

Efficacy and safety of herbal medicines in treating gastric ulcer: A review

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Core tip: Gastric ulcer is a common digestive disorder. Herbal medicines can effectively treat gastric ulcers in humans and various animal models. The efficacy of herbal medicines is comparable or superior to drugs such as omeprazole or cimetidine, and herbal medicines display fewer adverse effects. The mechanisms by which herbal medicines benefit gastric ulcer include stimulation of mucous cell proliferation, anti-oxidation, and inhibition of gastric acid secretion as well as H(+)/K(+)-ATPase activity. Some herbal medicines also exhibit antimicrobial properties. Utilization of herbal medicines could be a valuable alternative to treat gastric ulcer in humans effectively, with few adverse effects.

Abstract

Gastric ulcer is a common disorder of the digestive system. Current therapeutic regimens largely rely on Western medicine. However, numerous studies have demonstrated that herbal medicines can effectively treat gastric ulcer in humans and various animal models *via* divergent mechanisms. This review updates the efficacy and safety of herbal medicines in treating gastric ulcer, and the mechanisms of their action in humans and animal models. Studies have demonstrated that the efficacy of herbal medicines is comparable or superior to that of drugs such as omeprazole or cimetidine in humans and animal models, and herbal medicines display fewer adverse effects. The mechanisms by which herbal medicines benefit gastric ulcer include stimulation of mucous cell proliferation, anti-oxidation, and inhibition of gastric acid secretion and H(+)/K(+)-ATPase activity. Some herbal medicines also exhibit antimicrobial properties. Utilization of herbal medicines could be a valuable alternative to treat gastric ulcer in humans effectively, with few adverse effects.

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INTRODUCTION

Gastric ulcer is the most common disorder of the upper digestive tract. The prevalence of gastric ulcer is 2.4% in the Western population^[1] and annual incidence rates range from 0.10% to 0.19%^[2]. In certain regions of Mainland China, the prevalence of gastric ulcer is as high as 6.07% in the general population, and 22.5% of patients with gastrointestinal symptoms have gastric ulcer^[3,4]. Higher incidence usually occurs in people who smoke, use nonsteroidal anti-inflammatory drugs (NSAIDs), or consume alcohol^[5-8]. The recurrence rate is as high as 60%^[9]. Gastric ulcer has a significant economic

impact. Average annual medical costs are \$23819 for gastric ulcer in the United States^[10]. In South Korea, the annual medical costs for gastric ulcer range from \$959.6 to \$2553.10^[11]. Although some studies have demonstrated that *Helicobacter pylori* (*H. pylori*) eradication therapy is cost-effective^[12], a more systematic study indicated that there was no significant cost difference per subject between eradication therapy and placebo^[13]. Although conventional regimens are effective, their side effects are often inevitable and limit clinical utility^[14-16]. However, both clinical and experimental studies have demonstrated that herbal medicines exhibit therapeutic benefit for gastric ulcer with fewer side effects. Moreover, the cost of herbal medicine for gastric ulcer is only about one-sixth of that of Western medicine^[17]. In this paper, the efficacy, safety and mechanisms of action of herbal medicines in treating gastric ulcer are reviewed.

EFFICACY OF HERBAL MEDICINES

Animal models

The beneficial effects of herbal medicines in treating gastric ulcer are demonstrated primarily in various animal models, including ulcers induced by NSAIDs, ethanol, cold-restraint stress, pylorus ligation, as well as erosive agents. In each model, the therapeutic efficacy varies depending on the preparation and utilization of herbal medicines.

NSAID-induced gastric ulcer model: Induction of gastric ulcer is a major adverse effect caused by NSAIDs. Therefore, they have been used widely to establish animal models of gastric ulcer. A single dose of oral indomethacin can induce gastric ulcer-like damage in rats, which reaches a maximum 3 d after administration^[18,19]. Oral administration of *Myristica malabarica* extract once daily for 3 d induced a > 60% reduction in macroscopic damage score^[18]. Similarly, oral *Piper betel* extract at a dose of 2 mg/kg per day for 7 d significantly reduced ulcer index in a rat model of indomethacin-induced gastric ulcer^[20]. Its efficacy was comparable to misoprostol, a conventional anti-ulcer drug. Mehrabani *et al.*^[21] have reported that oral *Teucrium polium* extract lowered ulcer index in 24 h and induces a > 90% reduction in ulcer index. Likewise, oral administration of *Phyllanthus emblica* fruit extract for 7 d induced 79.39% inhibition of ulcer index^[22]. Moreover, oral beeswax extract for 5 d induced significant acceleration of ulcer healing in a rat model^[23]. These results suggest that herbal medicines could be useful in treating NSAID-induced gastric ulcer.

Acetic acid-induced gastric ulcer model: A gastric ulcer model can be established by injection or topical application of acetic acid solution into the stomach. Oral *Qualea grandiflora* extract once daily for 14 d accelerated ulcer healing in an acetic acid-induced gastric ulcer model (ulcer area $6.86 \pm 1.46 \text{ mm}^2$ for control, $1.13 \pm 1.3 \text{ mm}^2$ for *Qualea grandiflora* extract, and $1.63 \pm 1.11 \text{ mm}^2$ for

cimetidine)^[24]. Oral *Centella asiatica* for only 3 d also resulted in dose-dependent acceleration of ulcer healing^[25]. Dharmani *et al.*^[26] reported that oral administration of *Ocimum sanctum* Linn at a daily dose of 100 mg/kg for 10 d achieved a comparable efficacy to omeprazole in ulcer healing in an acetic acid-induced gastric ulcer model. In some cases, the efficacy of herbal medicines is superior to that of conventional drugs. For example, oral *Alchornea glandulosa* extract at a dose of 250 mg/kg per day for 14 d achieved a higher curative rate than cimetidine^[27]. Moreover, administration of extract of herbal mixture also benefited ulcer healing^[28] and reduced recurrence rates^[29]. Oral *Bacopa monniera* or *Azadirachta indica* extract for 5 d not only accelerated gastric ulcer healing in normal rats, but also in rats with type 2 diabetes mellitus^[30]. The efficacy of herbal extracts on ulcer healing varies with molecular size. For instance, lower molecular weight chitosan is more potent than high molecular weight chitosan in treating gastric ulcer induced by acetic acid^[31]. One study showed that following induction of gastric ulcer, rats were given oral *Salvia miltiorrhiza* at 840 mg/d for 5 d, followed by 410 mg/d for 25 d. Cimetidine was used as a positive control. Ulcer index was significantly lower in *Salvia miltiorrhiza*-treated than cimetidine-treated rats. Further improvement in ulcer was observed 3 mo after *Salvia miltiorrhiza* treatment^[32]. Herbal medicines that benefit gastric ulcer are listed in Table 1^[18-55].

Other gastric ulcer models: Water immersion restraint stress results in formation of gastric ulcer *via* oxidative stress^[53,54]. Ohta *et al.*^[54] reported that oral extracts of several herbal mixtures for 3 h markedly reduced ulcer indices in gastric ulcer models induced by water immersion restraint stress. Similarly, oral curcumin resulted in a dose-dependent reduction of ulcer indices in a pylorus ligation-induced gastric ulcer model^[55]. These results demonstrate that herbal extracts of single ingredients or mixtures are beneficial in gastric ulcer healing.

Patients with gastric ulcer

Herbal medicines have been used to treat human gastric ulcer for millennia. Several controlled clinical studies have demonstrated that herbal medicines are effective in treating human gastric ulcer (Table 2). He *et al.*^[56] reported that > 86% of patients with gastric ulcer showed improvement after orally given a herbal mixture three times daily for 6 wk. Similarly, oral herbal mixtures two or three times daily for 2 mo induced a > 90% improvement in patients with gastric ulcer^[57,58]. Improvement of clinical symptoms occurred as early as 3 d after oral herbal medicines^[59]. The efficacy of herbal medicines in treating gastric ulcer is comparable to that of famotidine, a histamine H₂-receptor antagonist^[60]. Studies have demonstrated that herbal medicine is comparable or superior to cimetidine in treating either gastric^[61-64] or duodenal^[61,62] ulcers. One study showed that oral herbal medicines for 4 wk achieved superior efficacy to cimetidine in treating gastric and duodenal ulcers, as well as gastritis^[65]. Moreover,

Table 1 Efficacy and safety of herbal medicines for gastric ulcer in animal models and possible mechanisms

Herbal extracts	Model	Treatment course (d)	Efficacy		Possible mechanisms	Adverse effects	Ref.
			Herbal extract	Positive control			
<i>Myristica malabarica</i>	NSAID	3	62%-86% ¹	76%-79% ¹	↑ EGF, ↑ VEGF, ↓ endostatin	None	[18]
<i>Piper betel</i>	NSAID	7	93.4% ²	85.4% ²	Antioxidant, ↑ mucus content	N/D	[20]
<i>Teucrium polium</i>	NSAID	28	90% ²	N/D	↑ Proliferation, ↓ inflammation	N/D	[21]
<i>Phyllanthus emblica</i> fruits	NSAID	7	80% ²	N/D	Antioxidant	N/D	[22]
Beeswax	NSAID, acetic acid	3 h for NSAID, 5 d for acetic acid	56% ³ for NSAID; 65.8% ³ for acetic acid	N/D	N/D	N/D	[23]
<i>Qualea grandiflora</i>	Acetic acid	14	83% ⁴	76% ⁴	↑ Mucus production, ↑ Proliferation, ↓ acid secretion	N/D	[24]
<i>Centella asiatica</i>	Acetic acid	7	50% ⁴	N/D	↑ bFGF, ↑ proliferation, ↓ MPO	N/D	[25]
<i>Ocimum sanctum</i> Linn.	Acetic acid	20	92.75% ²	87% ²	↑ Mucin content, ↑ proliferation, ↓ acid secretion	N/D	[26]
<i>Alchornea glandulosa</i>	Acetic acid	14	43% ⁴	16% ⁴	↑ Proliferation, ↓ acid secretion	None	[27]
<i>Radix Bupleuri, Radix Codonopsis, radix paeoniae alba, rhizoma corydalis, rhizoma bletilla, margarita, indigo naturalis, radix glycyrrhizae</i>	IL-1b, acetic acid	7-92	56% ² at 7 d, 12.5% recurrence rate at 92 d	27% ² at 7 d, 25% recurrence rate at 92 d	↑ VEGF, ↓ inflammation, ↑ Microvasculature density, ↓ NF-κB mrna and protein	N/D	[28,29]
<i>Bacopa monniera</i>	Acetic acid	10	85.9% ² in normal; 52.5% ² in diabetes rats	68% ² in normal; 41.8% ² in diabetes rats	N/D	N/D	[30]
<i>Azadirachta indica</i>	Acetic acid	10	65.6% ² in normal; 71.5% ² in diabetic rats	68% ² in normal; 41.8% ² in diabetic rats	N/D	N/D	[30]
<i>Chitosan, chitin</i>	Acetic acid	14	60% ²	46% ²	↓ Acid secretion, ↑ mucus	N/D	[31]
<i>Salvia miltiorrhiza</i>	Acetic acid	5-30	31% ² for 5 d, 59% ² for 30 d	19% ² for 5 d, 33% ² for 30 d	↑ Proliferation	N/D	[32]
<i>Ganoderma lucidum</i>	Acetic acid	14	55.9% ²	82.8% ²	↑ Mucus content, ↑ PGE2	N/D	[33]
<i>Tea catechin</i>	Acetic acid	14	66% ²	59%-77% ²	Antioxidant	N/D	[34]
<i>Solanum nigrum</i>	Acetic acid	7	70.1% ²	75.7% ²	H ⁺ /K ⁺ -atpase activity, ↓ gastrin, ↓ acid secretion	None	[35]
<i>Cochinchina momordica</i> seed	Acetic acid	14	71.2% ³	N/D	↑ VEGF (protein and mrna), ↑ Microvasculature density	N/D	[36]
<i>Rhizoma Coptis Chinensis</i>	Acetic acid	10	53.86% ³	36.47% ³	↓ Acid secretion	N/D	[37]
Glycyrrhetic acid, β-sitosterol, berberine, baicalin and ginsenoside	Acetic acid				↓ Endothelin-1, ↑ leptin		[38]
Curcumin and bisdemethoxycurcumin	Acetic acid	10	86.05% ⁴	82.42% ⁴	↓ iNOS, ↓ acid secretion, ↓ inflammation	N/D	[39]
<i>Bupleurum falcatum</i> L.	Acetic acid	14	51.9% ⁴	83.1% ⁴	N/D	N/D	[40]
<i>Plantago lanceolata</i> L	Acetic acid	10	77.9% ²	76.2% ²	↑ Mucus content, ↓ gastric secretion, ↓ acid secretion	None	[41]
<i>Croton lechleri</i>	Acetic acid	7	55% ³	N/D	↓ Bacterial colonization, ↓ MPO, ↓ iNOS, ↓ inflammation	N/D	[42]
<i>Panax notoginseng, rhizoma bletilla, Poria cocos, Taraxacum mongolicum</i> Hand	Acetic acid	7	N/D	N/D	N/D	N/D	[43]
<i>Tabebuia avellanedae</i>	Acetic acid	7	36% ³	48% ³	↑ Proliferation, ↑ mucus content	N/D	[44]
Sea buckthorn bark	Acetic acid	14	80% ²	70% ²	↑ Plasma EGF, ↑ EGFR, ↑ PCNA	N/D	[45]
<i>Astaxanthin</i>	Acetic acid	10	93.5% ³	N/D	Antioxidant, ↓ inflammation	N/D	[46]
<i>Angelica sinensis</i>	Acetic acid	3-7	95% ³ for 3 d, 62% ³ for 7 d	N/D	↑ Mucus content	N/D	[47]
<i>Radix Aristolochiae, Potentilla bifurca</i> L, <i>Resina Draconis, Taraxacum mongolicum</i> Hand, <i>radix paeoniae alba, Saussurea costus</i> (Falc.) Lipech, <i>radix glycyrrhizae</i>	Acetic acid	16	N/D	N/D	↑ Proliferation, ↑ NO, ↑ EGF	N/D	[48]
<i>Rhizoma Atractylodis macrocephalae, Radix Linderae, Rhizoma Dioscoreae, rhizoma bletilla, Pericarpium Citri Reticulatae</i> Viride, <i>Rhizoma Alpiniae Officinarum, Radix Paeoniae Rubra, Herba Agrimoniae</i>	Acetic acid	14	45.15% ⁴	72.12% ⁴	↑ Serum EGF, ↑ serum no, ↓ Acid secretion, ↑ PGE2	N/D	[49]
<i>Nyctanthes arbortristis</i> Linn	Acetic acid	10	55%-60% ³	N/D	↓ Inflammation	N/D	[50]

<i>Radix Codonopsis</i> , <i>Radix Adenophorae</i> , <i>Radix Angelica Sinensis</i> , <i>Rhizoma Chuanxiong</i> , <i>radix paeoniae alba</i> , <i>Poria</i> , <i>Rhizoma Atractylodis macrocephalae</i> , <i>Radix Bupleuri</i> , <i>Radix Scutellariae</i> , <i>Rhizoma Coptidis</i> , <i>Fructus Aurantii Immaturus</i> , <i>Radix Salviae Miltiorrhiza</i> , <i>Taraxacum mongolicum Hand</i> , <i>rhizoma corydali</i> , <i>Panax notoginseng</i> , <i>Radix Glycyrrhizae</i> . <i>Preparata</i>	Acetic acid	14	49% ³	30% ³	↑ Serum and mucosal EGF, ↑ EGFR	N/D	[51]
<i>Bacopa monniera</i>	HCl	10	91.8% ² in normal; 76.2% ² in diabetes	92.5% ² in normal; 71.5% ² in diabetes	N/D	N/D	[30]
<i>Azadirachta indica</i>	HCl	10	93.4% ² in normal; 91.2% ² in diabetes	92.5% ² in normal; 71.5% ² in diabetes	N/D	N/D	[30]
<i>Prumnopitys andina</i> wood and bark	Acetic acid	14	92.5% ⁴	79.6% ⁴	↑ Proliferation, antioxidant (only lipoperoxidation, no change in reduced glutathione content), ↑ PGE2	N/D	[52]
<i>Bupleuri Radix</i> , <i>Pinelliae Tuber</i> , <i>Scutellariae Radix Glycyrrhizae</i> , <i>Radix Cinnamomi Cortex</i> , <i>Ginseng Radix</i> , <i>Paeoniae Radix</i> , <i>Zizyphi Fructus</i> , <i>Zingiberis Rhizoma</i>	Cold water restraint stress	3 h	24% ²	N/D	N/D	N/D	[54]
<i>Coptidis Rhizoma</i> , <i>Scutellariae Radix</i> , <i>Phellodendri Cortex</i> , <i>Gardeniae Fructus</i>	Cold water restraint stress	3 h	62% ²	N/D	Antioxidant	N/D	[54]
<i>Bupleuri Radix</i> , <i>Paeoniae Radix</i> , <i>Aurantii Fructus Immaturus</i> , <i>Glycyrrhizae Radix</i>	Cold water restraint stress	3 h	20% ²	N/D	N/D	N/D	[54]
<i>Curcumin</i>	pyloric ligation	19 h	90.79% ²	N/D	Antioxidant, ↓ acid secretion, ↓ inflammation	N/D	[55]

¹Reduction in macroscopic damage score; ²Reduction in ulcer index; ³Reduction in ulcer size; ⁴Cure rate. bFGF: Basic fibroblast growth factor; MPO: Myeloperoxidase; N/D: Not determined; None: Not toxic; PGE2: Prostaglandin E2; VEGF: Vascular endothelial growth factor.

combination of herbal medicine and ranitidine exhibited a synergistic effect in treating gastric ulcer^[66-68]. Herbal medicines effectively cure gastric ulcer and prevent its recurrence. For example, one study showed that oral herbal tablets induced a 62.4% cure rate while the recurrence rate was 17.7% after 1-year follow-up. In contrast, treatment with ranitidine only achieved a 50.7% cure rate, and the recurrence rate was 54.1%^[69]. Likewise, oral combination of omeprazole and herbal medicine for 4 wk significantly reduced gastric ulcer recurrence rate (25%) compared with omeprazole alone (57.1%) after 6 mo follow-up^[70]. Taken together, these results demonstrate that herbal medicines alone are effective in treating gastric ulcer and preventing recurrence. Combination of herbal medicines and conventional regimens exhibits a synergistic effect in the management of gastric ulcer. Although all mixtures listed in Table 2 are effective for gastric ulcer, herbal medicines should be given according to each patient's internal conditions as defined by the theory of traditional Chinese medicine in order to gain an optimal benefit.

SAFETY

Although herb-drug interactions have raised safety concerns^[71,72], and some herbs can cause severe side effects^[73,74], herbal medicines used to treat gastric ulcer are

generally safe in both animal models and humans. For instance, *Myristica malabarica* extract at a daily dosage of 40 mg/kg accelerated ulcer healing in a mouse model of indomethacin-induced gastric ulcer^[18,19,75]. However, mice treated with oral *Myristica malabarica* extract at a dose of 500 mg/kg daily for 1 mo showed no observable physical sign of adverse effects. In addition, the histology and function of mouse liver and kidneys appeared normal^[18]. Likewise, oral *Gnaphalium grandiflora* extract at a dose of 500 mg/kg for 14 d induced an 83% cure rate of gastric ulcer induced by acetic acid^[24]. Mice fed *Gnaphalium grandiflora* extract at a dose of 5 g/kg per day for 14 d showed no significant differences in the weight of the heart, liver, kidney or lungs compared with those of the control group. None of the treated mice died during the 14 d of observation^[24]. Again, methanolic extract of *Alchornea glandulosa* at a dose of 250 mg/kg per day was more potent than cimetidine in treating acetic acid-induced gastric ulcer^[27]. Oral *Alchornea glandulosa* at 5 g/kg daily for 14 d caused no significant changes in weight of several organs, such as the liver, kidneys, heart, lungs, as well as spleen. Moreover, there were no dramatic differences in liver and renal function between control and herbal treatment^[27]. Furthermore, oral *Solanum nigrum* extract at a daily dose of 200 mg/kg for 7 d significantly reduced ulcer index (10.1 ± 0.91 for herbal extract vs 16.9 ± 1.4 for controls)^[35]. However, oral administration of *Solanum nigrum* extract

Table 2 Efficacy and safety of herbal medicines for gastric ulcer in humans

Herbal extracts	No. of patients (M/F)	Treatment course (d)	Efficacy		Adverse effects	Ref.
			Herbal extract	Positive control		
<i>Rhizoma Coptidis</i> , <i>Radix Sanguisorbae</i> , <i>radix paeoniae alba</i> , <i>rhizoma bletilla</i> , <i>Chickens Gizzard membrane</i>	60 (41/19)	42	Cure rate: 20% Effective rate: 85%	Cure rate: 10% Effective rate: 71.67%	None	[56]
<i>Radix Astragali</i> , <i>Radix Aucklandiae</i> , <i>Fructus Aurantii Immaturus</i> , <i>Cortex Magnoliae Officinalis</i> , <i>Chickens Gizzard membrane</i> , <i>radix notoginseng</i> , <i>radix paeoniae alba</i> , <i>Radix Scutellariae</i> , <i>Radix Glycyrrhizae</i>	50 (35/25)	60	Cure rate: 72% Effective rate: 96%	N/D	Vomiting in one case	[57]
<i>Radix Astragali</i> , <i>radix codonopsis</i> , <i>poria</i> , <i>Rhizoma Atractylodis Macrocephalae</i> , <i>dried orange peel</i> , <i>Radix Glycyrrhizae</i>	84 ¹ (43/41)	60	Effective rate: 92.9%	N/D	N/D	[58]
<i>Radix Bupleuri</i> , <i>Radix Codonopsis</i> , <i>radix paeoniae alba</i> , <i>rhizoma corydalis</i> , <i>rhizoma bletilla</i> , <i>margarita</i> , <i>indigo naturalis</i> , <i>radix glycyrrhizae</i>	26 (15/11)	28	Effective rate 92.3%	Effective rate 92.3%	Temporary diarrhea at beginning	[60]
<i>Margarita</i> , <i>borax</i> , <i>Rhizoma Coptidis</i> , <i>rhizoma bletilla</i> , <i>indigo naturalis</i> , <i>amber</i>	90 (N/D)	30	Cure rate: 88.9% Effective rate: 96.7%	Cure rate: 82.8% Effective rate: 89.7%	None	[61]
<i>Rhizoma curculiginis</i> , <i>Herba Epimedii</i> , <i>Radix Astragali</i> , <i>rhizoma bletilla</i> , <i>poria</i> , <i>Fructus Amomi</i> , <i>Radix Glycyrrhizae Preparata</i>	62 ² (44/18)	30	Cure rate: 82.3% Effective rate: 98.4%	Cure rate: 81.4% Effective rate: 93.0%	5 cases had dry mouth; 7 cases had constipation	[62]
<i>Radix Codonopsis</i> , <i>Herba Taraxaci</i> , <i>Radix Salviae miltiorrhizae</i> , <i>Rhizoma Atractylodes alba</i> , <i>Radix Glycyrrhizae</i>	30 (22/8)	56	Cure rate: 50% Effective rate: 86.7%	Cure rate: 40% Effective rate: 70%	N/D	[63]
<i>Ramulus Cinnamomi</i> , <i>Radix Paeoniae Alba</i> , <i>Radix Glycyrrhizae Preparata</i> , <i>Rhizoma Zingiberis Recens</i> , <i>Fructus Jujubae</i> , <i>Saccharium Granorum</i> , <i>Radix Cynanchi Paniculati</i>	80 (58/22)	28	Cure rate: 45% Effective rate: 93.75%	Cure rate: 10.26% Effective rate: 74.36%	N/D	[64]
<i>Radix Astragali</i> , <i>Taraxacum mongolicum Hand</i> , <i>tokyo violet herb</i> , <i>Bulbus Lilii</i> , <i>Radix Linderae</i> , <i>Radix Salvia miltiorrhiza</i> , <i>radix paeoniae alba</i> , <i>Radix Glycyrrhizae</i>	12 (ND)	28	Cure rate: 100%	Cure rate: 62.5%	N/D	[65]

¹Including gastritis; ²Including 41 cases of duodenal ulcer and 4 cases of gastric and duodenal ulcers. M: Male; F: Female; Cure: Clinical symptoms disappeared; Effective: Clinical symptoms improved; N/D: Not determined.

at dose of 4 g/kg per day for 14 d caused no changes in red blood cell count, white blood cell count, hemoglobin, hematocrit, or mean corpuscular volume^[35]. Finally, a number of clinical studies have demonstrated that herbal medicines are safe for humans. As seen in Table 2, only minimal adverse effects occur following herbal treatment in humans. Although these results indicate that herbal medicines are safe for treating gastric ulcer, special caution should be taken when using herbal medicines because of the potential adverse effects and herb-drug interactions.

MECHANISMS OF ACTION

Studies in humans and animal models suggest that herbal medicines exert their beneficial effects on gastric ulcer *via* multiple mechanisms, including antioxidant activity, stimulation of mucosal proliferation, inhibition of acid production and secretion, increased mucus production, as well as inhibition of inflammation (Figure 1).

Antioxidant activity

The link of oxidative stress and gastric ulcer is well recognized^[76]. That some herbal medicines benefit gastric ulcer is likely due to their antioxidant properties. In indomethacin-induced gastric ulcer models, the gastric levels

of malondialdehyde (MDA) were increased while the levels of superoxide dismutase (SOD) and catalase (CAT) were decreased^[20]. *Piper betel* extract treatment not only normalized MDA levels, but also significantly increased the levels of SOD and CAT with a comparable efficacy to misoprostol^[20]. Oral *Phyllanthus emblica* fruit extract for 7 d dramatically lowered gastric MDA levels and elevated the contents of reduced glutathione and CAT^[22]. Likewise, oral administration of astaxanthin for 10 d not only reduced ulcer area, but also lowered MDA levels, while the activities of mucosal SOD, CAT and glutathione peroxidase (GSH-Px) were significantly increased^[46]. Regarding the involvement of NO (a reactive oxygen species), the results were controversial. Some studies showed that herbs that benefit gastric ulcer increased NO content in gastric tissue^[48,49,77,78], while others demonstrated that herbal extracts reduced inducible NO synthase^[39,41] and NO production^[39].

Stimulation of mucosal proliferation

Mucosal proliferation is required for ulcer healing. Certain herbal medicines that promote ulcer healing act *via* stimulation of cell proliferation. One study showed that oral *Centella asiatica* for 3 d stimulated cell proliferation and angiogenesis, and increased basic fibroblast growth factor expression^[25,60]. Moreover, oral ethanol extract of

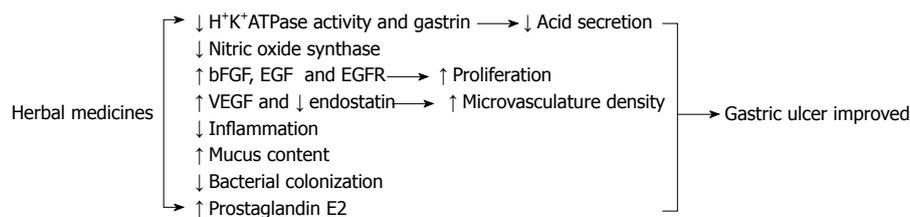


Figure 1 Schematic diagram of possible mechanisms by which herbal medicines benefit gastric ulcer. bFGF: Basic fibroblast growth factor; VEGF: Vascular endothelial growth factor; EGFR: Epidermal growth factor receptor.

Tabebuia avellanedae for 7 d also increased cell proliferation in acetic acid-induced gastric ulcer in rats^[44]. Stimulation of cell proliferation by herbal medicine could be attributed to upregulation of epidermal growth factor^[45,48,49,51] and its receptor expression^[45,51,78].

Inhibition of acid production

Inhibition of acid production can improve gastric ulcer^[79]. Many herbal medicines with anti-gastric ulcer activity reduce gastric acid secretion (Table 1). For example, oral *Ocimum sanctum* extract for 3 d induced a > 50% reduction in total gastric acidity^[26]. Similarly, oral *Solanum nigrum* fruits extract at a dose of 400 mg/kg lowered gastric acid concentration comparable to omeprazole (10 mg/kg)^[35]. Herbal medicine-induced reduction in acid production could be due to: (1) inhibition of H(+)/K(+)-ATPase activity, as demonstrated in animal models of gastric ulcer^[35,50]; or (2) stimulation of prostaglandin E2 production^[33,49,52,62,65].

Others

H. pylori infection is closely associated with peptic ulcers^[80]. Some herbal medicines that cure gastric ulcer can be attributed, at least in part, to their antimicrobial property. Oral *Croton lechleri* extract for 7 d induced an about 30% reduction in bacterial colony forming units in acetic acid-induced gastric ulcer^[42]. Some herbal extracts exhibit anti-inflammatory activity. For example, oral *Centella asiatica* extract for 3 d inhibited myeloperoxidase activity, which is a marker of neutrophil infiltration during inflammation^[81,82], at the ulcer site^[25]. Oral administration of *Croton lechleri* extract for 7 d resulted in an approximately 70% reduction in myeloperoxidase activity at the ulcer site in a rat model of gastric ulcer^[42].

Mucus consisting of mucin provides an important protective barrier against acid and pepsin^[83,84]. Certain herbal medicines cure gastric ulcer *via* increasing mucus production. One study showed that oral *Piper betel* extract for 7 d normalized gastric mucin levels with a comparable efficacy to misoprostol in a rat model of indomethacin-induced gastric ulcer^[20]. Another study revealed that gastric mucus content was normalized 5 h after administration of chitosan at a dose of 250 mg/kg in ethanol-induced gastric ulcer^[31]. A clinical study demonstrated that oral herbal mixture for 1 mo significantly increased mucosal MUC5AC (human mucin gene) level in patients with gastric ulcer^[66]. Pertinent to mucus, pepsin is also involved in the development of gastric ulcer *via* degrada-

tion of mucus^[85]. Studies demonstrated that anti-gastric ulcer herbs decreased pepsin content^[57] and activity in pyloric ligation-induced gastric ulcer^[49,57]. Collectively, these data indicate that herbal medicines benefit gastric ulcer *via* divergent mechanisms. The mechanisms whereby each herb or herbal mixture improves gastric ulcer are listed in Table 1.

In summary, herbal medicines are effective in treating gastric ulcer with fewer adverse effects and lower recurrence rates. Combination of herbal medicines and conventional anti-gastric ulcer drugs displays a synergistic effect against gastric ulcer. Thus, herbal medicines alone or in combination with conventional drugs could be used as an alternative for treating certain gastric ulcers and preventing recurrence. Only some anti-gastric ulcer herbal ingredients display antimicrobial properties^[42,86], thus, combination of herbal medicines and anti-*H. pylori* therapy could improve the outcome for patients with gastric ulcer.

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