

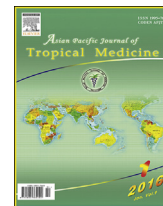
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## Therapeutic and recurrence-preventing effects of Qi-Replenishing and Blood-Activating Formula in rats with acetic acid-induced gastric ulcer

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## ABSTRACT

**Objective:** To explore the therapeutic and recurrence-preventing effects of Qi-Replenishing and Blood-Activating Formula in rats with acetic acid-induced gastric ulcer.

**Methods:** A total of 138 SD rats were selected to make rat models with gastric ulcer induced by acetic acid (24 rats with sham operation served as sham operation group), and were randomly divided into model group ( $n = 30$ ), western medicine group ( $n = 30$ ), traditional Chinese medicine (TCM) group ( $n = 24$ ) and combination group (combined western medicine and TCM group,  $n = 30$ ). Western medicine group was gavaged with omeprazole in the morning and with iso-volumetric distilled water in the afternoon; TCM group and TCM sham operation group were gavaged with iso-volumetric distilled water in the morning and with Qi-Replenishing and Blood-Activating Formula in the afternoon; combination group was gavaged with omeprazole in the morning and with Qi-Replenishing and Blood-Activating Formula in the afternoon; sham operation group and model group were gavaged with iso-volumetric distilled water both in the morning and afternoon. Ulcer indexes and degree of mucosal degree in rats at different time points after gavage were observed. Twenty-eight days after gavage, interleukin (IL)-1 $\beta$  was given to induce ulcer recurrence so as to observe the recurrent severity and rate of ulcer in each group.

**Results:** Compared with model group and western medicine group, treatment in combination group could prominently reduce the ulcer index of rats with peptic ulcer, and increase the healing rate and inhibition rate of peptic ulcer. After IL-1 $\beta$ -induced ulcer recurrence, combination group was significantly superior to model group and western medicine group in ulcer recurrent rate [50% (3/6) vs. 100% (6/6)] and severity.

**Conclusions:** Basic acid-suppression therapy combined with Qi-Replenishing and Blood-Activating Formula can effectually improve the ulcer healing quality and reduce ulcer recurrence.

## 1. Introduction

With the development of H2 receptor inhibitor, proton-pump inhibitor (PPI) and anti-helicobacter pylori therapies, the short-

term cure for peptic ulcer has no longer been intractable. However, after drug withdrawal, about 70%–80% patients recur within 1 year after duodenal ulcer healing, and almost 100% of them recur within 5 years [1,2]. Gastric ulcer is easy to recur, and the average recurrent rate is 50% after 6 months [3,4]. Therefore, the high recurrent rate after peptic ulcer healing is still a sharp issue in clinical treatment. This study used rats with acetic acid-induced gastric ulcer as research models to observe the therapeutic and recurrence-preventing effect of Qi-Replenishing and Blood-Activating Formula, hoping to provide a theoretical basis for the development of new clinical therapeutic protocols for gastric ulcer.

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## 2. Materials and methods

### 2.1. Materials

#### 2.1.1. Experimental animals and therapeutic drugs

Male SD rats weighed 180–220 g were purchased from Suzhou Industrial Park Aier Maite Technology Co., Ltd, China, with certification No. being 2006112 and Production License No. being SCXK (Su) 2009-0001.

Omeprazole Enteric Capsules were purchased from Changzhou Siyao Pharmaceutical Co., Ltd, with Specification: 20 mg/piece and Approved No.: H20023053. Chinese herbal pieces were bought from Suzhou Chunhuitang Pieces Factory, including raw Puhuang (Cattail pollen) (Batch No.: 091013, Jiangsu), Wulingzhi (Troglodytes dung) (Batch No.: 100224, Hebei), fried Baishao (Radix Paeoniae Alba) (Batch No.: 100507, Zhejiang), grilled Huangqi (Radix Astragali) (Batch No.: 100405, Inner Mongolia), Chuanguizhi (Cassia twig) (Batch No.: 100119, Guangdong), prepared Ruxiang (Frankincense) (Batch No.: 100115, Hainan), Tieshuye (Folium cycas) (Batch No.: 100115, Jiangsu), and grilled Gancao (*Glycyrrhiza uralensis*) (Batch No.: 100305, Inner Mongolia).

#### 2.1.2. Primary instruments and reagents

TP1020 automatic hydroextractor and RM2135 paraffin slicing machine (LEICA Company, Germany), CS-VI Water Bath-Slide Drier (Hubei Xiaogan Hongye Medical Instruments Co., Ltd, China), Tissue-Tek TEL tissue Beichert Histostat (SAKURA Company, Japan), FA1104N electronic balance (Balance Instrument Factory of Shanghai Sophisticated Scientific Instrument Co., Ltd, China), DMLS2 optical microscope (LEICA Company, Germany), Water-jacket Thermostatic Incubator (First Factory of Shanghai Yuejin Medical Instrument, China), and microwave oven (TCL Co., Ltd, China).

Acetic acid (Shanghai Chemical Reagent Co., Ltd, China), pentobarbital sodium (Sigma Company, USA), interleukin (IL)-1 $\beta$  (PeproTech Company, USA), and other reagents were analytic alcohol bought from market.

### 2.2. Methods

#### 2.2.1. Preparation of tested drugs

Components of prescription: Wulingzhi 10 g, Puhuang 10 g, prepared Ruxiang 3 g, Tieshuye 30 g, grilled Huangqi 30 g, Chuanguizhi 10 g, fried Baishao 20 g and grilled Gancao 6 g. Extraction methods: The pieces were added with 10-fold of water by quality, immersed for 2 h, and extracted by heat for twice, 1 h/time. The extracting solution was mixed and concentrated into decoction containing crude drugs 1.3 g/mL.

#### 2.2.2. Molding, grouping and administrating

A total of 144 SD rats were selected and fed with normal diet. Three days after adaptive feeding, molding was performed: 3% pentobarbital sodium 40 mg/kg was intraperitoneally injected for anesthesia. The rats were fixed on anatomy plate in supine position, sterilized by routine 2% iodine tincture and 75% ethanol on abdominal skin, after which gauze drapes were paved. The length of median incision of xiphoid lower abdomen in rats was 2.0–2.5 cm. Abdominal wall tissues were sheared along Hunter's line to open enterocoelia. Abdominal retractor was used to expose surgical field, and smooth forceps was adopted to poke

the intestines to localize the rats' stomach. Glass round tube (internal diameter: 4 mm) was applied to press the location about 5 mm away from the inferior incision of gastric lesser curvature, and then 100% ethanol 0.1 mL was injected into the tube for continuously 60 s on the junction of gastric body and pylorus (avoiding vessels) (24 rats were given sham operation, with normal saline replacing ethanol). And then, after being washed by 0.85% sodium chloride solution, gastric body was returned, and the incision was sutured layer by layer, and sterilized with iodine tincture so as to protect the incision.

Three days after molding, 6 rats were randomly selected and sacrificed to anatomize the stomach, so as to observe the conditions of gastric ulcer. If the gastric ulcer met the requirements of models, the rats were randomly divided into model group ( $n = 30$ ), western medicine group ( $n = 30$ ), traditional Chinese medicine (TCM) group ( $n = 24$ ) and combination group (combined western and TCM group,  $n = 30$ ) on next day (4 d after molding). And 24 rats undergoing sham operation served as sham operation group ( $n = 24$ ).

Western medicine group was gavaged with omeprazole (OME) in the morning and with iso-volumetric distilled water in the afternoon; TCM group and TCM sham operation group were gavaged with iso-volumetric distilled water in the morning and with Qi-Replenishing and Blood-Activating Formula in the afternoon; combination group was gavaged with OME in the morning and with Qi-Replenishing and Blood-Activating Formula in the afternoon; and sham operation group and model group were gavaged with iso-volumetric distilled water both in the morning and afternoon. OME: 15 mg/(kg·d); Qi-Replenishing and Blood-Activating Formula: crude drugs 11 g/(kg·d). All groups were gavaged by 10 mL/kg, bid. General conditions of all rats were observed before and after drug administration.

#### 2.2.3. Observation on gastric mucosa

After being gavaged for continuously 14, 21 and 28 d following successful molding, 8 rats were randomly selected from each group, and sacrificed after anesthesia to observe the conditions like the size and depth of gastric ulcer, the presence of white fur as well as the color, elasticity and congestion edema of peripheral mucous membrane in sinuses ventriculi. Under magnifying lens, vernier caliper was used to measure the long diameter (DL) and short diameter (DS) of gastric ulcer so as to calculate the ulcer size (S):  $S = 1/4 \times DL \times DS \times \pi$ . Ulcer indexes were evaluated to calculate the ulcer inhibition rate.

Ulcer healing surface was found and embedded by paraffin. 5  $\mu$ m slices (with the maximum diameter of ulcer nidus or scar as the center) were continuously made and stained with hematein (HE) to observe the ulcer healing condition.

#### 2.2.4. IL-1 $\beta$ -induced ulcer recurrence

Twenty-eight days after gavage, the rest 6 rats in model group, western medicine group and combination group were intraperitoneally injected with IL-1 $\beta$  1.00 g/kg, and sacrificed 48 h later to observe the recurrent degree and rate of gastric ulcer in each group.

### 2.3. Evaluation criteria

Criteria for ulcer index scale: 1 point: ulcer size was 1 mm<sup>2</sup>–12 mm<sup>2</sup>; 2 points: ulcer size was 13 mm<sup>2</sup>–25 mm<sup>2</sup>; 3 points:

ulcer size was 26 mm<sup>2</sup>–37 mm<sup>2</sup>; 4 points: ulcer size was 38 mm<sup>2</sup>–50 mm<sup>2</sup>; 5 points: ulcer size was ≥50 mm<sup>2</sup> or with perforated ulcer. As to ulcer spot ≤1 mm<sup>2</sup>, 10 spots were considered as 1 mm<sup>2</sup>. Ulcer inhibition rate (%) = (ulcer index in sham operation group – ulcer index in each administrative group) / ulcer index in sham operation group × 100%.

Diagnostic criteria for severity of mucosal injury: degree 0: no injury; degree 1: epithelial cell injury on mucosal surface; degree 2: injury involving foveolae gastricae; degree 3: injury invading superficial gastric gland; degree 4: injury reaching to deep glands.

#### 2.4. Statistical data analysis

SAS 9.3 software was applied for data analysis. Quantitative data were expressed by mean ± SD, and comparison among groups were detected with *q* test, while intra-group comparison with *t* test. Enumeration data were detected by  $\chi^2$  test, while ranked data by Ridit analysis.

### 3. Results

#### 3.1. General conditions of rats

After successful molding, in the first week, foraging initiative and food-intake volume of rats decreased markedly in each administrative group than those in sham operation group, with poor general conditions and slowly increased body weight observed; in the second week, there was no significant difference among groups in food-intake conditions, but each administrative group was slightly higher than model group and still lighter than sham operation group in body weight; in the third week, there was no significant difference between each administrative group and sham operation group, but they were all higher than model group in body weight; in the fourth week, no statistical significance was observed among groups in both food-intake conditions and body weight.

#### 3.2. Ulcer index and injury severity of gastric mucosa

Fourteen and twenty-one days after gavage, western medicine group and combination group were notably lower than model group in ulcer size and indexes ( $P < 0.01$  or  $P < 0.001$ ), but there was no significant between TCM group and model group ( $P > 0.05$ ); 21 d after gavage, combination group was markedly lower than western medicine group in ulcer size, and 14 and 21 d after gavage, combination group was prominently lower than western medicine group in ulcer indexes ( $P < 0.05$ ); 28 d after gavage, the ulcer size and index were 0 in all groups, with ulcer healing rate being 100%, as shown in Tables 1 and 2.

Fourteen days after gavage, mucosal structure of gastric ulcer nidi was in disordered arrangement without integrity and continuousness in model group, but epithelial layer of mucosa in partial region was lost with injury involving deep gastric glands, which was marked by sub-mucosal hemorrhage, intravascular congestion and infiltration of inflammatory cells. Each mucosal layer was arranged regularly without necrotic tissues and hemorrhage in TCM group and western medicine group, and TCM group showed occasional injury involving foveolae gastricae and gastric glands; and in combination group, the mucosal layer was complete and continuous, and slices indicated injury on epithelial cells on mucosal surface. Twenty-one days after gavage, sub-mucosal hemorrhage, intravascular congestion and improved infiltration of inflammatory cells were observed in model group, while TCM group, western medicine group and combination group showed injury on epithelial cells on mucosal surface without infiltration of inflammatory cells. Twenty-eight days after gavage, model group showed sub-mucosal hemorrhage and intravascular congestion without infiltration of inflammatory cells, whereas in TCM group, western medicine group and combination group, the structures of mucosal layer, lamina propria and muscular layer were complete and continuous, with successive arrangement, close arrangement of glands without infiltration of inflammatory cells, and only several layers showed injury on epithelial cells on mucosal surface. Above

**Table 1**

Comparison of ulcer size (mm<sup>2</sup>, mean ± SD) and healing rates [*n*(%)] at different time points among groups.

Groups	<i>n</i>	14 d After gavage		<i>n</i>	21 d After gavage		<i>n</i>	28 d After gavage	
		Ulcer size	Healing rate		Ulcer size	Healing rate		Ulcer size	Healing rate
Model group	8	52.5 ± 27.0	0 (0.00)	8	36.9 ± 31.2	0 (0.00)	8	0.0 ± 0.0	8 (100)
Western medicine group	8	14.0 ± 8.1**	2 (25.00)	8	14.5 ± 3.2**	3 (37.50)	8	0.0 ± 0.0	7 (100)
TCM group	8	37.2 ± 27.2 <sup>Δ</sup>	0 (0.00)	8	26.9 ± 7.8 <sup>Δ</sup>	2 (25.00)	8	0.0 ± 0.0	8 (100)
Combination group	8	8.2 ± 2.5** <sup>Δ</sup>	3 (37.50)	8	9.9 ± 1.3***	6 (75.00)	8	0.0 ± 0.0	8 (100)

Compared with model group, \*\* $P < 0.01$ , \*\*\* $P < 0.001$ ; Compared with western medicine group, <sup>Δ</sup> $P < 0.05$ . <sup>ΔΔ</sup> $P < 0.01$ , <sup>ΔΔΔ</sup> $P < 0.001$ .

**Table 2**

Comparison of ulcer indexes (mean ± SD) and ulcer inhibition rates (%) at different time points among groups.

Group	<i>n</i>	14 d After gavage		<i>n</i>	21 d After gavage		<i>n</i>	28 d After gavage	
		Ulcer index	Inhibition rate		Ulcer index	Inhibition rate		Ulcer index	Inhibition rate
Model group	8	3.9 ± 1.4	–	8	2.9 ± 1.0	–	8	0.0 ± 0.0	–
Western medicine group	8	1.6 ± 1.1**	61.28	8	1.2 ± 1.0**	65.22	8	0.0 ± 0.0	–
TCM group	8	3.3 ± 1.6 <sup>Δ</sup>	16.13	8	2.0 ± 1.3 <sup>Δ</sup>	30.43	8	0.0 ± 0.0	–
Combination group	8	0.6 ± 0.5** <sup>Δ</sup>	85.25	8	0.3 ± 0.5** <sup>Δ</sup>	91.30	8	0.0 ± 0.0	–

Compared with model group, \*\* $P < 0.01$ , \*\*\* $P < 0.001$ ; Compared with western medicine group, <sup>Δ</sup> $P < 0.05$ .

**Table 3**Comparison of IL-1 $\beta$ -induced recurrent mucosal injury severity.

Groups	n	0	1	2	3	4
Model group	6				2	4
Western medicine group	6			3	3	
Combination group	6		3	3		

results demonstrated that at the end of treatment, the gastric ulcer nidi recovered in all groups, but there was significant difference in healing quality among groups.

### 3.3. Ulcer recurrence and mucosal injury severity after IL-1 $\beta$ induction

The recurrent ulcer index was  $1.8 \pm 0.4$ ,  $1.2 \pm 0.4$  and  $1.0 \pm 0.0$  in model group, western medicine group and combination group, respectively, which was markedly higher in model group than those in other two groups ( $P < 0.05$  or  $P < 0.01$ ); the recurrent rates was 100% (6/6), 100% (6/6) and 50% (3/6) in model group, western medicine group and combination group, respectively. Mucosal injury severity showed significant difference in western medicine group and combination group when compared with model group, which was prominently better in combination group than that in western medicine group, as shown in Table 3.

## 4. Discussion

The healing process of peptic ulcer is a positive process of proliferative or transitional epithelial cells and connective tissues supplementing damaged or necrotic mucosa, whose completion needs the participation of numerous tissue and cellular systems [5,6]. Tarnawski *et al.* [7] found that though endoscopy showed healed gastric ulcer in partial patients, there was still abnormality of tissues and ultra-structure. The above phenomenon is also named seemingly ‘healed’, but in reality, local tissue structures and functional maturity is low, marked by thin mucosal layer, filling of large amount of function-free connective tissues, decreased glands, and dilated gastric glands in disordered arrangement, especially the decreased sub-mucous micro-vessels, disordered micro-vascular structure and reduced defensive ability of mucosa to aggressive factors, so ulcer is easily to reoccur. Thus the concept of ‘quality of ulcer healing (QOUH)’ is proposed, which believes that QOUH is either high or low after treatment, and the low quality is the cause and histological basis for the recurrence after ulcer healing [8]. Improving QOUH is critical in resolving the clinical issue of decreasing ulcer recurrent rate [9]. The treatment for ulcer is ‘QOUH’-targeted, and its core indicates that ulcer healing not only needs to heal the general apparent superficial mucosa, but also to recover their normal histological structures and function [10].

Qi-Replenishing and Blood-Activating Formula is a clinical empirical formula inherited by Yifeng Huang, a prestigious doctor in Wuzhong. In the prescription, Huangqi, Guizhi and Baishao, as monarch drugs, could tonify qi and harmonize spleen and stomach with sweetness and warmth to invigorate spleen and nourish stomach, so as to replenish Ying blood and nourish limit membrane; Wulingzhi and Puhuang, as assistant drugs, could rectify qi to transform the blood, transform stasis to

free the networks and engender flesh to close the sores [11]. Huangqi and Guizhi could also dilate vessels, improve blood flow and promote associated repair of necrotic tissues, which means the functions of ‘supplementing blood and engendering flesh’ [12]. Prepared Ruxiang and Tieshuaye, as adjuvant drugs, could strengthen the function of activating blood to relieve pain, meaning ‘the pain is caused by diseases of blood and qi, so regulating and activating blood and qi can alleviate pain’, and removing swelling to produce muscle [13]; grilled Gancao, as guiding drug, could tonify primordial qi of triple energizer, which could ‘form yang with sweetness and acidity’ when combined with Guizhi and ‘form yin with sweetness and sourness’ when combined with Shaoyao, and it is also effective in relaxing tension to relieve pain and harmonize all drugs in the prescription [14]. The whole prescription could repair and consolidate the local ulcer pathological damage by regulating the holistic blood and qi.

Glacial acetic acid that has been widely used in clinic was applied in this study to induce rat models with gastric ulcer. This method is reliable in efficacy, favorable in repeatability, and deep and large in ulcer, whose induced ulcer is similar to that in human, so it is advisable to observe the effect of drugs in improving ulcer healing [15,16]. Watanabe [17] method was adopted to induce ulcer recurrence, in which IL-1 $\beta$  was intraperitoneally injected to induce the healing of primary ulcer in rats. In this study, IL-1 $\beta$  was used to induce ulcer recurrence after ulcer surfaces were generally healed by guideline-specific western medicines and controlled therapy with TCM and western medicines, so as to be consistent with clinical practical treatment, which could be used to compare and observe QOUH and recurrent condition after treated with different therapies. Research results of this study were evaluated by semi-quantitative method combined with morphology, which showed that compared with model group and western medicine group, combination group could significantly reduce the ulcer index of rats with peptic ulcer, increase the healing rate and ulcer inhibition rate, which were consistent with the results of previous clinical observations [18–20]. Additionally, the results of IL-1 $\beta$ -induced ulcer recurrence also illustrated that the ulcer recurrent condition (3/6, with recurrent rate being 50%) and severity were obviously better in combination group than those in model group and western medicine group (6/6, with recurrent rate being 100%), suggesting that application of Qi-Replenishing and Blood-Activating Formula on basis of acid-suppression therapies could markedly improve QOUH, which in turn could help reduce ulcer recurrence.

### Conflict of interest statement

We declare that we have no conflict of interest.

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