Original Article

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Glycyrrhizic acid and the aqueous extract of *Glycyrrhiza glabra* attenuate hepatotoxicity in mice

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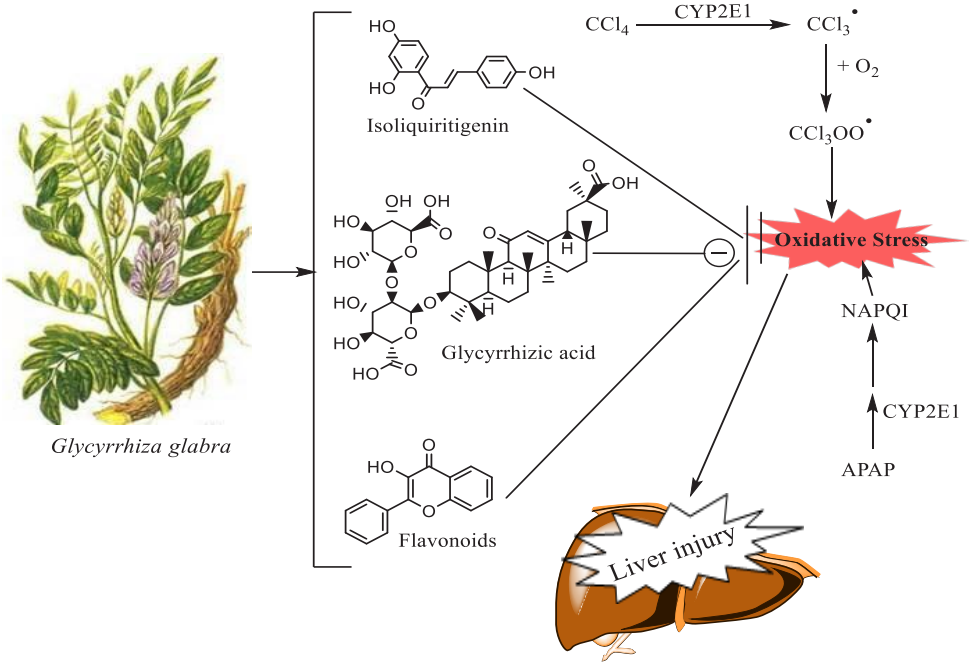
Graphical Abstract



The bioactive component and their role in alleviating xenobiotics-induced tissue injury. The effects of Glycyrrhiza glabra extract and glycyrrhizic acid on oxidative stress and its associated complications play an essential role in its hepatoprotective mechanisms.

Abstract

The liver injury could be induced in the association of a wide range of etiologies. Therefore, finding hepatoprotective agents with the potential clinical application has great value. *Glycyrrhiza glabra* (GG) is widely used in traditional medicine. The natural habitats of this plant are abundantly found in Iran. Besides, this plant could be cultivated on an industrial scale. The current study was designed to evaluate and compare the hepatoprotective effects of GG aqueous extract in two animal models. Moreover, the ef-

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fect of GG extract was compared with glycyrrhizic acid (GHZA) as one of its most abundant components. Mice were treated with APAP (800 mg/kg, i.p) and CCl4 (0.8 ml/kg, in olive oil, i.p) as hepatotoxicants. Then, animals were treated with GG (150, 300, and 600 mg/kg, oral) and GHZA (30 mg/kg, oral). Moreover, animals were pre-treated with GG (600 mg/kg, seven consecutive days) before hepatotoxicity induction. A significant increase in serum biomarkers of liver injury and liver histopathological alterations were detected in APAP and CCl4-treated animals. Moreover, significant glutathione depletion and lipid peroxidation were evident in the liver of hepatotoxin-treated mice. It was found that GG water extract and GHZA significantly alleviated APAP and CCl4-induced liver injury. However, the effects of GG extract pre-treatment were more significant in comparison with post-treatment groups. Moreover, GG extract had a more significant hepatoprotective effect in comparison with GHZA. The effects of GG extract and GHZA on oxidative stress parameters seem to play a fundamental role in its hepatoprotective properties.

Keywords: Oxidative stress; Hepatotoxicity; Liver Injury; Reactive oxygen species

1. Introduction

Liver disease is among the leading cause of mortality and morbidity worldwide (1, 2). The liver injury could be induced by a wide range of etiologies (1-6). Drugs, toxins, infectious diseases, fatty liver, and autoimmune disorders could cause liver injury (1, 2, 7-17). Therefore, finding hepatoprotective agents with the clinical application could have great value.

Herbal medicines have been traditionally used against several human diseases (18-20). Our country also has an old history of using herbal remedies (21, 22). Glycyrrhiza glabra (GG) is a perennial herb prevalently found in Iran (23, 24). A plethora of investigations mentioned the importance of this herb in folk medicine (25-27). GG rhizome extract and its constituents have been used for various human diseases, including respiratory, hepatic, gastric, and renal disorders (25, 28-32). Several lines of evidence also indicate the protective effects of GG extract against oxidative stress in biological systems (23, 33, 34).

Some studies mentioned the hepatoprotective properties of various Glycyrrhiza species (35-37). The difference between the current study with previous investigations about the hepatoprotective effects of GG is the administration of GG aqueous extract in two models of liver injury. The data obtained with two models were compared. Besides, the impact of GG extract pre-treatment on the liver injury was evaluated. Moreover, we assessed the hepatoprotective effects of glycyrrhizic acid (GHZA) in these two models. The effect of glycyrrhizic acid is also compared with the GG extract. The current investigation results could help develop therapeutic options against a wide range of liver diseases.

2. Material & methods

2.1. Chemicals

2′,7′ Dichlorofluorescein diacetate (DCFH-DA), citric acid, 2,4,6-Tri(2-pyridyl)-s-triazine (TPTZ), coomassie brilliant blue, bovine serum albumin (BSA), dithiothreitol, dimethyl sulfoxide, 4,2 Hydroxyethyl,1-piperazine ethane sulfonic acid (HEPES), dithiobis-2-nitrobenzoic acid, ethylenediaminetetraacetic acid (EDTA), reduced glutathione (GSH), malondialdehyde, meta-phosphoric acid, trichloroacetic acid, and thiobarbituric acid were purchased from Sigma (St. Louis, MO, USA). Glycyrrhiza glabra water extract was purchased from Shirin Daru® (Shiraz, Iran). Hydroxymethyl aminomethane hydrochloride (Tris-HCl), n-butanol, sodium chloride, and potassium chloride were purchased from Merck (Darmstadt, Germany). Kits used for assessing plasma biomarkers of liver injury were purchased from Pars Azmoon® Co. (Tehran, Iran).

2.2. Animals

Male BALB/c mice (20-25 g) were obtained from Shiraz University of Medical Sciences. Animals were acclimated to an environmentally controlled environment (23±1 °C, ≈50% relative humidity, and a 12 h light/dark cycle). Mice had free access to a commercial rodent's pellet (RoyanFeed, Isfahan, Iran) and tap water during the

experiments. Animal experiments were approved by the Animal Care and Use Committee of Shiraz University of Medical Sciences (94-01-05-9172).

2.3. Animal models of liver injury

In the current study, acetaminophen (acetyl para-amino phenol; APAP) and CCl4 were used to induce hepatotoxicity in mice (38-41). For this purpose, animals received APAP (1000 mg/kg, i.p) and CCl4 (0.8 ml/kg, in olive oil, i.p) (38, 42). Animals were anesthetized (thiopental 70 mg/kg, i.p) 24 hours after APAP or CCl_4 administration and serum biomarkers of liver injury, liver tissue markers of oxidative stress, and tissue histopathological alterations were monitored. The treatments were as follow: A) Control animals received normal saline (2.5 ml/kg, i.p); B) APAP (1000 mg/kg, i.p); C) APAP + GG extract (150 mg/kg, gavage); D) APAP + GG extract (300 mg/kg, gavage); E) APAP + GG extract (600 mg/kg, gavage); F) APAP + GG extract pre-treatment (600 mg/kg, gavage) for one week; G) APAP+ GHZA (30 mg/kg, i.p); H) Control animals received olive oil (0.8 ml/kg, i.p); I) CCl_4 (0.8 ml/kg, in olive oil, i.p); J) CCl_4+ GG extract (150 mg/kg, gavage); K) CCl_4 + GG extract (300 mg/kg, gavage); L) CCl_4 + GG extract (600 mg/kg, gavage); M) CCl_4 + GG extract pre-treatment (600 mg/kg, gavage) for one week; N) CCl_4 + GHZA (30 mg/kg, i.p).

2.4. Serum biochemistry and tissue histopathology

Blood samples were collected from the inferior vena cava of deeply anesthetized mice (thiopental, 50 mg/kg, i.p). Samples were transferred to gel-coated standard tubes (Vacutest® Kima; Italy), and serum was prepared by centrifugation (3000 g, 4 °C, 20 min). A Mindray BS-200® autoanalyzer (Guangzhou, China) and commercial kits (Pars Azmun®, Tehran, Iran) were used to evaluate plasma biochemistry (43-48). For assessing liver histopathology, tissue samples were fixed in buffered formalin solution (0.4% w: v NaH_2PO_4, 0.64% w: v Na_2HPO_4, and 10% v: v formaldehyde in double-distilled water). Then, the paraffin-embedded tissue was prepared, and tissue sections (5 µm) were stained with hematoxylin and eosin (H&E) (49-54).

2.5. Lipid peroxidation in the liver tissue

The thiobarbituric acid reactive substances (TBARS) were measured as an index of lipid peroxidation in the liver tissue (40, 55-58). For this purpose, a reaction mixture consisted of 1 mL of thiobarbituric acid (0.375%, w: v) and 3 mL of 1% w: v meta-phosphoric acid (pH=2, adjusted with HCl) was prepared. Then, 500 µL of tissue homogenate (10% w/v in KCl, 1.15% w: v) was added to the reaction mixture, vortexed (10 sec), and heated in a water bath (100 °C, 45 min). After the incubation period, samples were cooled, and 2 ml of n-butanol was added. Samples were mixed well (30 sec) and centrifuged (10000 g, 10 min) (59-66). Finally, the absorbance of the n-butanol phase was measured at λ=532 nm (EPOCH® plate reader, BioTek®, USA) (39, 55, 67-70).

2.6. Hepatic glutathione (GSH) content

For assessing hepatic GSH content, 5 mL of the liver homogenate (10% w: v in 40 mM Tris-HCl buffer, 4 °C) was added to 4 mL of deionized water (4 °C) and 1 mL of trichloroacetic acid (50%; w: v) (71). The mixture was vortexed and centrifuged (10,000 g, 4 °C, 15 minutes). Then, 2 mL of the supernatant was treated with 4 mL of Tris-HCl buffer (40 mM, pH=8.9, 4 °C) and 100 µl of DTNB solution (freshly-prepared, 10 mM in methanol) (9, 59, 72-76). Finally, the absorbance was measured at λ=412 nm (EPOCH® plate reader, BioTek®, USA) (55, 77-80).

2.7. Statistical methods

Data are represented as mean±SD. The comparison of data sets was conducted by the one-way analysis of variance (ANOVA) with Tukey's multiple comparison test as the post hoc. A $P<0.05$ was considered as a statistically significant difference.

3. Results

Evaluating serum biomarkers of liver injury revealed a significant increase in serum ALT, AST, and LDH in both APAP and CCl_4-treated mice (Figure 1). It was found that GG extract significantly decreased serum biomarkers of organ injury (Figure 1). GHZA administration also alleviated serum biomarkers in APAP and CCl_4-treated

animals (Figure 1). The effect of GG extract on serum biomarkers was not dose-dependent in the current study (Figure 1). However, it was found that GG extract pre-treatment had a more prominent effect on serum biomarkers than the post-treatment groups (Figure 1). On the other hand, GG extract had a more significant impact in alleviating serum markers of liver injury than the GHZA group (Figure 1).

Liver tissue biomarkers of oxidative stress were significantly changed in hepatotoxicants-treated mice (Figure 2). APAP and CCl_4 caused significant lipid peroxidation and depletion of liver glutathione stores in the current study (Figure 2). It was found the GG extract significantly mitigated biomarkers of oxidative stress in both CCl_4 and APAP-treated animals (Figure 2). GHZA also alleviated oxidative stress in the liver tissue of APAP and CCl_4-treated mice (Figure 2). It noteworthy to mention that the effects of GG extract on oxidative stress markers were not dose-dependent in the current study, but GG extract pre-treatment had a more significant impact on the liver tissue oxidative stress biomarkers (Figure 2). On the other hand, the effect of GG extract on liver tissue markers of oxidative stress was more significant, in most cases, in comparison with the GHZA group (Figure 2).

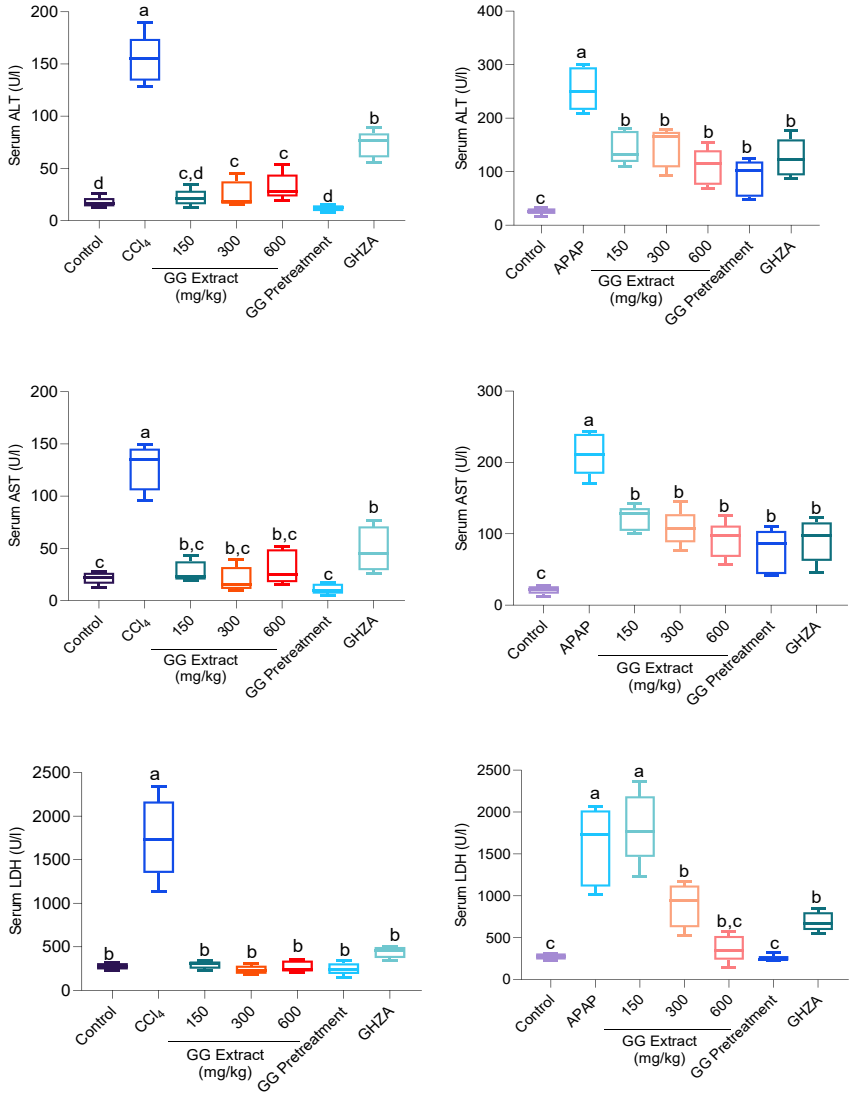

Figure 1. Serum biochemical measurements in *Glycyrrhiza glabra* extract and glycyrrhizic acid-treated animals. APAP: acetaminophen; GG: *Glycyrrhiza glabra* water extract; GHZA: Glycyrrhizic acid. Columns with different alphabetical superscripts are statistically different ($P<0.05$).

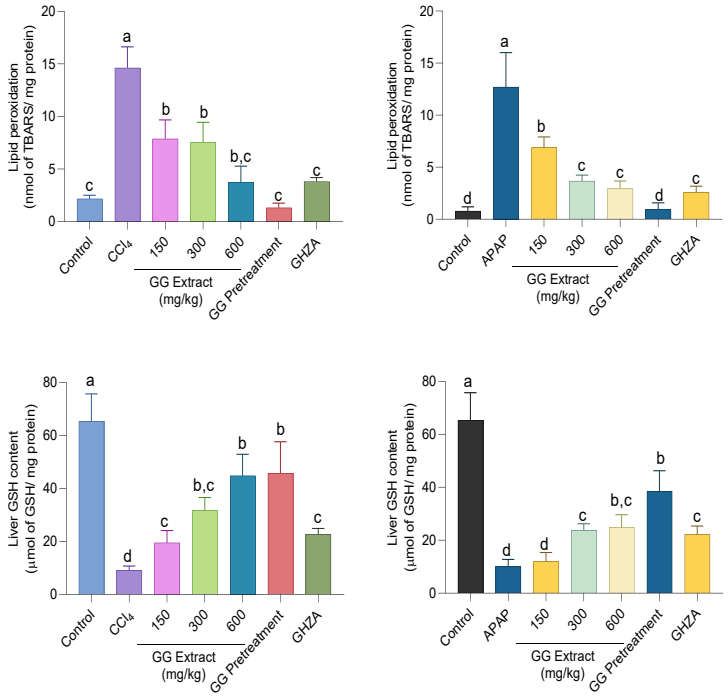

Figure 2. Markers of oxidative stress in CCl4 and APAP-treated mice. APAP: acetaminophen; GG: *Glycyrrhiza glabra* water extract; GHZA: Glycyrrhizic acid. Data are expressed as mean ± SD (n=5). Columns with different alphabetical superscripts are statistically different (P<0.05).

CCl_4-induced liver tissue histopathological alterations included ballooning degeneration, tissue necrosis, and inflammatory cell infiltration in the current study (Figure 3). Inflammatory cell infiltration was the most prominent histopathological change in APAP-treated mice (Figure 3). It was found that various doses of GG extract and GHZA significantly alleviated liver tissue histopathological changes in hepatotoxicant-treated animals (Figure 3).

4. Discussion

Several xenobiotics, as well as diseases, could affect liver function. It has been found that oxidative stress and its associated complications play a pivotal role in the pathogenesis of liver injury with various etiologies (81-92). Therefore, antioxidant compounds could have potential protective effects in this complication. The data obtained from the current investigation revealed significant hepatoprotective properties of GG extract and GHZA in two models of acute liver injury. The primary mechanism of hepatoprotective effects of GG and GHZA seems to be mediated through their effects on oxidative stress and its associated complications. It was found that the impact of GG extract on liver tissue markers of oxidative stress was more significant in comparison with GHZA therapy. On the other hand, it was found that pre-treatment of animals could lead to more efficient hepatoprotective effects.

Previous studies indicate that GG and its constituents could preserve the balance between pro-oxidants and antioxidants (enzymatic and non-enzymatic) in various experimental models (33, 93). In the current study, GG extract significantly decreased biomarkers of oxidative stress in the liver tissue. On the other hand, GG pre-treatment had a more significant effect against hepatotoxicants-induced oxidative stress. These findings could mention the importance of the time-dependent effects of GG extract in the expression of antioxidant systems in the liver tissue.

The nuclear factor-related factor 2 (Nrf2) is the major signaling pathway involved in regulating antioxidants in biological systems (94, 95). Several compounds have been identified as Nrf2 signaling activators (94, 95). Polyphenols are the most investigated naturally-derived agents for their potential in activating Nrf2 signaling (96,

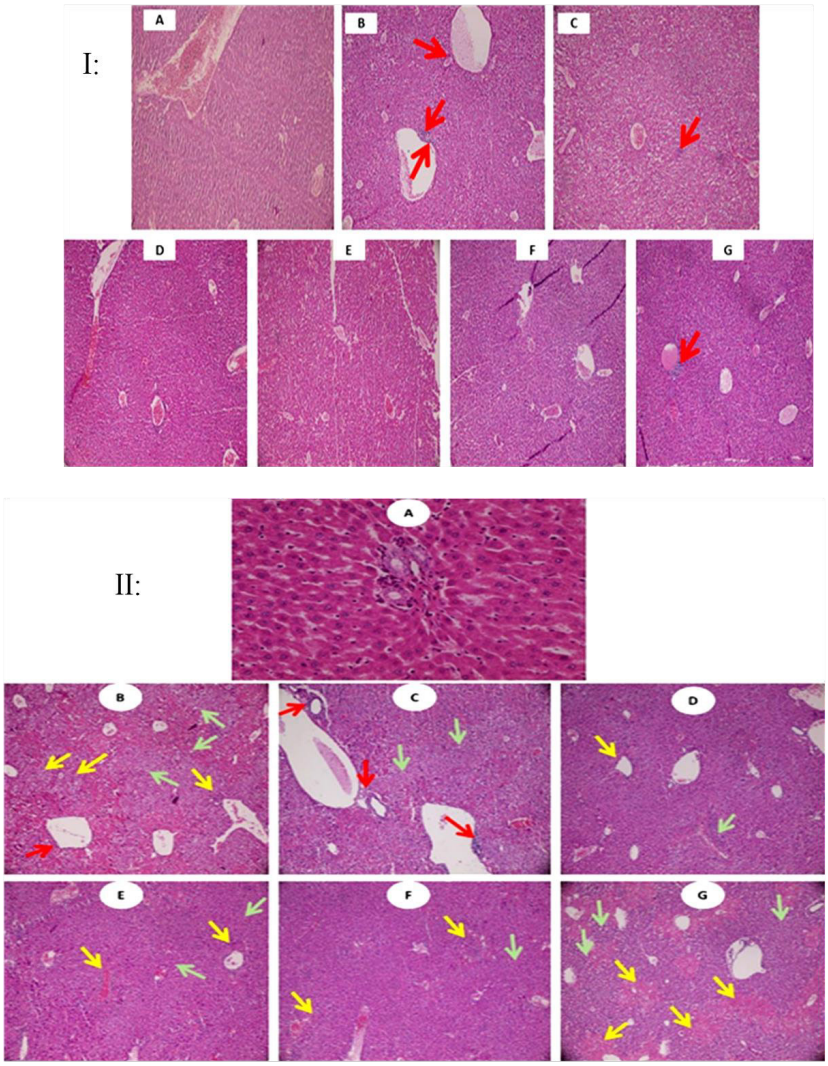

Figure 3. Liver tissue histopathological alterations in APAP (I) and CCl_4 (II)-treated animals.
Panel I: A: Control; B: APAP; C, D, E: APAP+ GG extract 150, 300, and 600 mg/kg respectively; F: APAP + GG extract (600 mg/kg) pretreatment; and G: APAP + GHZA (30 mg/kg). Panel II: A: Control; B: CCl_4; C, D, E: CCl_4+ GG extract 150, 300, and 600 mg/kg respectively; F: CCl_4 + GG extract (600 mg/kg) pretreatment; and G: CCl_4 + GHZA (30 mg/kg). Red arrow: Inflammatory cells infiltration; Green arrow: Ballooning degeneration; Yellow arrow: Necrosis. APAP: acetaminophen; GG: *Glycyrrhiza glabra*; GHZA: Glycyrrhizic acid. Scores of the liver histopathological changes are represented at Table 1.

97). These compounds are able to enhance cellular antioxidant capacity (98, 99). Interestingly, some studies mentioned the positive role of GG components on the Nrf2 pathway (100, 101). Hence, the effect of GHZA and other GG aqueous extract components could be associated, at least in part, with their impact on essential antioxidative signaling.

The radical scavenging capacity of compounds such as GHZA also has been investigated (102). It has been reported that GHZA could significantly scavenge dangerous species such as hydroxyl radical (OH•-) (102). Previous studies revealed that GHZA administration could substantially decrease the damage to cellular targets such as DNA, lipids, and proteins (102). In the current study, the effects of GHZA on oxidative stress markers were significant. On the other hand, GG extract showed a more significant antioxidant profile in the present investigation. Based on these data, it could be concluded that other GG extract components are also involved in its antioxidant

Table 1. Scores of the liver histopathological alterations in Glycyrrhiza glabra (GG) extract-treated mice.

Treatments	Inflammation	Lipid changes	Necrosis
Control	-	-	-
APAP (800 mg/kg)	+++	-	++
+GG 150 mg/kg	++	-	+
+GG 300 mg/kg	+	-	-
+GG 6000 mg/kg	+	-	-
+GG pre-treatment	+	-	-
+GHZA 30 mg/kg	+	-	-
CCl4 (2.5 ml/kg)	+++	+++	+++
+GG 150 mg/kg	++	++	++
+GG 300 mg/kg	+	+	++
+GG 600 mg/kg	+	+	+
+GG pre-treatment	+	-	+
+GHZA 30 mg/kg	+	++	+

- Indicates no significant histopathological changes. +, ++, and +++ indicate mild, moderate, and severe liver histopathological alterations.

properties.

Hispaglabridin, isoliquiritigenin, and paratocarpin are potent antioxidant molecules identified in various GG species (93). As mentioned, GG extract had a more significant effect in comparison with GHZA. The role of other antioxidant molecules in GG extract could be involved in its considerable antioxidant effects. More investigations are warranted to reveal the potential synergistic effects of GG extract components.

A significant concern about the administration of GG products is associated with its effects on the renin-angiotensin and aldosterone system (103). The major GG component known for these effects is glycyrrhizic acid (103). Hence, some deglycyrrhizinated preparations of GG have been produced. More studies on the efficacy and safety of these products in liver diseases could lead to the development of safe hepatoprotective agents for clinical use.

The data obtained from the current study indicate that GG is a promising therapeutic agent for abrogating oxidative stress in liver disease with various etiologies. However, further studies are necessary to identify additional cytoprotective mechanisms of GG and its constituents.

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Conflict of Interest

None declared.

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