burning Oral Ulcers in Rats. *Medical Information*, **33**, 61-63.

[11] Li, J., Chen, Z.J., Shi, J.F., Xiao, Q., Wang, M., Jiang, H.J., Fu, C.M., Geng, F.N. and

Zhang, J.M. (2018) Preparation of American Cockroach Oral Patch and Its Anti-Mouth Ulcer Effect. *Chinese Journal of Experimental Formulary*, **24**, 29-36.

[12] Ji, L., Yuan, S.M., Chen, F.Y., Chen, H.Y., Han, P.F. and Wang, F. (2018) Study on the Control Optimization of the Animal Model of Oral Ulcer in Rats by Chemical Cautery Method. *Chinese Journal of Laboratory Animals*, **26**, 554-560.

[13] Han, X.S., Jia, J.X., Chen, F.Y., Wu, L.L., Zhang, H., Zhang, X.G., Ming, H.W. and Tan, X.R. (2023) Effects of Ten Flavors of Oral Ulcer Clearing Compound on Inflammatory Factors and Epidermal Growth Factor in Rats with Oral Ulcer Model. *Chinese Folk Therapy*, **31**, 87-90.

[14] Chen, Z., Wang, J.L., Zhuang, P.W., *et al.* (2016) Experimental Study on the Treatment of Oral Ulcer in Rats with Qing Pharynx Drops. *Chinese Sonchifolia Medicine*, **47**, 106-109.

[15] Li, Z.Q., He, Y.Z. and Tao, Y. (2018) Research Progress of Cytokine Assay and Its Application in Intraocular Fluid Detection. *Chinese Journal of Ophthalmology* (*Electronic Edition*), **8**, 140-144.

[16] Hu, X., Zhang, Y., Li, K. and Yang, Z.F. (2021) Clinical Pharmacological Analysis of Berberine, the Main Component of *Coptidis Rhizoma*. *Modern Distance Education in Chinese Traditional Medicine*, **19**, 203-205.

[17] Zhao, D.N., Sun, X., Zhou, X. and Zhao, C. (2019) Research Progress on Chemical Composition and Pharmacological Effects of the Plant of the Genus Adaceae. *Chinese Patent Medicine*, **41**, 1654-1661.

[18] Dai, L.M., Dai, L.P., Chen, Y.J., Ren, L.Y., Yu, Z. and Huang, Q.L. (2021) Study on the Therapeutic Effect and Mechanism of Kangfu Xin Liquid on Traumatic Oral Ulcer Rat Model. *Chinese Medicine and Clinical Practice*, **12**, 25-29.

[19] Zhang, W.K., Wang, J.P., Hu, J., Song, S.T. and Zhu, J.H. (2019) Effects of Teprenone Treatment on the Expression of *IL-2* and *TNF-α* in Rats with Oral Ulcer. *Heilongjiang Pharmaceutical Science*, **42**, 11-12.

[20] Sun, L.F., Liu, H., Tian, N.P., Yu, G.Y., Fan, J.B. and Wang, J.T. (2001) Modulatory Effect of *IL-2* on Cellular Immune Function in Patients with Recurrent Oral Ulcer. *Journal of Avant-Garde Medicine*, **4**, 252-254, 257.