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ANTIULCER EFFECT OF GLYCYRRHIZA GLABRA BY USING EXPERIMENTAL MODEL

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Abstract

In traditional medicine, Glycyrrhiza glabra L. is used to treat gastrointestinal conditions such as peptic ulcers. The antiulcerogenic efficacy and acute toxicity profile of Glycyrrhiza glabra L. (HEGG) hydroalcoholic extract were assessed in mice. Oral HEGG dosages ranging from 50 to 200 mg/kg were given to animals belonging to distinct groups. Positive controls included cimetidine (100 mg/kg) and omeprazole (30 mg/kg), respectively. The stomach was opened along its larger curvature, and the inside lining of the stomach was examined to assess the ulceration index.

The extract orally at 1600 mg/kg did not experience toxic symptoms or death. Oral LD50 was found to be 2950 mg/kg. The HEGG (50–200 mg/kg) demonstrated a noteworthy decrease in the ulcer index in ulcers caused by HCl and ethanol. Dose-dependent antiulcer efficacy against indomethacin-induced stomach lesions was demonstrated by G. glabra extract (50-150 mg/kg). The extract successfully prevented ethanol-induced stomach lesions from forming. Compared to omeprazole (30 mg/kg), the extract (200 mg/kg) has greater potency. When hypothermic stress caused gastric ulcers in mice, HEGG decreased the ulcer index, and its antiulcer activity was similar to that of cimetidine.

The findings showed that the hydroalcoholic extract of G. glabra had an antiulcergenic action that might be linked to an increase in defense components of the stomach mucosa.

Keywords:

Peptic Ulcer; Stress; Ethanol; Indomethacin; Glycyrrhiza glabra L.

Introduction:

There are about thirty species in the genus Glycyrrhiza, of which six species yield the delicious saponin Glycyrrhizic acid (GA), which is widely employed in the pharmaceutical and confectionery sectors across the globe (1). One of the first medicinal plants utilized was licorice, which is made from the roots and stolons of the Glycyrrhiza species as a peptic ulcer remedy (2). The chemicals found in liquorice root include flavonoids (liquritin, glabrol), isoflavones (glabrene, glabridin), chalcones (isoliquiritin), coumarines (liquocoumarin), and stilbenoides, along with trace amounts of essential oil and polysaccharides (3). Numerous research investigations have demonstrated the expectorant, diuretic, laxative, sedative, antipyretic, antibacterial and anxiolytic, antiviral, anti-inflammatory, and antioxidant properties of Glycyrrhiza glabra extract or its derivatives, primarily glycyrrhizin (4).

In clinical practice, gastric and duodenal peptic ulcers are the most prevalent gastrointestinal illnesses, affecting thousands of patients. While the exact causation of stomach ulcers is still unknown, imbalances in mucosal aggressive and self-protective elements are widely acknowledged to be the cause. Acid-pepsin secretion, cellular regeneration, mucus secretion, blood flow, mucosal barrier, prostaglandins, epidermal development (5), and Helicobacter pylori infection (6) all have an impact on its pathogenesis. Antacids, sucralfate, prostaglandins, muscarinic and histaminic antagonists, and proton pump inhibitors are among the specific therapy choices. Furthermore, hematological problems, weakness, hypersensitivity, and arrhythmia are among the negative effects that some of these medications may induce (7). It is therefore urgently necessary to look for a better, more natural option that has fewer adverse effects for treating peptic ulcers.

Numerous experimental studies (2, 3, 5, 7) have been conducted to identify and create ulcer-healing agents using different substances derived from plants in order to get around the disadvantages. Therefore, the current study's goal was to confirm the antiulcer function that G. glabra is thought to have. In order to further understand its antiulcer properties, the hydroalcoholic extract of G. glabra was tested on four experimental models of acute gastric ulcers .

The identification of Helicobacter pylori in 1982 significantly altered our knowledge of how ulcers occur in general. Treatment methods have changed and our understanding of the pathophysiology and etiology of ulcers has improved since the identification of H. pylori.The idea that an acid-driven mechanism causes ulcers was replaced with the knowledge that aspirin and H. pylori are both significant factors. The current focus of ulcer treatment efforts should be on reducing the role that aspirin plays in ulcer development and eliminating H. pylori with antibiotics. It is astonishing to learn that over 50% of people on the planet suffer from a chronic H. pylori infection, and that between 5% and 10% of those people will experience symptoms such as ulcers.(8)

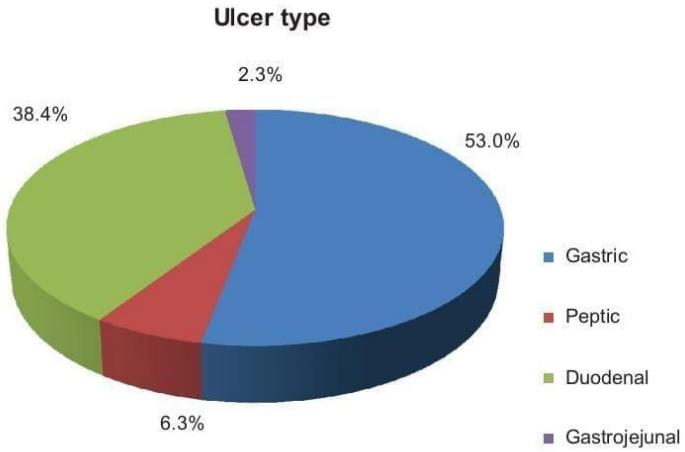

Figure 1 Hospitalizations based on ulcer type from 1998–2005.

Despite the fact that H. pylori infection is frequently linked to PUD, many infected individuals do not exhibit any symptoms, making diagnosis difficult.(9) It is known that an untreated peptic ulcer perforation can lead to serious consequences, including perforations, and even death.(10,11)

While effective GI protection therapy may be able to disguise or postpone the onset of symptoms in some high-risk patients, any delay in obtaining the proper diagnosis may raise the risk of consequences and death. Nearly 30% of related upper GI events among patients with symptomatic ulcers result in hospitalization or death,(12,13) and the overall direct and indirect costs for PUD have been estimated to be around $3.4 billion.(14) Therefore, one crucial step in preventing the progression of simple ulcers into complex ulcers is to evaluate patients for H. pylori infection.

The use of NSAIDs, such as aspirin, and H. pylori infection are independently linked to gastrointestinal side effects that can range from mild dyspepsia to severe GI bleeding, and they may also raise the risk of PUD.(15)There are additionally, albeit far less prevalent causes of PUD (Table 1).(16) Even in individuals without an H. pylori infection, aspirin use is frequently linked to ulcers.Thirteen About 40% to 50% of patients

experience GI mucosal injury after receiving daily low-dose aspirin (LDA); GI hemorrhage is also seen to be more likely in these patients. These risks usually rise with patient age and peak closer to the start of therapy.

Table 1 General classifications of peptic ulcers

Aspirin use	*H. pylori* infection	
	Yes	No
Yes	*H. pylori* and aspirin-positive	Aspirin-induced
No	*H. pylori*-positive	Other rare causes – Acid hyper-secretion (eg, Zollinger-Ellison syndrome) – Tumors – Crohn's disease – Viral infections – Idiopathic ulcers

Abbreviation: *H. pylori, Helicobacter pylori.*

Because 15% of patients with ulcer bleeding report recurrent bleeding within a year, it is vital to take the patient's history of GI bleeding into account. Accordingly, doctors should be aware that during the duration of aspirin medication during cardiovascular disease therapy, patients may get silent ulcers. Patients without a history of aspirin use or H. pylori infection may very rarely develop ulcers.

Owing to the combination of these factors, the optimal course of treatment for all patients with ulcers should involve testing for H. pylori infection, even if the patient is taking aspirin. There could be serious clinical repercussions for certain patients that go beyond GI hemorrhage. Patients should be referred for upper endoscopy if they still have recurrent PUD symptoms. Although GI bleeding is a common reason for surgery, other factors such as high-risk factors (such as a history of PUD or dependence on NSAID or steroid therapy) and the development of complications from PUD, as well as unresponsiveness to therapy or the need for multiple rounds of medical therapy for ulcers, may make surgery more necessary. For these patients, surgical options include oversewing of the blood vessel and gastroduodenotomy; in the case of bleeding gastric ulcers, vagotomy and drainage/partial gastrectomy are used to excise the ulcer.(20)Angiography is a possibility if endoscopy is not successful (bleeding persists) or if the patient is not a good candidate for surgery.

Ulcers brought on by aspirin

One of the most popular drugs in the US is aspirin, which is prescribed for a wide range of conditions.(22)Moreover, it can be easily obtained over-the-counter.(23) Aspirin was once developed as a pain and inflammation reliever, but because of its antiplatelet characteristics, it is now frequently used as a preventative measure for cardiovascular disease.

While aspirin doses between 75 and 325 mg daily are typically prescribed as antiplatelet therapy for primary and secondary prevention of cardiovascular and cerebrovascular events, standard aspirin doses ranging from 500 to 1,000 mg daily are typically prescribed for inflammatory conditions and pain relief.(24, 25) The recommended daily allowance (LDA) for cardiovascular disease is either 300 mg or 162 mg; however, it will be designated as #325 mg for the review purpose.

Antithrombotic medications all cause bleeding, but aspirin raises the risk of severe bleeding by approximately 60%.Long-term bleeding and intracranial or significant extracranial events are linked to LDA (26) although the upper gastrointestinal tract is also frequently affected by aspirin side effects (27). These include modest ailments like dyspepsia and more serious side effects including PUD and severe gastrointestinal hemorrhage.More than 50% of aspirin users who use the drug chronically also experience lower GI bleeding, suggesting that GI damage is not just confined to the upper GI tract.

Over the course of the last 20 years, aspirin has become one of the most common causes of peptic ulcer bleeding in developed nations (29), and it is linked to a 2- to 4-fold increased risk of upper gastrointestinal bleeding and ulcers.(3

The risk of ulceration can be significantly increased by combining aspirin and H. pylori, even though they cause ulcers through separate pathways (Figure 2).

Table 3 Classification of treatments for peptic ulcers

Ulcer treatment	Typical use	Rating	*H. pylori* status
PPI – Omeprazole – Pantoprazole – Lansoprazole – Rabeprazole – Esomeprazole	Standard treatment of *H. pylori*-positive and -negative ulcers; prevention of NSAID/aspirin-induced ulcers; intravenous administration for bleeding ulcers	Most potent acid inhibition	+ or –
***H. pylori* eradication + PPI**	Standard for *H. pylori*-positive ulcers	Most potent acid inhibition + cure for infection	+
H_2 receptor antagonists – Cimetidine – Ranitidine – Famotidine – Nizatidine – Roxaditine	*H. pylori*-negative ulcers	Acid inhibition	–
Prostaglandin analogs – Misoprostol	*H. pylori*-negative ulcers; prevention of NSAID/aspirin-induced ulcers	Weak acid inhibition	–
Bismuth salts – Subcitrate – Subsalicylate	Quadruple therapy for *H. pylori* eradication	Weak antibacterial effect	+
Phosphatidylcholine-aspirin – PL2200	*H. pylori*-negative ulcers; prevention of aspirin-induced ulcers	Acid inhibition	–

Depending on the type of ulcer, different recommendations are made for its treatment and long-term prevention. While patients taking aspirin are advised to adopt gastroprotective measures, such as a daily PPI or fixed-dose combination medication, patients with H. pylori-associated ulcers should undergo therapy tailored to H. pylori eradication (Figure 3).(32) A long-term H. pylori infection may cause asymptomatic chronic gastroenteritis, chronic dyspepsia, duodenal ulcer disease, gastric ulcer disease, or stomach cancer if left untreated.(33)

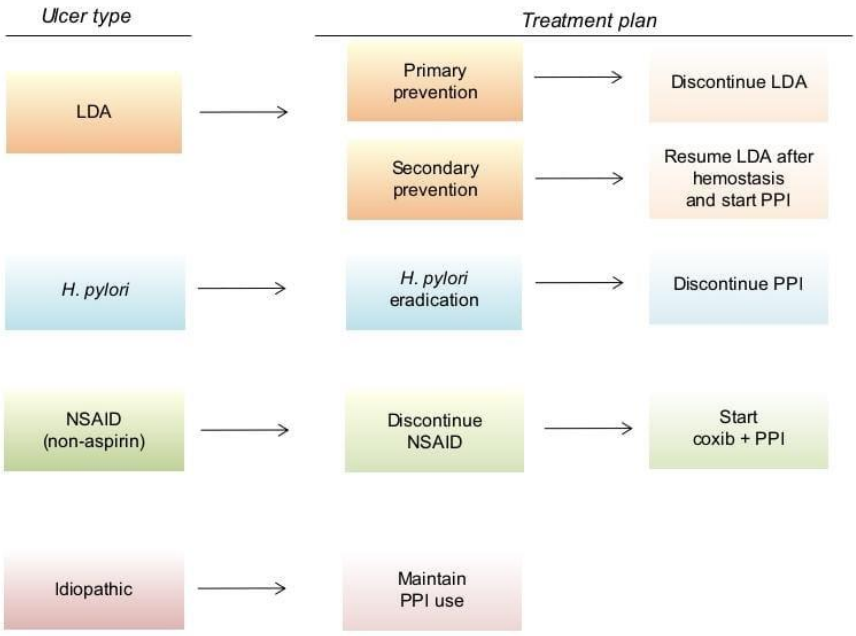

Figure 3 Flow chart of recommended management to prevent recurrent ulcer bleeding based on type. Reprinted by permission from Macmillan Publishers Ltd: American Journal of Gastroenterology. Laine L, Jensen DM. Management of patients with ulcer bleeding. *Am J Gastroenterol.* 2012;107(3):345–360. Copyright 2012.[3]

When H. pylori was eliminated or a PPI was given in addition to LDA, bleeding ulcer patients who were H. pylori-positive demonstrated a decrease in the frequency of recurrent bleeding.(34,35)Another study discovered that in individuals receiving LDA therapy who had previously experienced ulcer bleeding, eliminating H. pylori alone was adequate to lower the long-term risk of recurrent bleeding.(36) These findings point to a potential risk-reduction strategy that involves using a test-and-treat approach to eradicate H. pylori; however, it is yet unclear if this approach to lessen ulcer bleeding is financially advantageous.

Educating people about potential asymptomatic ulcers

In 46.9% of patient visits between 2007 and 2008, doctors recommended aspirin and other antiplatelet drugs for patients suffering from ischemic vascular disease.(37) Additionally, these data demonstrated that, for unknown reasons, cardiologists prescribed antiplatelet medications more frequently than primary care doctors (68% versus 35%, respectively).

Aspirin prescriptions should be accompanied by an increase in knowledge of the GI side effects associated with aspirin use. As the risk of GI side effects increases with dose escalation, the American College of Cardiology Foundation/American College of Gastroenterology/American Heart Association Task Force actually advises against routinely prescribing aspirin doses more than 81 mg.(39)

Patients at risk of GI side events should be provided gastroprotection at the commencement of LDA medication because the use of enteric-coated or buffered formulations of aspirin for cardioprotection is insufficient to limit the risk of GI hemorrhage.In the context of cardiology, proper examination of the patient's history and follow-up are crucial for risk stratification, management, and patient education regarding GI adverse events.

Patients at risk of GI side events should be provided gastroprotection at the commencement of LDA medication because the use of enteric-coated or buffered formulations of aspirin for cardioprotection is insufficient to limit the risk of GI hemorrhage.In the context of cardiology, a thorough evaluation of the patient's medical history and ongoing monitoring are crucial for risk assessment, treatment planning, and patient education regarding GI adverse events. One recommended tactic is to ask about the patient's medical history while writing a prescription, paying particular attention to the risk factors for gastrointestinal bleeding. If a patient has a history of illness, cardiologists will be aware of the necessity for gastroprotection or H. pylori screening. This strategy could aid in avoiding problems like ulcers down the road.

In general, H. pylori screening is advised for individuals who have a higher risk of ulcers in order to prevent the compounding impact of aspirin use and H. pylori infection. Speaking with the doctor about the signs and symptoms of peptic ulcers may help the patient identify a possible peptic ulcer before it becomes worse and possibly prevent any additional major issues.

Beyond the apparent health benefits, proper patient evaluation and physician awareness are beneficial. Patients who are prescribed an antibiotic eradication program and belong to the high-risk category for gastrointestinal bleeding may benefit financially from preventive and follow-up screening in addition to a reduction in adverse events.

The value of early noninvasive H. pylori testing for patients with suspected PUD has been shown by economic analysis. Even though the majority of patients will not benefit, costeffectiveness studies indicate that H. pylori testing and therapy are appropriate for all individuals with suspected PUD.Few regimens are able to satisfy the requirements of being easy, affordable, and successful, despite the fact that clinicians have a number of options for getting rid of H. pylori.(41) Furthermore, aspirin use alone makes it more challenging to diagnose an H.pylori-negativeasymptomatic ulcer, despite the fact that early detection of asymptomatic H. pylori infection may assist to lower the risk of ulcer formation.

Furthermore, aspirin use alone makes it more challenging to diagnose an H. pylori-negative asymptomatic ulcer, despite the fact that early detection of asymptomatic H. pylori infection may assist to lower the risk of ulcer formation. Although endoscopy is often unavailable or not always supported by health insurance for people who have no symptoms, endoscopic techniques are available and sensitive to this identification. Early detection can save major complications and save patients money, even though it's not always achievable.

Final thoughts and potential paths

It is commonly known that cardiovascular disease is the primary cause of death in the United States and many developing nations worldwide.(43) The use of LDA for cardioprotection has obvious benefits, but both symptomatic and asymptomatic patients have significant morbidity as a result of GI side effects.About one-third of asymptomatic people receiving LDA and gastroprotective medications have gastroduodenal ulcers and erosions, which has led guidelines to advocate aspirin usage exclusively in patients who have a risk of cardiovascular disease above a specific threshold.(44)(45)(46-49) Nonetheless, data from the National Hospital Ambulatory Medical Care Survey and the National Ambulatory Medical Care Survey show that 50%

of Medical Care Survey and the National Ambulatory Medical Care Survey show that 50% of patients who are considered suitable for LDA therapy also receive an aspirin prescription.

Although the GI effects of aspirin may result in substantial morbidity and mortality, a continued downward trend is observed for the rate of hospitalizations due to PUD over the past decade. The decline in PUD hospitalization rates is attributed in part to a decline in H. pylori infections due to awareness, improvements in antibiotic treatment regimens, and possibly trends in safer use of NSAIDs and gastroprotective agents.(51) Data such as these suggest an optimistic future where physician and patient awareness may reduce aspirininduced GI bleeding.

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