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

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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 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.

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[5,6]. The recurrence rate is as high as 60%[7]. Gastric ulcer has a significant economic impact on both individuals and society.
impact. Average annual medical costs are $23819 for gastric ulcer in the United States\[^9\]. In South Korea, the annual medical costs for gastric ulcer range from $959.6 to $2553.10\[^10\]. 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 *Tencrium palium* 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 ± 1.46 mm\(^2\) for control, 1.13 ± 1.3 mm\(^2\) for *Qualea grandiflora* extract, and 1.63 ± 1.11 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 *Baopra monnieri* 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\[^18\]-\[^51\].

**Other gastric ulcer models:** Water immersion restraint stress results in formation of gastric ulcer via oxidative stress\[^52\]-\[^54\]. Ohta et al\[^51\] 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\[^57\]-\[^59\]. 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\[^60\]-\[^62\]. 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,
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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. |
|----------------------------------------|-------|----------------------|----------|---------------------|----------------|------|
| Myristica malabarica                   | NSAID | 3                    | 62%-86%1 | ↑ Mucus content, ↑ proliferation | None [18]       |      |
| Piper betel                             | NSAID | 7                    | 93.4%2   | ↑ Proliferation, ↑ inflammation | N/D [20]       |      |
| Teucrium polium                        | NSAID | 28                   | 90%2     | Antioxidant, ↓ mucus content | N/D [21]       |      |
| Phyllanthus emblica fruits             | NSAID | 7                    | 80%2     | Antioxidant | N/D [22]       |      |
| Beeswax                                | Acetic acid 3 h for 5 d | 56%-8% for Acetic acid | 65.8% for Acetic acid | ↑ Mucus production, ↑ Proliferation, ↓ acid secretion | N/D [23] |      |
| Qualea grandiflora                     | Acetic acid 14 | 83%4 | 76%4 | ↑ Mucus production | N/D [24]       |      |
| Centella asiatica                      | Acetic acid 7 | 50%4 | N/D | ↑ Proliferation, ↓ acid secretion | N/D [25]       |      |
| Ocimum sanctum Linn.                   | Acetic acid 20 | 92.75%3 | 87%3 | ↑ Mucus content, ↑ proliferation, ↓ acid secretion | N/D [26]       |      |
| Alchornea glandulosa                   | Acetic acid 14 | 43%4 | 16%4 | ↑ Proliferation, ↓ acid secretion | None [27]      |      |
| Radix Bupleuri, Radix Codonopsis, radix paeoniae alba, rhizoma cordatula, rhizoma bletilla, margarita, indigo naturalis, radix glycyrrhizae | Acetic acid 7-92 | 56%3 for 12 d | 27%4 for 7 d | ↑ Proliferation, ↑ inflammation, ↑ Microvasculature density, ↑ NF-kB mRNA and protein | N/D [28,29] |      |
| Bacopa monniera                        | Acetic acid 10 | 85.9%2 in normal; 52.5%2 in diabetes rats | 68%3 in normal; 41.8%4 in diabetes rats | ↑ Microvasculature density, ↑ NF-kβ mRNA and protein | None [30] |      |
| Azadirachta indica                     | Acetic acid 10 | 65.6%2 in normal; 71.5%4 in diabetic rats | 68%3 in normal; 41.8%4 in diabetic rats | ↑ Microvasculature density | N/D [30] |      |
| Chitonan, chinin                       | Acetic acid 14 | 60%2 | 46%2 | ↑ Acid secretion, ↑ mucus | N/D [31]       |      |
| Salvia miltiorrhiza                    | Acetic acid 5-30 | 31% for 5 d | 19% for 5 d | ↑ Proliferation | N/D [32] |      |
| Canodontera lucidum                    | Acetic acid 14 | 55.9%3 | 82.8%2 | ↑ Mucus content, ↑ PGE2 | N/D [33]       |      |
| Tea catechin                           | Acetic acid 14 | 66%4 | 59%7%3 | Antioxidant | N/D [34] |      |
| Solanum nigrum                        | Acetic acid 7 | 70.1%3 | 75.7%2 | H/K-ATPase activity, ↓ gastrin, ↓ acid secretion | None [35] |      |
| Cachinchina momordica seed             | Acetic acid 14 | 71.2%3 | N/D | ↑ VEGF (protein and mRNA), ↑ Microvasculature density | N/D [36] |      |
| Rhizoma Copitis Chinensis              | Acetic acid 10 | 53.86%3 | 36.47%2 | ↓ Acid secretion | N/D [37]       |      |
| Glycyrrhetic acid, β-sitosterol, berberine, baicalin and ginsenoside | Acetic acid 10 | 86.05%4 | 82.42%4 | ↓ iNOS, ↓ acid secretion, ↓ inflammation | N/D [38] |      |
| Curcumin and bisdemethoxycurcumin      | Acetic acid 10 | 51.9%4 | 83.3%4 | ↑ Mucus content, ↑ gastric secretion, ↓ acid secretion | N/D [40] |      |
| Bupleureum falcatum L.                 | Acetic acid 10 | 77.9%3 | 76.2%2 | None | None [41] |      |
| Plantago lanceolata L.                 | Acetic acid 14 | 55%3 | N/D | ↑ Bacterial colonization, ↑ MPO, ↓ iNOS, ↓ inflammation | N/D [42] |      |
| Croton lechleri                        | Acetic acid 7 | 7%4 | N/D | ↑ Proliferation, ↑ NO, ↑ EG | N/D [43] |      |
| Panax notoginseng, rhizoma bletilla, Poria cocos, Taraxacum mongolicum Hand | Acetic acid 10 | 36%3 | 48%3 | ↑ Proliferation, ↑ mucus content | N/D [44] |      |
| Tuberosia avellanoidae                 | Acetic acid 14 | 80%3 | 70%3 | ↑ Plasma EGF, ↑ EGFR, ↑ PCNA | N/D [45] |      |
| Sea buckthorn bark                     | Acetic acid 10 | 93.5%3 | N/D | Antioxidant, ↓ inflammation | N/D [46] |      |
| Astaxanthin                            | Acetic acid 3-7 | 95%3 for 3 d, 62% for 7 d | N/D | ↑ Mucus content | N/D [47] |      |
| Angelica sinensis                      | Acetic acid 16 | N/D | N/D | ↑ Proliferation | N/D [48] |      |
| Radix Aristolochiae, Potentilla bifurca L, Resina Draconis, Taraxacum mongolicum Hand, radix paeoniae alba, Sinusareas costus (Falcat.) Lipech, radix glycyrrhizae | Acetic acid 14 | 45.15%4 | 72.12%4 | ↑ Serum EGF, ↑ serum no, ↓ Acid secretion | N/D [49] |      |
| Rhiizma Atractlodis macrocephalae, Radix Linderae, Rhiizoma Dioscoreae, rhizoma bletilla, Pericarpium Citri Reticulatae Viride, Rhiizoma Alpiniae Officinarum, Radix Paeoniae Rubra, Herba Agrimoniae | Acetic acid 10 | 55%-60%3 | N/D | ↓ Inflammation | N/D [50] |      |
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Radix Codonopsis, Radix Adenophorae, Radix Angelica Sinensis, Rhizoma Chuanxiong, radix paeniae alba, Portia, Rhizoma Atractylodis macrocephalae, Radix Bupleuri, Radix Scutellariae, Rhizoma Coptidis, Fructus Aurantii Immaturus, Radix Salviae Militirrhiza, Taraxacum mongolicum Hand, rhizoma corydali, Panax notoginseng, Radix Glycyrrhizae.

Preparata

Bacopa monniera

Acetic acid 14 49%[^1] 30%[^3] ↑ Serum and mucosal EGF, ↑ Proliferation, antioxidant (only lipoperoxidation, no change in reduced glutathione content), ↑ EGFR

Azadirachta indica

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]

Prunus amygdalus wood and bark

Acetic acid 14 92.5%^4 79.6%^4 N/D N/D [52]

Bupleuri Radix, Pinelliae Tuber, Scutellariae Radix Glycyrrhizae, Radix Cinnamomi Cortex, Gingseng Radix, Paeniae Radix, Zizyphi Fructus, Zingiberis Rhizoma

Cold water restraint stress 3 h 24%^2 N/D PGE2 N/D N/D [54]

Aurantii Fructus Immaturus

Cold water restraint stress 3 h 62%^2 N/D Antioxidant N/D [54]

Bupleuri Radix, Paeniae Radix, Aurantii Fructus Immaturus, Glycyrrhizae Radix

Cold water restraint stress 3 h 20%^2 N/D N/D [54]

Curcumin

pyloric ligation 19 h 90.79%^3 N/D Antioxidant, ↓ acid secretion, ↓ inflammation N/D [55]

[^1]: Reduction in macroscopic damage score;  ^[^2]: Reduction in ulcer index;  ^[^3]: Cure 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[^6^-^8]. 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%^[^9]. 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[^10]. 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[^7^-^13], and some herbs can cause severe side effects[^14^-^16], 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]. 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[^20]. Likewise, oral *Gualda grandiflora* extract at a dose of 500 mg/kg for 14 d induced an 83% cure rate of gastric ulcer induced by acetic acid[^21]. Mice fed oral *Gualda 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[^22]. 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[^23]. 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[^24]. 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[^25]). However, oral administration of *Solanum nigrum* extract...
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\cite{13}. 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\cite{115}. 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\cite{20,48,49,77,78}. \textit{Piper betel} leaf extract treatment not only normalized MDA levels, but also significantly increased the levels of SOD and CAT with a comparable efficacy to misoprostol\cite{20}. Oral \textit{Phyllanthus emblica} fruit extract for 7 d dramatically lowered gastric MDA levels and elevated the contents of reduced glutathione and CAT\cite{20}. 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\cite{20}. 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\cite{69,70,71,72,73}, while others demonstrated that herbal extracts reduced inducible NO synthase\cite{69,41} and NO production\cite{15}. Moreover, oral ethanol extract of

### 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. |
|-----------------|-----------------------|----------------------|----------|-----------------|------|
| Rhizoma Coptidis, Radix Sanguisorbae, radix paonae alba, rhizoma bletilla, Chickens Gizzard membrane | 60 (41/19) | 42 | Cure rate: 20% | Cure rate: 10% | None | [56] |
| Radix Astragali, Radix Aucklandiae, Fructus Aurantii Immaturus, Cortex Magnoliifoliae Officinalis, Chickens Gizzard membrane, radix notoginseng, radix paonae alba, Radix Scutellariae, Radix Glycyrrhizae | 50 (35/25) | 60 | Cure rate: 72% | Cure rate: N/D | Vomiting in one case | [57] |
| Radix Astrogali, radix codonopsis, poria, Rhizoma Atractylodis Macrocephalae, dried orange peel, Radix Glycyrrhizae | 84 (43/41) | 60 | Cure rate: 92.9% | Cure rate: N/D | None | [58] |
| Radix Bupleuri, Radix Codonopsis, radix paonae alba, rhizoma corydalis, rhizoma bletilla, margarita, indigo naturalis, radix glycyrrhize | 26 (15/11) | 28 | Effective rate: 92.3% | Effective rate: 92.3% | Temporary diarrhea at beginning | [60] |
| Margarita, herba, Rhizoma Coptidis, rhizoma bletilla, indigo naturalis, amber | 90 (N/D) | 30 | Cure rate: 88.9% | Cure rate: 82.8% | None | [61] |
| Rhizoma curcaselignis, Herba Epimedi, Radix Astragali, rhizoma bletilla, poria, Fructus Anomi, Radix Glycyrrhizae | 62 (44/18) | 30 | Cure rate: 82.3% | Cure rate: 81.4% | 5 cases had dry mouth; 7 cases had constipation | [62] |
| Radix Codonopsis, Herba Taraxaci, Radix Salviae miltiorrhize, Rhizoma Atractylodis alba, Radix Glycyrrhizae | 30 (22/8) | 56 | Cure rate: 50% | Cure rate: 40% | N/D | [63] |
| Ramulus Cinnamomi, Radix Paonae Alba, Radix Glycyrrhizae Preparata, Rhizoma Zingiberis Recens, Fructus Jujubae, Saussurium Cramorum, Radix Cynanchi Paniculati | 80 (58/22) | 28 | Effective rate: 86.7% | Effective rate: 70% | N/D | [64] |
| Radix Astragali, Taraxacum mongolicum Hand, tokyo violet herb, Balbus Lii, Radix Lindereae, Radix Salviae miltiorrhize, radix paonae alba, Radix Glycyrrhizae | 12 (ND) | 28 | Cure rate: 100% | Cure rate: 62.5% | N/D | [65] |

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

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**Table 1.** Herbs and herbal ingredients that show anti-ulcer activity. The numbers represent the percentage of studies showing efficacy. The rows of the table are listed in descending order of efficacy. 

| Herb/Herbal Mixture | Percentage of Studies | Notes |
|---------------------|-----------------------|-------|
| *Croton lechleri* | 100% | Anti-inflammatory, antimicrobial properties. |
| *Tabebuia avellanedae* | 75% | Antimicrobial properties, reduces gastric acid secretion. |
| *Solanum nigrum* | 50% | Anti-inflammatory, antimicrobial properties. |
| *Ocimum sanctum* | 25% | Anti-inflammatory, antimicrobial properties. |

**Figure 1** Schematic diagram of possible mechanisms by which herbal medicines benefit gastric ulcer. 

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