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*Original Research Article*

# The Counter-Effect of *Glycyrrhiza glabra* Against Gastrointestinal Tract Toxicity of Indomethacin on Rats

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ABSTRACT

*Glycyrrhiza glabra L.* has been used in treating various medical conditions, including stomach disorders such as flatulence and dyspepsia. Its anti-ulcer activity has been reported to be conflicting. The present study aims to evaluate the protective effects of *G. glabra* extract on indomethacin-induced gastritis and other gastrointestinal toxicities in rats. Thirty Wistar rats were used in the study and divided into three groups, ten rats in each group. Group I (Control) had free access to standard rat food and water; Group II (Test) had indomethacin administered orally at a dose of 30 mg/kg, given daily; Group III (Intervention) had an ethanol extract of *G. glabra* administered at 200 mg/kg body weight suspended in distilled water. *G. glabra* was collected locally in Egypt. The gastroprotective effect of the extract was studied in rats in combination with indomethacin. The present study shows that *G. glabra* extract significantly protects the stomach mucosa against indomethacin-induced gastritis in rats, where the inflammation grade caused by a combination of extract of *G. glabra* and indomethacin in the intervention group was less than that of the test group with indomethacin alone ($p < 0.01$). However, the inflammation grade of gastric mucosa in the intervention group was insignificant compared to the control group ($p > 0.01$). Furthermore, *G. glabra* extract significantly increases gastric pH, decreases the stomach's secretion volume and total acidity, and enhances serum iron, hemoglobulin, and vitamin B12 levels ($p \leq 0.05$). Based on the results of this study, it was concluded that *G. glabra* exerted a gastric protective effect.

***Keywords***: *Glycyrrhiza glabra L*; gastroprotective; indomethacin; gastritis; vitamin B12; iron, hemoglobulin

## Introduction

There are more than 23 species in the genus *Glycyrrhiza*. Roots of the *Glycyrrhiza* species (licorice) are among the oldest medicinal plants used to treat digestive disorders (e.g., gastric ulcers, hyperdipsia, flatulence, and colic).[1,2] *Glycyrrhiza glabra* roots contain several active substances, including liquirtin, rhamnoliquirilin, liquiritigenin, prenyllicoflavone A, and saponins, namely, glycyrrhizin.[3,4] Glycyrrhizin is the potent component in *G. glabra*;[5,6] there are many therapeutic effects associated with *G. glabra*, including expectorating, diuretic, laxative, hypnotic, antipyretic, antimicrobial, anxiolytic, antiviral, anti-inflammatory, and antioxidant effect. [7–9] It has been shown that non-steroidal anti-inflammatory drugs (NSAIDs), including indomethacin, can damage the gastrointestinal mucosa in experimental animals and humans, and their use has been linked to hemorrhage, erosion, and perforation of gastric and intestinal ulcers.[10,11]

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NSAIDs cause gastrointestinal toxicity by inhibiting cyclooxygenase, interfering with prostaglandin production and their action. When prostaglandin synthesis is suppressed, gastric mucosal blood flow is reduced, microcirculation is disrupted, mucus secretion decreases, lipid peroxidation occurs, and neutrophil activation contributes to gastrointestinal mucosal disorders.[12,13]

Gastritis is the gastric mucosa inflammation associated with gastric mucosal injury; this inflammation can be classified into acute and chronic gastritis according to the duration of mucosal inflammation. *Helicobacter pylori (H. pylori)* infection is among the predominant causes of chronic gastritis that could lead to gastric atrophy and intestinal metaplasia and could be diffuse (pangastritis or multifocal gastritis), antrum-predominant, or corpus-predominant. [14–16] Some studies have found that *H. pylori* infection may pass out in young children. However, this was not reported in adult patients.[17–19] Irritants such as bacterial endotoxins, alcohol, coffee, and aspirin consumption were reported as causes of acute gastritis characterized by transient non-specific dyspeptic symptoms.[20] Furthermore, it is self-limiting, and the symptoms of acute gastritis include heartburn, temporal gastric distress, vomiting, massive proximal and distal stomach mucosal inflammation (pangastritis), and, in severe cases, may develop bleeding and hematemesis.[21] Acute gastritis often correlates with hypochlorhydria, which may persist for months. The treatment options for acute gastritis include antacids, antibiotics, sucralfate, histamine-2-receptor antagonists, proton pump inhibitors, and many other agents. In addition, some of these treatments may cause side effects like hypersensitivity, arrhythmia, weakness, and hematopoietic disorders.[22] However, treating this problem with alternatives that could have minimal side effects is urgently needed. Several clinical studies [22,23] have been



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performed to investigate agents from various plant origins that could treat this condition.

The anti-inflammatory properties of the ethanol extract of *G. glabra* were investigated through several previous studies, which found that *G. glabra* can directly bind to lipoxygenase, producing inflammatory mediators.[24] Furthermore, *G. glabra* inhibits the activation of inflammatory mediators' phosphorylation.[25] Also, *G. glabra*, through their constituents, can inhibit the formation of inflammatory chemokines such as interleukin (IL)-8 and eotaxin 1, which are both considered strong chemo-attractants to leukocytes during inflammation.[25,26]

Various plant-origin substances act as natural drug enhancers, such as piperine, ginger, drumstick pod, licorice, black cumin, caraway, garlic, etc. However, only a limited number of these have been scientifically proven to improve the bioavailability of specific micronutrients in humans and animals upon consumption.[27,28] This study aimed to assess the protective role of *G. glabra* against indomethacin-induced gastritis in rats. In addition, we aimed to evaluate the effect of an ethanol extract of *G. glabra* on promoting the bioavailability of vitamin B12 and enhancing serum iron and hemoglobin levels.

## Materials and Methods

*Plant material*

Dried roots of *G. glabra L*. were purchased locally (Cairo, Egypt), collected from the El-Alaemeen coastal area, Sedi Abd El-Rahman, Egypt, during February–March 2023 and identified by Professor Rewaa S El-shatoury (Faculty of Agriculture, Suez Canal University, Egypt, Email: r_elshatoury@agr.suez.edu.eg) (#202004RA3). Roots were first cleaned and crushed using a sterilized electrical blender, and the obtained yellow-colored powder was stored in air-tight containers. A dipping method was used to prepare the dried root extract. [29] Next, 20 g of the powder was mixed with absolute ethanol (Sigma, Merck ®), ethanol: water (1:1), and water (sterile) using a powder solvent ratio of 1:5 (w/v) and permitted to stand at room temperature for 60 mins. The root extract was dipped in this extraction solvent. Hence, the glycyrrhizic acid was dissolved in the solvent.[30] The ethanol extract of licorice roots contains glycyrrhizin, isoliquiritin, and glycyrrhizic acid.[31]

*Gastric protection study in rats using indomethacin-induced gastritis*

The institutional research ethics committee approved the study protocol and animal care procedures (#202004RA3) at the Faculty of Pharmacy, Suez Canal University. Maximum efforts were applied to decrease animal suffering. The NIH guidelines for using and caring for laboratory animals (8th edition) were followed during the study. Qualified personnel were responsible for animal feeding, handling, and drug delivery throughout the research.

The study utilized Wistar rats that were two months old, weighed between 200 and 300 g, and were acclimated for three days before starting the present study.[32] They were randomized into three groups, each group having ten animals. They were starved for 36 hours, only having access to drinking water. Group I (Control) had free access to standard rat food and water. Group II (Test) had indomethacin dissolved in water and administered orally at 30 mg/kg (the quantity selected according to previous studies[33,34]), given daily. Group III (Intervention) had an ethanol extract of the roots of *G. glabra* at a dose of 200 mg/kg body weight daily. Aqueous preparation of extract of *G. glabra* was given orally 30 mins before indomethacin administration in the intervention group. The dose of ethanol extract of the roots of *G. glabra* was selected according to previous studies, where this dose shows a significant anti-ulcer effect without toxicity.[35]

Twelve weeks later (the period to induce gastritis was adopted depending on previous studies[36]), all stomachs of rats were removed after rats were sacrificed. Gastric mucosa for histological examinations were cut along the lesser curvature from the lower esophagus to the upper duodenum. Samples were immersed in buffered 40 g/L formaldehyde and embedded in paraffin. For the histological study, paraffin sections were sliced, mounted on glass slides, and stained with hematoxylin and eosin (H&E). Four inflammation grades were classified by a pathological diagnosis of chronic gastritis set up at the Huston symposium in 1994.[37] Inflammation grades of gastric antrum and body were semi-quantitative.

This study's L8 (27) orthogonal test comprised three study groups: control, indomethacin-treated, and intervention groups. Four typical signs of inflammation grades were described: 0: No inflammation, the presence of few leukocyte infiltrations in the gastric mucosa; 1: Mild inflammation, a few leukocyte infiltrations in the upper mucosa or at the bottom of the gastric glands; 2: Moderate inflammation, a large number of leukocyte infiltrations in the total mucosa; 3: Severe inflammation, extensive leukocyte infiltration in the entire mucosa. Each inflammation grading result was based on an average of grades of 10 fields under a microscope. Lamina propria thickness was measured at points 150 x10 μm from the forestomach boundary in the body and 150 x10 μm from the pyloric ring in the antrum, respectively. The pyloric ring area as a percentage of the total lamina propria area at the gastric antrum was 100 μm to 200 μm away. The parietal cells in each gland and the median number in each gland were calculated for the ten intact oxyntic glands at the above points in the gastric body.

*Gastric juice collection*

Dissection of the stomach was performed after opening the anterior abdominal wall. Two ml of distilled water was injected into the rat's stomachs after their pylorus and lower esophagus were tied. Each fore of the stomach was incised, and its contents were expelled. Tubes were used to collect gastric contents and measure their volume. For determining pH and total acidity, centrifugation of gastric juice was performed at 4,000 rpm for 15 mins.[38]

*Biochemical analysis*

The volume of gastric juice, pH, and total acidity were determined according to the standard methods reported by Parmar and Desai's study.[38] Hemoglobin serum concentration ($g/dL^{-1}$) was determined by the Colorimetric Detection method in whole blood samples using a Hemoglobin Assay Kit (ab234046, Abcam, Canada). Serum iron and vitamin B12 were measured after blood plasma separation by using Electrogenerated Chemiluminescence (ELC) immunoassay technology (Cobas, e 411, Roche diagnostic, Japan).

*Statistical analysis*

All data were analyzed using variance analysis of an L8 (27) orthogonal test. $p < 0.05$ was considered statistically significant.

## Results and Discussion

*Effect of inflammation grades on gastric mucosa*

As a control group, the normal glandular structure of the gastric mucosa was observed at both the base and the upper regions. Furthermore, the inner mucosa, submucosa, muscularis propria, and outer serosa were normal (Figure 1).

On the other hand, in the stomach of indomethacin-treated rats, some of the parietal cells and surface mucous cells were open to the lumen through short, narrow pits in the upper region of the cells. In addition, there was degeneration of columnar epithelium, goblet cells, and basement with congestion of blood, degeneration with necrosis at the tip of the villi, and goblet cell distortion (Figure 2).

Treatment with *G. glabra* improved the effects induced by indomethacin, and the cytotoxic effect on the architecture was reduced but still showed an abnormal appearance. Furthermore, there was erosion of mucin, degeneration of columnar tissue, degeneration of gastric glands/mucosa, and blood vessel distortion, but to a lesser extent than in indomethacin-treated rats (Figure 3).

At the antrum, the inflammation grade of gastric mucosa induced by indomethacin was 1.37, 1.56, and 1.70, respectively, on three repeated tests. It was significantly higher than the control and intervention group (ethanol extract of *G. glabra* plus indomethacin) (Table 1, Figures 1, 2, 3). The grade caused by a combination of extract of *G. glabra* and indomethacin in the intervention group was less than that of the test group with indomethacin alone ($p < 0.01$, Table 1, Figures 2, 3). However, the inflammation grade of gastric mucosa in the intervention group was insignificant compared to the control group ($p > 0.01$, Table 1).



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*Effect of the ethanol extract of G. glabra on gastric pH, volume, and total acidity*

As shown in Table 2, the indomethacin treatment group significantly increased the volume and total acidity and dramatically decreased the pH of gastric secretions ($p \leq 0.05$). Conversely, *G. glabra* reduced the stomach's volume and total acidity and increased the pH of gastric secretions ($p \leq 0.05$).

*Effect of ethanol extract of G. glabra and indomethacin on vitamin B12, iron, and hemoglobin content*

The effects of the ethanol extract of *G. glabra* and indomethacin on the plasma vitamin B12, iron, and hemoglobin levels of induced gastric ulcers in rats are illustrated in Table 3. Giving indomethacin to rats significantly reduced the level of vitamin B12 compared to the control group ($p \leq 0.05$). The reduction level was 24%, from 760.3 to 578.0 pg/mL$^{-1}$ in the control and test groups. In the intervention group, administering an ethanol extract of *G. glabra* treated the induced ulcer, which increased vitamin B12 levels because *G. glabra* is considered a vitamin bioavailability enhancer. The effect of the ethanol extract of *G. glabra* on intestinal absorption, particularly vitamin B12, is demonstrated through the increasing level of vitamin B12 from 578.0 to 793.2 pg/mL$^{-1}$ in the test and intervention groups, respectively.

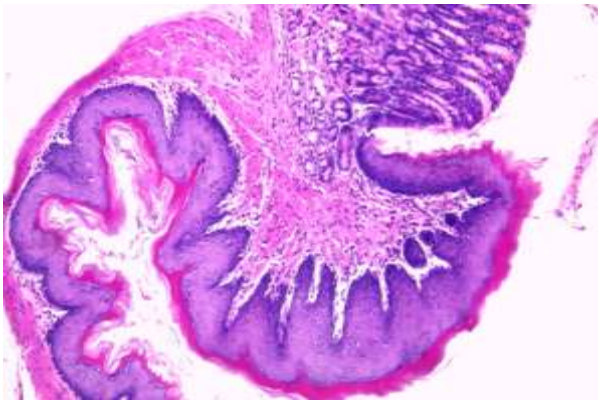

**Figure 1:** Thin section for the normal stomach tissue of the untreated control group. H & E stain.

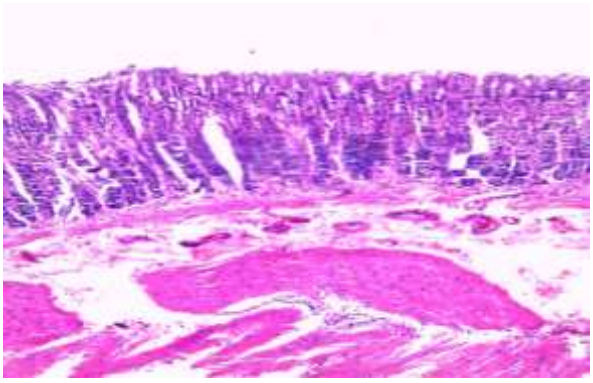

**Figure 2:** Thin section of the stomach of Indomethacin-treated rats. H & E stain showed degeneration of columnar epithelium, goblet cell (arrow) with congestion of blood (bold arrow), degeneration with necrosis at the tip of the villi, and goblet cell distorted (star). H & E stain.

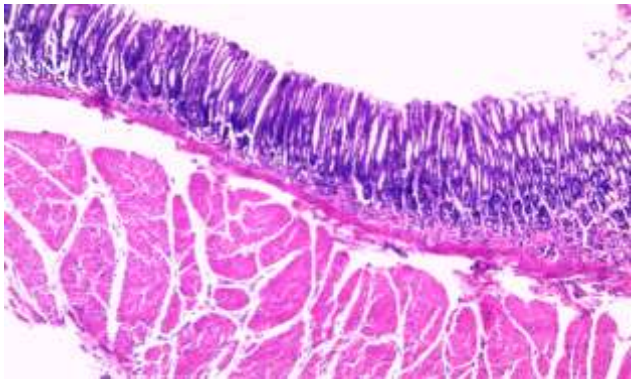

**Figure 3:** A thin section of the stomach of Indomethacin and ethanol extract of *G. glabra*-treated rats Showed there was Erosion of mucin (arrow), degeneration of columnar tissue (bold arrow), and blood vessel distortion (star). ). H & E stain

Table 3 illustrates the studied groups' iron (µmol/L−1) and blood hemoglobin (g/dL−1) levels. Using indomethacin caused a notable decrease in serum iron and hemoglobin levels. The reduction rate was 19.2% and 26.2% for iron and hemoglobin levels in the test group, respectively. Findings illustrated no significant difference in hemoglobin levels between the control and intervention groups.

It has been known that indomethacin can cause gastrointestinal lesions as a side effect, and its ulcerogenic potential is higher than other non-steroidal drugs. This compound inhibits prostaglandin synthesis, which, along with free radicals, has a significant role in gastric ulcers and gastritis pathogenesis.[33] Data in Table 1 show that indomethacin caused significant inflammation in gastric mucosa and induced necrosis and degeneration of columnar epithelium, which was in harmony with other studies.[39–41]

In the present study, the gastric protective effect of the ethanol extract of *G. glabra* was investigated in rats using indomethacin-induced gastritis models. In addition, the ethanol extract of *G. glabra* inhibits gastric mucosa inflammation significantly. This finding is compatible with the results of previous studies.[42,43]

Presently, the drugs used in treating gastritis are costly and have several adverse effects that reduce their administration. Scientists pay particular attention to investigating agents with fewer side effects, low cost, and confirmed effectiveness. Medicinal plants are among the most promising sources of new drugs for treating peptic ulcers.[44] *G. glabra* is a plant with broad, widespread uses. However, further research must demonstrate its safety. Acute and chronic toxicity studies are essential to determine the extract's doses and possible clinical symptoms.

Indomethacin, a non-steroidal anti-inflammatory agent, inhibits cyclooxygenase enzyme activity and then decreases the production levels of endogenous prostaglandin in the gastric mucosa. This reduction in prostaglandin levels will contribute to gastric hypermotility and vascular disturbances, thus stimulating reactive oxygen species (ROS) production, lipid peroxidation, and infiltration of neutrophils.[45] Among the vital roles of the endogenous prostaglandins are the regulation of mucosal blood flow, proliferation of epithelial cells, epithelial restitution, enhancement, and regulation of mucosal immunocyte function, secretion of bicarbonate and mucus, and the secretion of basal acid. All the effects resulting from inhibiting prostaglandin synthesis by indomethacin will lead to ulcer formation.[46] On the other hand, *G. glabra* has gastric protective activity and significantly minimizes gastric mucosa damage caused by indomethacin, suggesting that its gastroprotective effect may involve the enhancement of prostaglandin synthesis. Elevation of the local concentration of prostaglandins will promote mucous and bicarbonate secretions and cell proliferation in the stomach, leading to the healing of ulcers in experimental studies.[47] The possibility of *G. glabra* exerting a gastroprotective effect is indicated because it successfully prevents gastric mucosa inflammation in the indomethacin-induced gastritis model. In the present study, as shown in Figures 2 and 3, *G. glabra* provides a protective effect against the cytotoxicity induced by indomethacin, where the cytotoxicity on the architecture was reduced;



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the erosion of mucin, degeneration of columnar tissue, degeneration of gastric glands/mucosa, and blood vessel distortion was to a lesser extent compared to indomethacin-treated rats. However, this finding is consistent with the results of other studies.[48,49]

Indomethacin caused a significant increase in the volume and total acidity and a marked decrease in the pH of gastric secretions ($p \leq 0.05$). On the other hand, licorice increases the pH of gastric secretions ($p \leq 0.05$) and decreases the volume and total acidity of the stomach ($p \leq 0.05$). This result is consistent with [50] who reported that indomethacin caused alterations in rats' gastric secretions. Gastric secretions are controlled by several mechanisms, where high levels of histamine and low levels of prostaglandins can elevate gastric acid production, resulting in increased acidity levels.[51] In cases where gastric juice has a low pH, it could indicate a high concentration of $H^+$. Such a scenario could risk gastric damage and ulcers.[52] The ulcer can also result from direct oxidative action.[53]

The ethanol extract of *G. glabra* in the present study showed an improvement in vitamin B12 level and serum iron, consistent with other studies demonstrating the vitamin B12 bioavailability enhancement effect of the *G. glabra* extract.[54] The gastroprotective effect of *G. glabra* extract observed in the present study may be associated with its anti-inflammatory action, antioxidant properties, cytoprotective activity, and increased prostaglandin formation.[55]

## Conclusion

*G. glabra* extracts protected the stomachs of the rats from indomethacin-induced gastric mucosa inflammation, and no toxic effects were observed after *G. glabra* administration, encouraging the usage of licorice roots for this purpose. This effect could be due to an enhancement of gastric mucosal defensive mechanisms. Further pharmacological studies are being undertaken to elucidate the mechanisms of action involved in this activity.

**Table 1:** L8 ($2^7$) orthogonal test results of inflammation grades in stomachs of rats

| Treatment factors | Triple orthogonal test results | | | | | |
|---|---|---|---|---|---|---|
| | Antrum | | | Body | | |
| Test Group | 1.37[a] | 1.56[a] | 1.70[a] | 1.20[a] | 1.15[a] | 1.33[a] |
| Intervention group | 0.92[b] | 0.91[b] | 0.89[b] | 0.60[b] | 0.52[b] | 0.60[b] |
| Control group | 0.85 | 0.88 | 0.77 | 0.55 | 0.58 | 0.50 |

Abbreviation: [a]P < 0.05 vs. the control, [b]P > 0.05 vs. the control. Test group: Indomethacin 3 mg daily; Intervention group: combined treatment of Indomethacin 3 mg, extract of *G. glabra* in a 200 mg/ kg dose.

**Table 2:** Effect of ethanol extract of *G. glabra* and indomethacin treatment on volume, pH, and Total Acidity on rat

| Parameter | | | |
|---|---|---|---|
| **Group** | **Volume (ml)** | **pH** | **Total Acidity (mEq/L/100 g)** |
| Control group | 1.53 ± 0.04[c] | 5.02 ± 0.03[ab] | 37.3 ± 2.34[bc] |
| Test Group | 3.01 ± 0.20[a] | 3.42 ± 0.20[c] | 58.5 ± 3.23[a] |
| Intervention group | 1.22 ± 0.03[c] | 4.11 ± 0.05[a] | 33.2 ± 2.33[c] |

Values are means ± standard errors. Means without a common superscript in a column differ significantly (P ≤ 0.05). Group I: control, Test Group: Indomethacin, Intervention group: licorice

**Table 3:** Effect of ethanol extract of *G. glabra* and indomethacin treatment on Iron, Hb, and Vitamin B12 levels in rat

| | Experimental Groups * | | |
|---|---|---|---|
| **Physicochemical Parameters** | **Control group** | **Test Group** | **Intervention group** |
| Iron [µmol/ $L^{-1}$] | 26.04 [ac] ± 2.72 | 21.03 [a c] ± 1.15 | 29.70 [a] ± 2.23 |
| Hb [g/$dL^{-1}$] | 15.10 [b] ± 0.10 | 11.13 [c] ± 0.04 | 14.30 [b] ± 0.03 |
| Vitamin $B_{12}$ (pg/$mL^{-1}$) | 760.3 [c] ± 2.14 | 578.0 [a] ± 3.21 | 793.2 [a b] ± 0.04 |

* Control group: negative control; Test Group: indomethacin-treated group; Intervention group: Indomethacin + ethanol extract of *G. glabra* treated group.

## Conflict of Interest

The authors declare no conflict of interest.

## Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

## References

1. Parveen A, Singh A, Rajendiran A, Jough SS, Verma SK. Herbal elicited Hepatoprotection and Hepatotoxicity–A Comprehensive Review. Asian J Pharm Res. 2022;12(2):155–61.
2. Shi Y, Leng Y, Liu D, Liu X, Ren Y, Zhang J, Chen F. Research advances in protective effects of ursolic acid and oleanolic acid against gastrointestinal diseases. Am J Chin Med. 2021;49(02):413–35.
3. Thakur P, Thakur U, Kaushal P, Ankalgi AD, Kumar P, Kapoor A, Singh Ashawat M. A Review on GC-MS Hyphenated Technique. Asian J Pharm Anal. 2021; 27;1(4):285–92.
4. Rajasekaran R, Suresh PK. Physical and chemical methods of extraction of bioactive molecules from Lepidium sativum Linn. And antioxidant activity-based screening and selection of extracts-probable phytochemical, chromatography and mass spectroscopy analysis-based correlates. Res J Pharm Technol. 2021;14(6):3082–92.
5. Salunke C, Chittam K, Pawar A, Chaudhari H. Development of an Analytical Method to Determine Extracts of Different Species of Glycyrrhizin by HPTLC. Res J Pharm Dos Forms Technol. 2020;12(2):89.
6. El-Saber Batiha G, Magdy Beshbishy A, El-Mleeh A, M. Abdel-Daim M, Prasad Devkota H. Traditional uses, bioactive chemical constituents, and pharmacological and



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toxicological activities of Glycyrrhiza glabra L.(Fabaceae). Biomolecules. 2020;10(3):352.
7. Michielsen HJ, De Vries J, Van Heck GL, Fiorillo A, Gorwood P, Braga-Neto MB, Warren CA, Oriá RB, Monteiro MS, Maciel AAS, Brito GAC, Lima AAM, Guerrant RL, Brooks SK, Webster RK, Smith LE, Woodland L. Mental Health Care Measures in Response to the 2019 Novel Coronavirus Outbreak in Korea. Dig Dis Sci. 2020; 14;17(2):85–6.
8. Gunjal SD, Shirolkar S V. Optimizations of Spray Drying Process Parameters for Liquorice ( Glycyrrhiza glabra Linn. ) Extract. Res J Pharm Technol. 2018;11(11):51-05.
9. Tewari D, Stankiewicz AM, Mocan A, Sah AN, Tzvetkov NT, Huminiecki L, Horbańczuk JO, Atanasov AG. Ethnopharmacological approaches for dementia therapy and significance of natural products and herbal drugs. Front Aging Neurosci. 2018;10(3):3-10
10. Turkyilmaz IB, Coskun ZM, Bolkent S, Yanardag R. The effects of antioxidant combination on indomethacin-induced gastric mucosal injury in rats. Cell Mol Biol. 2019;65(3):76–83.
11. Kwon DA, Kim YS, Baek SH, Kim SK, Kim HK, Jo SK, Jung U, Park HR, Lee HS. Protective effects of a standardized extract (HemoHIM) using indomethacin-and ethanol/HCl-induced gastric mucosal injury models. Pharm Biol. 2019;57(1):543–9.
12. Fearon AD, Stokes GY. Thermodynamics of indomethacin adsorption to phospholipid membranes. J Phys Chem B. 2017;121(46):10508–18.
13. Lim JM, Song CH, Park SJ, Park DC, Jung GW, Cho HR, Bashir KMI, Ku SK, Choi JS. Protective effects of triple fermented barley extract (FBe) on indomethacin-induced gastric mucosal damage in rats. BMC Complement Altern Med. 2019;19(3):1–11.
14. Sumithra M, Prabhabanik A. A Prospective Study of Drug Utilization and Evaluation of Gastro Intestinal Agents. Res J Pharm Technol. 2017;10(1):16-6.
15. Alsarhan A, Shoiab AA, Gardouh A, Khwaldeh A, Khashroum AO. Comparison between Ibuprofen Nanoparticles and Suspension Ibuprofen Regarding GIT Side Effects. Lat Am J Pharm. 2022;41(11): 1210-15
16. Camilo V, Sugiyama T, Touati E. Pathogenesis of Helicobacter pylori infection. Helicobacter. 2017;22:e12405.
17. Porth C. Pathophysiology - Altered Physiological States. InTech; 2018.
18. Morais S, Costa AR, Ferro A, Lunet N, Peleteiro B. Contemporary migration patterns in the prevalence of Helicobacter pylori infection: a systematic review. Helicobacter. 2017;22(3):e12372.
19. Malfertheiner P, Megraud F, O'morain CA, Gisbert JP, Kuipers EJ, Axon AT, Bazzoli F, Gasbarrini A, Atherton J, Graham DY. Management of Helicobacter pylori infection—the Maastricht V/Florence consensus report. Gut. 2017;66(1):6–30.
20. M D, Samraj P A, C D, Venkatesh J, R S K, K P A. Case Report on Mild Anemia and Gastritis due to Zidovudine, Lamivudine and Nevirapine (ZLN) Regimen. Res J Pharm Technol. 2021; 30;14(11):5911–2.
21. Kotelevets SM, Chekh SA. The use of Biomarkers in blood serum as identifiers of the influence of production factors on prevalence of Atrophic gastritis. Res J Pharm Technol. 2019;12(9):43-53.
22. Zaghlool SS, Abo-Seif AA, Rabeh MA, Abdelmohsen UR, Messiha BAS. Gastro-protective and anti-oxidant potential of Althaea officinalis and solanum nigrum on pyloric ligation/indomethacin-induced ulceration in rats. Antioxidants. 2019;8(11):512-20.
23. Wahab S, Annadurai S, Abullais SS, Das G, Ahmad W, Ahmad MF, Kandasamy G, Vasudevan R, Ali MS, Amir M. Glycyrrhiza glabra (Licorice): A comprehensive review on its phytochemistry, biological activities, clinical evidence and toxicology. Plants. 2021;10(12):2751-58.
24. Man S, Luo C, Yan M, Zhao G, Ma L, Gao W. Treatment for liver cancer: From sorafenib to natural products. Eur J Med Chem. 2021;22(4):113690.
25. Richard SA. Exploring the pivotal immunomodulatory and anti-inflammatory potentials of glycyrrhizic and glycyrrhetinic acids. Mediators Inflamm. 2021; 20(5):20-25.
26. Dwivedi, Shiv Prasad D. Comparative Study Of Yashtimadhu Siddha Ghrita (Glycyrrhiza Glabra Medicated Ghrita) And Silver Sulphadiazine Local Application In Angnidagdha Vrana (Burns Wound) Management. J Med Pharm Allied Sci. 2022;3(5):1231-34.
27. Anand U, Jacobo-Herrera N, Altemimi A, Lakhssassi N. A comprehensive review on medicinal plants as antimicrobial therapeutics: potential avenues of biocompatible drug discovery. Metabolites. 2019;9(11):258-61.
28. Laux A, Gouws C, Hamman JH. Aloe vera gel and whole leaf extract: functional and versatile excipients for drug delivery? Expert Opin Drug Deliv. 2019;16(12):1283–5.
29. Ong ES. Extraction methods and chemical standardization of botanicals and herbal preparations. J Chromatogr B. 2004;812(1–2):23–33.
30. Santulli C, Rallini M, Puglia D, Gabrielli S, Torre L, Marcantoni E. Characterization of Licorice Root Waste for Prospective Use as Filler in more Eco-Friendly Composite Materials. Processes. 2020;8(6):733-37.
31. Pastorino G, Cornara L, Soares S, Rodrigues F, Oliveira MBPP. Liquorice (*Glycyrrhiza glabra*): A phytochemical and pharmacological review. Phyther Res. 2018;32(12):2323–39.
32. Capdevila S, Giral M, Ruiz de La Torre JL, Russell RJ, Kramer K. Acclimatization of rats after ground transportation to a new animal facility. Lab Anim. 2007;41(2):255–61.
33. Sabiu S, Garuba T, Sunmonu TO, Sulyman AO, Ismail NO. Indomethacin-induced gastric ulceration in rats: Ameliorative roles of *Spondias mombin* and *Ficus exasperata*. Pharm Biol. 2016;54(1):180–6.
34. Ugan RA, Un H. The Protective Roles of Butein on Indomethacin Induced Gastric Ulcer in Mice. Eurasian J Med. 2020;52(3):265–70.
35. Wu Y, Wang Z, Du Q, Zhu Z, Chen T, Xue Y, Wang Y, Zeng Q, Shen C, Jiang C. Pharmacological effects and underlying mechanisms of licorice-derived flavonoids. Evidence-Based Complement Altern Med. 2022; 25(5):201-22.
36. Wei X, Feng XP, Wang LY, Huang YQ, Liang LL, Mo XQ, Wei HY. Improved method for inducing chronic atrophic gastritis in mice. World J Gastrointest Oncol. 2019;11(12):1115.
37. Hassan TMM, Al-Najjar SI, Al-Zahrani IH, Alanazi FIB, Alotibi MG. Helicobacter pylori chronic gastritis updated Sydney grading in relation to endoscopic findings and H. pylori IgG antibody: diagnostic methods. J Microsc Ultrastruct. 2016;4(4):167–74.
38. Khushtar M, Ahmad A, Rahman MA. Gastroprotective effect of hydro-alcoholic extract of Polygonum bistorta Lin root in indomethacin-induced gastric ulcers in sprague dawley rats. Indian J Pharm Educ Res. 2018;52(4):618–25.
39. Fazalda A, Quraisiah A, Nur Azlina MF. Antiulcer effect of honey in nonsteroidal anti-inflammatory drugs induced gastric ulcer model in rats: a systematic review. Evidence-Based Complement Altern Med. 2018;2018.
40. Melcarne L, García-Iglesias P, Calvet X. Management of NSAID-associated peptic ulcer disease. Expert Rev Gastroenterol Hepatol. 2016;10(6):723–33.
41. Abd Al Haleem EN, Ibrahim FAM, Zaytoon SAB, Arafa HMM. Possible protective effect of TNF-α inhibition and triad NO/cGMP/VEGF activation on gastric ulcer in rats. Can J Physiol Pharmacol. 2021;99(9):864–74.



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42. Jalilzadeh-Amin G, Najarnezhad V, Anassori E, Mostafavi M, Keshipour H. Antiulcer properties of Glycyrrhiza glabra L. extract on experimental models of gastric ulcer in mice. Iran J Pharm Res IJPR. 2015;14(4):1163.
43. Sharma A, del Carmen Flores-Vallejo R, Cardoso-Taketa A, Villarreal ML. Antibacterial activities of medicinal plants used in Mexican traditional medicine. J Ethnopharmacol. 2017;208:264–329.
44. Fahmy NM, Al-Sayed E, Michel HE, El-Shazly M, Singab ANB. Gastroprotective effects of Erythrina speciosa (Fabaceae) leaves cultivated in Egypt against ethanol-induced gastric ulcer in rats. J Ethnopharmacol. 2020;248:112297.
45. Maseda D, Ricciotti E. NSAID–gut microbiota interactions. Front Pharmacol. 2020;11:1153.
46. Drini M. Peptic ulcer disease and non-steroidal anti-inflammatory drugs. Aust Prescr. 2017;40(3):91.
47. Hasan MK, Ara I, Mondal MSA, Kabir Y. Phytochemistry, pharmacological activity, and potential health benefits of Glycyrrhiza glabra. Heliyon. 2021;7(6).
48. Lim TK, Lim TK. "Glycyrrhiza glabra". Edible Med Non-Medicinal Plants. 2016;10 (7): 354–457.
49. Ghasemkhani N, Tabrizi AS, Namazi F, Nazifi S. Treatment effects of Shilajit on aspirin-induced gastric lesions in rats. Physiol Rep. 2021;9(7):e14822.
50. Katary MA, Salahuddin A. Gastroprotective effect of vanillin on indomethacin-induced gastric ulcer in rats: protective pathways and anti-Secretory mechanism. Clin Exp Pharmacol. 2017;7(2):1459–2161.
51. Gribble FM, Reimann F. Enteroendocrine cells: chemosensors in the intestinal epithelium. Annu Rev Physiol. 2016;78:277–99.
52. Meyer AR, Goldenring JR. Injury, repair, inflammation and metaplasia in the stomach. J Physiol. 2018;596(17):3861–7.
53. Suzuki H, Nishizawa T, Tsugawa H, Mogami S, Hibi T. Roles of oxidative stress in stomach disorders. J Clin Biochem Nutr. 2011;50(1):35–9.
54. 5Sharma P, Pathak P, Tyagi V, Khan F, Shanker K, Darokar MP, Pal A. Investigation of the potential of Glycyrrhiza glabra as a bioavailability enhancer of Vitamin B12. Front Nutr. 2022;9.
55. Monadi T, Azadbakht M, Ahmadi A, Chabra A. A comprehensive review on the ethnopharmacology, phytochemistry, pharmacology, and toxicology of the mandragora genus; from folk medicine to modern medicine. Curr Pharm Des. 2021;27(34):3609–37.



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