

Phytotherapy of Gastric Ulcer (Literature Review)

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Abstract: Pharmacotherapy of diseases of the stomach and duodenum should be aimed at restoring and normalizing the interaction of acid-pepsin and gastroduodenal mucosa protectors in the gastric mucosa. Peptic ulcer disease is a common disease that affects millions of people and has a high recurrence rate. "No stomach acid, no ulcer" is a false assumption. Excessive secretion of gastric acid is only one factor in the pathogenesis of peptic ulcer disease. Their etiology is multifactorial, both offensive and defensive. It develops when the balance of its components is disturbed. Due to the limited efficacy and serious side effects of currently available drugs, its treatment faces great difficulties. Natural products such as plants and their isolated compounds have been widely used in experimental models of gastric ulcer. In these studies is a literature review of flavonoid-containing herbal plants showing ulcer activity in experimental models using different mechanisms of action.

Keywords: gastric ulcer, pathogenesis, etiology, prevention of peptic ulcer, medicinal plants

Introduction: The last few decades have seen an increase in the use of plants in the field of medicine. The use of herbal medicines for the prevention and treatment of various pathologies is constantly expanding throughout the world [1,2]. It is popular in developed and developing countries due to its natural origin and less side effects. According to the World Health Organization, 80% of the world's population uses indigenous medicinal plants [3,4]. Several plants have been used to treat gastrointestinal disorders. In particular, in the treatment of gastric ulcer, in addition to synthetic means, **aloe** [5], **kalanchoe juices** [6], **ginger** [7], **propolis** [8], **oleander** [9], **nematok oils, bergenia** [10], **licorice** [11] are used today.] and preparations of many other plants are used as phytotherapeutic agents. Currently, many individual components have been isolated from plant materials and their biological activity has been determined in pharmacological tests. Among natural polyisoprenoids and carotenoids, various terpenoids and saponins, phenolic compounds, flavonoids, and alkaloids, antiulcer active substances have been found [12].

Phytochemical investigation of the root of *Glycyrrhiza glabra* revealed the presence of alkaloids, glycosides, carbohydrates, starches, phenolic compounds, flavonoids, proteins, pectins, mucilages, saponins, lipids, tannins, and steroids [13]. In experimental and clinical studies, licorice has been shown to have a number of pharmacological properties, including anti-inflammatory, antiviral, antimicrobial, antioxidant, anti-diabetic, anti-asthmatic and anti-cancer, as well as immunomodulatory, gastroprotective, hepatoprotective, neuroprotective and cardioprotective effects [14]. In recent years, several biochemical, molecular and cellular mechanisms of licorice and its active components have also been demonstrated in experimental studies. Akbar S. - according to the information provided by [15] In the 1950s, the first scientific articles appeared about gastric ulcers that healed after licorice treatment. It continues to be used in traditional medicine and remains a subject of scientific interest and is being investigated for various activities. Licorice (***Glycyrrhiza glabra* - G. glabra**) has been regularly used in traditional Chinese medicine for centuries for its anti-ulcer, antioxidant, antimicrobial, and antiviral activity. These characteristics can be confirmed by a number of conducted experiments. One of the reasons why peptic ulcers are common among the population of many countries is alcohol consumption.

A. E. In their experiment, Ligha and colleagues [16] investigated whether licorice, a plant belonging to the Fabaceae family, has a protective effect on the gastric mucosa. For this, gastric mucosa of rats was injured with 80% etonol. The treated group was administered 200 mg/kg licorice extract before alcohol-induced gastric mucosal injury. Histological studies, gastric ulcer index, alkaline phosphatase (IF), lipid peroxidation product, which is an indicator of lipid peroxidation (LPO), were studied. Prophylactic administration of

licorice has been shown to protect against etonol-induced gastric mucosal damage. The results show that licorice extract significantly protects the mucosa and exerts antioxidant effects on the gastric mucosa in rats. It was said above that *Helicobacter pylori* is the causative agent of gastritis and peptic ulcer disease. *Helicobacter pylori* eradication therapy is difficult and often requires multiple antibiotic regimens. These regimens are very expensive and have serious side effects. Jafarian M. and other scientists [17] studied the sensitivity of licorice extract to *Helicobacter pylori* at doses of 25, 50, 100, 150, 200, 300 and 400 mg/ml. Licorice extract inhibited *Helicobacter pylori* strains with a dose range of 50-400 mg/ml. The present results show that the therapeutically applied concentration of licorice extract had an inhibitory effect on the growth of *Helicobacter pylori* in vitro. Unlike antibiotics currently used in *Helicobacter pylori* treatment regimens, it has the advantage of leaving the normal bacterial flora of the body intact. Akbar S. According to [18] a former German commission considered licorice plant Formen E to be effective in the treatment of atopic dermatitis. Al-Snafi A. E. et al. [19] evaluated the anti-inflammatory activity of a hydroalcoholic extract of the root of *Glycyrrhiza glabra* against carrageenan-induced rat paw edema at oral doses of 100, 200, and 300 mg/kg in rats. Hydroalcoholic extract of *Glycyrrhiza glabra* at a dose of 200 mg/kg maximally (46.86%) reduced carrageenan-induced paw swelling and inhibited leukocyte migration in a dose-dependent manner. *Glycyrrhiza glabra* has been shown to inhibit SOG-2 [219] Glycyrrhizin has shown steroid-like anti-inflammatory activity similar to hydrocortisone due to its inhibition of phospholipase A2 activity[220]. Hashem A. et al [20] showed that licorice was more effective and safer than ranitidine in wound healing. Licorice shows strong anti-ulcer activity and has been shown to be safer in liver and kidney function compared to the standard commercial drug. Nugroho A.E. et al. [21] examined the antiulcer effect of licorice and its derivatives in the aspirin gastric ulcer model in laboratory animal experiments. Granular aspirin alone and mixtures coated with licorice or licorice derivatives, including the deglycyrosylated form, the highly glycyrrhized form, carbenoxolone, and enoxolone, were studied. Licorice-coated aspirin reduced the number and size of ulcers, reducing morbidity from 96% to 46%. De.H. Another study by Rohr [224] examined the protective effects of licorice or its derivatives against oral ibuprofen-induced gastric ulceration. Ibuprofen was studied alone or as a granular mixture coated with licorice or its derivatives, including deglycyrrhized licorice (DGL), highly glycyrrhized licorice (HGL), enoxolone (glycyrrhetic acid), and carbenoxolone. Ibuprofen coated with licorice, DGL, or enoxolone reduced the number and size of ulcers, the ulcer index from 1.86 to 1, and the incidence from 100 to 59%. Da Nagaoet et al [22] Licorice - *Glycyrrhiza glabra* has been found to promote healing by improving mucus production and blood supply to damaged gastric mucosa. Masoomah and Kiarash [21] reported the anti-ulcer effect of licorice root through inhibition of gastrin secretion in their experiments. Also Wittschietal. in their study[22] showed that licorice extract was effective in preventing *Helicobacter pylori* infection from adhering to the gastric mucosa and thus preventing gastric ulceration. In addition, Momeni A. et al. [23] in 2014 noted that *G. Glabra* extract is as effective as bismuth in preventing *Helicobacter pylori* and recommended effective treatment with licorice extract for patients who cannot take bismuth. Hajiagha Mohammadi and others [25] in 2016 *G. glabra* adding licorice to a triple clarithromycin-based regimen increases *Helicobacter pylori* eradication, especially in the presence of peptic ulcer disease. Nugroho A. E. in own studies [26] *Glycyrrhiza glabra* showed antiulcerogenic effects by increasing mucin secretion and prostaglandin E2 release and decreasing leukotrienes. This plant has also demonstrated antioxidant and anti-inflammatory activity, which may play a role in its antiulcerogenic effects. These activities are closely related to the flavonoids contained in it. Due to its strong gastroprotective activity, the plant is used as an anti-ulcer agent in the treatment of gastric ulcer. This medicinal plant is often combined with other plants for this purpose. Jalilzadeh-Amin G. [27] and others studied the gastroprotective property of *Glycyrrhiza glabra* in experimental mice by immobilization stress method. After 18 hours of starvation, *Glycyrrhiza Glabra* L (50, 100, 150 and 200 mg/kg), cimetidine (100 mg/kg) and saline (10 ml/kg) were administered orally to the animals. One hour after treatment, mice were immobilized in a plastic cage for 4 hours at 4°C to induce gastric ulceration. As a result, the gastroprotective effect of licorice was proven. Isbrucker R. A., Burdock G. A. et al[28] reported that the main and most consistent medicinal use for licorice was as a digestive sedative. Peskar B. M. According to [29], licorice dose-dependently inhibits the activity of 15-hydroxy-PG-dehydrogenase and delta 13-PG-reductase, enzymes involved in prostaglandin (PG) metabolism, in vitro, while this drug does not affect gastric mucosal PG synthesis at the same doses. *Glycyrrhiza Glabra* L inhibits gastric mucosal PG-inactivating enzymes both in vitro and in vivo. Thus,

decreased inactivation of cytoprotective PGs synthesized in the gastric mucosa may contribute to the wound-healing effect of carbenoxolone [30]. Rahnama M. et al. [31] aimed to compare quadruple therapy of amoxicillin, metronidazole, omeprazole and bismuth subnitrate in gastric ulcer patients with bismuth subnitrate replaced by licorice in 40 gastric ulcer patients referred to the Gastroentero-Hepatology Research Center of Shiraz University of Medical Sciences. divided into equal groups. All patients underwent endoscopic examination for histological evaluation of peptic ulcer and the presence of bacteria was confirmed by urease breath test. The first group included amoxicillin (500 mg, 3 times a day after meals for 15 days), metronidazole (250 mg, 4 times a day after meals for 15 days), omeprazole (20 mg, 2 times a day ½ hour before meals for 30 days), and bismuth subnitrate (500 mg, 3 times a day, ½ hour before meals for 30 days). In group 2, the regimen was the same, but licorice was replaced by bismuth subnitrate (250 mg, 3 times a day, half an hour before meals for 30 days). After one month of therapy, all patients underwent endoscopy again, providing a biopsy for histological examination to determine the rate of ulcer healing and a urease breath test to demonstrate the degree of eradication of *Helicobacter pylori*. Pain relief was also assessed. The study was approved by the University Ethics Committee and informed consent was obtained from each participant. 15 men and 5 women of group 1, 11 men and 9 women of group 2. Pathologically, the eradication effect against *Helicobacter Pylori* in group 1 was (45%) and in group 2 (70%). Based on urease breath test results, these rates were 55% and 40%, respectively. There are some studies to confirm the results, the positive effect of licorice in peptic ulcer was more. Studies have shown that licorice can be offered as a replacement for quadruple therapy, being inexpensive, highly tolerable, and with minimal side effects. Licorice (*Glycyrrhiza glabra*) plant has been used as medicine since ancient times. Currently, it is a well-known spice with pharmacological effects. However, some related articles have identified negative health effects of licorice [234]. Given the great interest in the use of medicinal plants, it is important to highlight the adverse health effects of herbal medicines. Currently, there are misunderstandings about the safety of herbal medicines. Here, we have collected scientific research projects on the toxic effects of licorice and glycyrrhizin to highlight their safety. In this regard, we classified our findings on the toxic effects of licorice and glycyrrhizin in acute and chronic conditions. In addition, we talked about the cytotoxicity, genotoxicity, mutagenicity and carcinogenicity of licorice and glycyrrhizin, as well as their developmental toxicity. This review *G. glabra* and glycyrrhizin salts were found to be moderately toxic. They should be used with caution during pregnancy [32]. *G. glabra* and glycyrrhizin have selective cytotoxic effects on cancer cells [33]. The most important side effects of licorice and glycyrrhizin are secondary to hypertension and hypokalemia [34]. Nazari S., Rameshrad M., et al. Licorice consumption during pregnancy significantly reduces gestational age [33] and induces preterm birth [35]. This may be due to the effects of licorice on cortisol and prostaglandin metabolism [34,36]. Kwon Y. J. et al [37] active metabolites in licorice extract are glycyrrhizic acid and glycyrrhetic acid. Glycyrrhetic acid is a more potent metabolite and has corticosteroid-like properties. There are two stereoisomers of glycyrrhetic acid: 18 α -glycyrrhetic acid and 18 β -glycyrrhetic acid. These two stereoisomers have different bioactivity: 18 α -glycyrrhetic acid selectively inhibits the enzyme 11 β -hydroxysteroid dehydrogenase-1 (11 β -HSD). Cortisol catalyzes the interconversion between active and inactive cortisone. (11 β -HSD) enzyme converts inactive cortisone to active cortisol in glucocorticoid target tissues such as adipose tissue, skeletal muscle, and liver. (11 β -HSD) regulates tissue-specific effects of circulating glucocorticoids. Thus, inhibition of (11 β -HSD) by glycyrrhetic acid may improve insulin resistance and type 2 diabetes. The enzyme 11 β -hydroxysteroid dehydrogenase-2 (11 β -HSD2) follows two main physiological pathways. First, an enzyme converts active cortisol to inactive cortisone. Second, it plays a role in preventing excess stimulation of mineralocorticoid tissues by cortisol. Interestingly, only the (11 β -HSD2) isomer is protective, so the (11 β -HSD)-deficient mouse does not have elevated mineralocorticoid levels. Thus, glycyrrhetic acid may enhance glucocorticoid-like effects, in addition to presenting potential mineralocorticoid risks. The main pharmacological mechanisms of glucocorticoids are mainly divided into immunological and metabolic effects. Glycyrrhetic acid has a greater effect on immunological responses [38]. Glycyrrhizin acts as an immunoregulator by inhibiting the activation of T cells and cytokines [39]. Many studies have been conducted to determine the effect of glycyrrhizin on the underlying inflammatory or autoimmune mechanisms of various skin diseases. Licorice T cell cytotoxicity, interferon- γ (IFN- γ) and interleukin (IL)-12. exerts an antiviral effect by enhancing T cell-mediated immunity by regulating Increases the rate of *Helicobacter pylori* eradication [37]. Adele and others. [40] licorice secondary metabolites are

known to have an anti-pepsin effect, which prolongs the life of gastric mucosal cells. Mamedov N. A., Egamberdieva D. P [41] licorice (*Glycyrrhiza*) is a leguminous plant, the roots of which have been used industrially worldwide as medicine. It is estimated that more than 400 compounds have been isolated from *Glycyrrhiza* species, where triterpene saponins and flavonoids are the main constituents showing a wide range of biological activities. Triterpenoid saponins (glycyrrhizin, glycyrrhizic acid), which are the main characteristic components of licorice, are responsible for the sweet taste. Major phenols include licuritin, isoliquiritin, and coumarins, including licuritin and glabrocoumaron A and B. Pharmacological studies have confirmed that plant extracts and individual biologically active compounds exhibit a wide range of biological activities such as antimicrobial, anti-ulcer, anti-tumor, antioxidant, anti-allergic, neuroprotective, anti-inflammatory, hepatoprotective and dermatological activities. Reddy V. T., Kumar S. H. H., Bakshi V. [42] focused on the evaluation of the anti-ulcer activity of the herbal combination of aloe vera and licorice. In this new approach, the anti-ulcer activity of licorice root extract was studied in rats and compared with omeprazole as a standard. Aspirin induced ulcers in rats using an experimental model. The anti-ulcer plant compound has significant activity in animal models compared to the standard drug Omeprazole. The results of this study show that aloe vera and licorice have anti-ulcer activity in an aspirin-induced acute wound model. Both models showed a significant reduction in gastric ulcers. Although the etiology of peptic ulcer is largely unknown, it is believed to result from an imbalance between aggressive factors and maintenance of mucosal integrity by endogenous defense mechanisms. To restore the balance, various therapeutic agents, including plant extracts (in experimental animals), are used to strengthen the protective mechanisms of the mucosa by inhibiting gastric acid secretion or increasing mucus production, stabilizing the epithelial surface, or enhancing prostaglandin synthesis. From the results discussed above, it can be concluded that aloe vera and licorice have anti-ulcer activity against an animal model for aspirin-induced gastric ulcer in rats. It showed no signs of toxicity in treated mice and rats at the tested dose level. In this study, the use of a combination of herbal preparations proved to be an effective alternative to chemical preparations. Thus, the anti-ulcer herbal mixture shows significant activity in aspirin-induced gastric ulcer.

Hypericum scabrum L. *Hypericum scabrum* is an erect, dichotomous, branched perennial rhizome of the Hypericaceae family. The roots are woody, 4-10 mm wide, the stems are numerous, reddish-purple, simple or less branched in the inflorescence, 20-50 cm high. The place of growth and distribution occurs on stony and gravelly slopes from the sub-mountain region to the middle mountain regions of Fergana, Tashkent, Samarkand, Jizzakh, Surkhandarya and Kashkadarya regions [46,47,48]. The chemical composition of the surface of the rough field and its pharmacological effects, as well as the properties of treatment of diseases in clinical conditions, were studied in depth. As a result, the presence of chemical compounds found in the surface of rough field land (flavonoids, vitamin C, carotene, organic acids, anthocyanins, tar, carbohydrates, etc.), gastrointestinal (ulcer, diarrhea, colitis, enterocolitis), oral cavity (gingivitis, stomatitis) and healing properties of wounds and burns were found to be the same [46,51,52]. Therefore, the VFM, approved by the General Department of the Ministry of Health of the Republic of Uzbekistan, (Quality Control of Medicines and Medical Equipment), was approved and it was allowed to use medicinal preparations in medical practice as astringent and antiseptic agents for the treatment of the above-mentioned diseases. Currently, the plant is used in various diseases (stomach, intestines, liver, heart, bladder). Red bean is highly antibacterial, and the sum of phenolic compounds shows antiviral activity. Moderate diuretic effect was found in the experiment. 10% tincture of flowers has a bacteriostatic and bactericidal effect on staphylococcus aureus, streptococcus, and *Escherichia coli* [53,54,55,61]. Ganji A. et al. [55] In an experimental study, *Hypericum scabrum* L. evaluated its anti-ulcer effect in rats through its effect on the antioxidant system. For this, the amount of lyridic peroxidation products under the influence of oxidative stress in experimental rats was determined. As a result of the experiment, the amount of catalase and superoxide dismutase decreased compared to the control. The combination of *Hypericum Scabrum* with a number of other medicinal plants, *Plantago major*, *Sambulous ebulus* and *Spartium junceum*, *Andrographis paniculata* has been proven to have anti-ulcer effects in experimental experiments in rats [56]. Olive oil extract of *Hypericum perforatum* L. is a popular folk remedy for wound healing in Turkey [57]. The effect of alcoholic extract of *Hypericum perforatum* on ethanol-induced experimental gastric ulcers was previously studied and potent antiulcer activity in rats was reported in the literature [58]. Additionally, olive oil maceration of *Hypericum perforatum* has been reported to be a popular

external home remedy for rapid healing of cuts and burns [59,60] **Mediasia macrophylla** is a perennial plant belonging to the Apiaceae family. The upper parts of the stems are 50-80 cm long, with leaves and flowers. Stems are round, sharply curved, sparsely hairy, widely branched in the middle. The leaves are thick, short along the veins on both sides, covered with hairs, rhizome leaves in short bands. Leaf bands are round, gray fluffy, the plate is in the form of an oblong triangle, divided into two and three parts. Distribution - it grows on rocky slopes, in the middle regions of the mountains. It is found in Tashkent, Kashkadarya and Surkhandarya regions. Chemical composition. Leaves, flowers and seeds contain vitamins A, C, E, B1, B2, B6, PP, as well as folic acid, choline. Use in medicine. In folk medicine, the decoction of the top part is used as an expectorant and tonic in the treatment of liver diseases, and is also used as a spice and flavor additive. Local people also use alcohol as a natural preservative, because meat and dairy products with the above-ground part of alcohol are preserved for a long time [62,63].

Ziziphora pedicellata Pazij is a perennial plant belonging to the Lamiaceae family. Stems are numerous, usually slightly curved, thin, lignified at the bottom, simple or branched at the top, finely hairy, often black, 20-40 cm high, leaves (medium) lanceolate or narrow-lanceolate, acute, lanceolate at the base. . The above-ground mass of the plant collected during flowering is used as a medicinal raw material.

Place of growth and distribution It grows on stony and gravelly slopes in the lower and middle regions of the mountains and is widespread in the Tashkent region. General distribution: Central Asia (West Tien-Shon). Chemical composition. The surface part contains up to 1.3% essential oil, organic acids, vitamins C, E, A provitamins, flavonoids, anthocyanins, mineral salts, microelements, etc. Application in medicine. Fenugreek herb is a good remedy to stimulate appetite, improve digestion, and treat hypertension and gallstones. For this purpose, it is consumed in the form of tea and decoction [63,64,65,66]. Mousavi Mobarake Sh., Rahnoma M, Bigdeli MR, Nasiri Semnani Sh. studied the effect of *Ziziphora clinopodioides* aqueous extract on acetic acid-induced gastric ulcer in rats In this experimental study, 60 Wistar rats weighing approximately 200-250 g were randomly divided into 4 groups: negative control, positive control, 1-experiment and experiment 2. One day after gastric ulcer, the experimental groups received *Ziziphora clinopodioides* aqueous extract for 14 consecutive days, and the positive control group received normal saline. Negative control animals received no substance. Wound evaluation of fibroblasts, neutrophils and macrophages per unit area was calculated after 14 days. Data were collected using SPSS 17 software and analyzed with one-way ANOVA and LSD tests. Results: Wound healing in the experimental group was significantly increased compared to the negative control and positive control groups ($p < 0.05$). Over time, the number of neutrophils and macrophages increased and the number of fibroblasts decreased in the experimental groups. Conclusion: *Ziziphora clinopodioides* extract is effective in the treatment of gastric ulcer induced by acetic acid [67,68,69].

Kalanchoe has been shown to have anti-ulcer activity in several studies. For example, it has an antioxidant effect by reducing the peroxidation of lipids, which develops under the influence of oxidative stress in experimental rats, thereby strengthening the protective mechanism of the gastric mucosal barrier [10,70,71].

Zingiber officinale Rose (medicinal Ginger, Ginger) has been used since ancient times in the treatment of gastrointestinal diseases. Its chemical composition contains useful elements. This root contains essential amino acids, carbohydrates, essential oils and cellulose. Ginger is very rich in vitamins (V-group vitamins, ascorbic acid, tocopherol, vitamin K should be highlighted). It also contains potassium, phosphorus, magnesium, iron, calcium, zinc and other micro and macro elements. It regulates food digestion [72,73,74].

Conclusions.

Drug therapy does not always meet the requirements of doctors, it is noted that these drugs are subject to side effects. In this regard, it is of great importance to search for the most reliable, effective, low-toxic drugs based on local raw materials, and at the same time, cost-effective treatment methods and introduce them to the treatment of these diseases.

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