Research Paper

Clinical Efficacy of Diammonium Glycyrrhizinate on Drug Induced Liver Injury and Influence on Related Inflammatory Factors

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To assess the clinical efficacy of diammonium glycyrrhizinate on drug induced liver injury and its effect on related inflammatory factors in the real world. A total of 234 inpatients diagnosed with drug induced liver injury in our hospital were continuously enrolled in this retrospective real world study, of whom 110 were treated with diammonium glycyrrhizinate and divided into three groups according to drug combination. Treatment group A (n=34) received diammonium glycyrrhizinate injection+reduced glutathione injection, treatment group B (n=45) received Kuhuang injection based on administration for treatment group A, and treatment group C (n=31) received ursodeoxycholic acid capsules based on administration for treatment group B. The remaining 124 cases did not undergo diammonium glycyrrhizinate treatment, including 37 cases in control group A receiving reduced glutathione injection alone, 55 cases in control group B receiving Kuhuang injection based on treatment for control group A, and 32 cases in control group C receiving ursodeoxycholic acid capsules based on treatment for control group B. The treatment lasted for 2 w. The biochemical indices such as serum gamma glutamyl transpeptidase, total bilirubin, alkaline phosphatase, glutamic pyruvic transaminase, tumor necrosis factor-α and interleukin-6 were observed before treatment and 1 w and 2 w after treatment, and adverse reactions were recorded. The efficacy was evaluated and compared. Compared with before treatment, the levels of alkaline phosphatase, glutamic pyruvic transaminase, tumor necrosis factor-α, interleukin-6 and total bilirubin in treatment group A, the levels of alkaline phosphatase, glutamic pyruvic transaminase, gamma glutamyl transpeptidase, tumor necrosis factor-α, interleukin-6 and total bilirubin in treatment group B, and the levels of alkaline phosphatase, glutamic pyruvic transaminase, tumor necrosis factor-α, interleukin-6 and gamma glutamyl transpeptidase in treatment group C all significantly declined ($p<0.05$). The levels of total bilirubin, tumor necrosis factor-α and interleukin-6 significantly declined in control group C ($p<0.05$), while the changes in biochemical indices had no significant differences in other control groups ($p>0.05$). Compared with before treatment, the levels of tumor necrosis factor-α, interleukin-6 and total bilirubin in treatment group A, the levels of alkaline phosphatase, glutamic pyruvic transaminase, tumor necrosis factor-α, interleukin-6 and gamma glutamyl transpeptidase in treatment group B, and the levels of alkaline phosphatase, tumor necrosis factor-α and interleukin-6 in treatment group C significantly declined ($p<0.05$), but the level of total bilirubin in treatment group C significantly rose ($p<0.05$). The response rates in treatment group A and B were higher than those in control group A and B, respectively ($p<0.05$), but it was lower in treatment group C than that in control group C ($p<0.05$). The response rates in treatment group A and B exceeded than in treatment group C ($p<0.167$), while it had no significant difference between treatment group A and B ($p>0.167$). The adverse reactions were all mild in treatment group A, B and C ($p>0.05$). Compared with reduced glutathione injection alone (control group A) and reduced glutathione injection+Kuhuang injection (control group B), double combination of reduced glutathione injection+diammonium glycyrrhizinate (treatment group A) and triple combination of reduced glutathione injection+Kuhuang injection+diammonium glycyrrhizinate (treatment group B) can improve the biochemical indices of liver function and increase the response rate, with a higher response rate than quadruple combination of reduced glutathione injection+Kuhuang injection+ursodeoxycholic acid capsules+diammonium glycyrrhizinate (treatment group C). The response rate had no clinical significance between quadruple combination and reduced glutathione injection+Kuhuang injection+ursodeoxycholic acid capsules (control group C). The administration for each treatment group was safe.

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Drug induced liver injury (DILI) refers to liver diseases caused by drugs or their metabolites during drug use[1]. DILI is one of the most common adverse drug reactions, which can lead to acute liver failure and even death in severe cases. According to the World Health Organization (WHO), DILI has become the fifth major cause of death in the world[2], so the treatment of DILI has attracted increasingly more attention. Diammonium glycyrrhizinate (DG) has anti-inflammatory and liver protective effects[3], and it has been included in the Guidelines for the Diagnosis and Treatment of DILI 2015, but it remains to be proved by high level evidence based medicine[4]. There has been no evidence yet, that the combination of two or more anti-inflammatory liver protective drugs has a better effect on DILI, and such a combination is not recommended in the above guidelines. The results of meta-analysis showed that DG alone can significantly reduce the levels of biochemical indices glutamic pyruvic transaminase (GPT) and aspartate transaminase, and raise the response rate in the treatment of DILI[5]. Moreover, the combination of liver protective drugs (double, triple, quadruple and quintuple) is adopted in 100 % of patients with DILI[6]. Currently, commonly used liver protective drugs include reduced glutathione injection, ursodeoxycholic acid capsules, Kuhuang injection and DG. It was found among 562 inpatients with DILI in our hospital that reduced glutathione injection+DG, reduced glutathione injection+Kuhuang injection+DG, and reduced glutathione injection+Kuhuang injection+ursodeoxycholic acid capsules+DG accounted for 13.93 %, 12.5 % and 10.37 %, respectively, in the double, triple and quadruple combinations of liver protective drugs. The double combination of DG and glutathione has a certain effect in the treatment of DILI[4], but the effectiveness and safety of the triple and more combinations of DG and other liver protective drugs have not been explored in the real world. To promote the rational use of liver protective drugs and reduce the waste of medical resources, it is necessary to comprehensively evaluate the clinical effectiveness and safety of combined use of DG with detoxification, choleretic and jaundice reducing liver protective drugs in the treatment of DILI in the real world.

MATERIALS AND METHODS

Subjects:

A total of 234 patients diagnosed with DILI and treated in our hospital from January 2018 to September 2020 were enrolled. Inclusion criteria were as follows: patients meeting the diagnostic criteria for DILI in the Guidelines for the Diagnosis and Treatment of DILI 2015. Exclusion criteria were as follows: patients complicated with underlying liver disease or liver injury caused by other reasons, or those allergic to any of the drugs (DG, reduced glutathione injection, Kuhuang injection and ursodeoxycholic acid capsules). Among them, 110 patients were treated with DG, and divided into three treatment groups (A, B and C) based on the drug combination. There were 34 cases in treatment group A, including 16 males and 18 females with an average age of (54.56±5.25) y old, 45 cases in treatment group B, including 16 males and 29 females with an average age of (54.61±5.21) y old, and 31 cases in treatment group C, including 12 males and 19 females with an average age of (54.69±5.32) y old. The remaining 124 patients, undergoing no DG treatment, were divided into three control groups (A, B and C). There were 37 cases in control group A, including 18 males and 19 females with an average age of (54.17±5.39) y old, 55 cases in control group B, including 17 males and 38 females with an average age of (54.21±5.39) y old, and 32 cases in control group C, including 9 males and 23 females with an average age of (54.16±5.25) y old. Before treatment, there were no statistically significant differences in age, gender and biochemical indices between treatment groups and control groups.

Administration methods:

In treatment group A, DG injection (Chiatai Tianqing Pharmaceutical Group Co., Ltd., 150 mg/bottle) was intravenously infused at 150 mg/time once a day, and reduced glutathione injection (Chongqing YaoPharma, 600 mg/bottle) was also intravenously infused at 600 mg/time once a day. On the basis of treatment in treatment group A, Kuhuang injection (Changshu Lei Yun Shang Pharmaceutical Co., Ltd., 10 ml/pcs) was intravenously infused at 60 ml/time once a day in treatment group B. Based on the treatment in treatment group B, ursodeoxycholic acid capsules (Losan Pharma GmbH, 250 mg/capsule) were orally taken at 250 mg/time once a day in treatment group C. Besides, reduced glutathione injection was intravenously infused alone at 600 mg/time once a day in control group A. On the basis of treatment in control group A, Kuhuang

injection was intravenously infused at 60 ml/time once a day in control group B. Based on the treatment in control group B, ursodeoxycholic acid capsules were orally taken at 250 mg/time once a day in control group C. The treatment lasted for 2 w in each group.

Detection of biochemical indices and inflammatory factors:

Biochemical indices serum alkaline phosphatase (ALP), GPT, gamma-glutamyl transpeptidase (GGT) and total bilirubin (TB) were detected using a Hitachi 7150 automatic biochemical analyzer. Inflammatory factors tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) were detected using a Siemens DPC1000 chemiluminescence immunoassay analyzer and kits (Wuhan BLY Biotechnology Co., Ltd.).

Detection of treatment response rate:

It is pointed out in the Guidelines for the Diagnosis and Treatment of DILI that changes in serum GPT, ALP, GGT and TB are currently the main laboratory indices for determining the absence or presence of liver injury and diagnosing DILI. According to the guidelines, the efficacy was evaluated as follows: Cured: clinical symptoms and signs disappear, and the levels of ALP, GPT, GGT and TB become close to normal. Effective: clinical symptoms and signs disappear or significantly relieved, and the levels of biochemical indices decline by 50 % compared with those before treatment. Ineffective: The above criteria are not met. Response rate=(cured case+effective cases)/total cases×100 %.

Observation of adverse reactions:

The adverse reactions of DG were recorded[7]: digestive system: anorexia, nausea, vomiting and abdominal distension, cardio-cerebrovascular system: headache, dizziness, chest tightness, palpitation and elevation of blood pressure, others: skin pruritus, urticaria, xerostomia and edema.

Statistical analysis:

All data were statistically analyzed using Statistical Package for the Social Sciences (SPSS) 24.0 software. Quantitative data in line with normal distribution were expressed as mean±standard deviation. Paired *t* test was performed within the group and independent samples, *t* test was performed between groups. Numerical data were expressed as constituent ratio or rate, and χ^2 test was performed. $p<0.05$ suggested that the difference was statistically significant.

RESULTS AND DISCUSSION

At 2 w after treatment, the response rates in treatment group A and B were significantly higher than those in control groups, and there were statistically significant differences ($p<0.05$). With the prolongation of treatment time, the response rates in treatment group A and B rose at 2 w compared with those at 1 w, and there was a statistically significant difference in treatment group B ($p<0.05$). In treatment group C, the response rate was significantly lower than that in control group C ($p<0.05$), while it declined at 2 w compared with that at 1 w, but no statistically significant difference was found ($p>0.05$). The response rate in each control group had no statistically significant difference at 2 w compared with that at 1 w ($p>0.05$). Moreover, χ^2 test was performed for the response rate in each treatment group, and the results revealed that the response rate was different among treatment group A, B and C at 2 w after treatment ($p<0.05$). It was found through further pairwise comparisons that the response rates in treatment group A and B were superior to that in treatment group C ($p<0.05$), while it had no statistically significant difference between treatment group A and B ($p>0.05$) (Table 1).

Compared with those before treatment, the levels of ALP, GPT and TB in treatment group A, the levels of ALP, GPT, GGT and TB in treatment group B, and the levels of ALP, GPT and GGT in treatment group C all significantly declined, and the differences were statistically significant ($p<0.05$). The changes in other biochemical indices in treatment groups had no statistically significant differences ($p>0.05$). In control group C, the level of TB significantly declined, while the level of GPT rose, showing statistically significant differences ($p<0.05$). The changes in biochemical indices in other control groups had no statistically significant differences compared with those before treatment ($p>0.05$).

The levels of biochemical indices in treatment groups declined within 2 w except treatment group C. In control group C, the level of TB showed a downward trend, while the level of ALP showed an upward trend, and the changes in biochemical indices within 2 w were not obvious in other control groups (Table 2).

Compared with those before treatment, the levels of inflammatory factors showed decreasing trends in each treatment group and control group, and there were no statistically significant differences between treatment groups and control groups at the same time point ($p>0.05$) (Table 3).

During treatment, no serious adverse reactions occurred in each group. There were 2 cases of stomach discomfort and constipation in treatment group A, 1 case of mild skin rash in treatment group B, and 1 case of mild constipation in treatment group C. No statistically significant difference was found in the incidence rate of adverse reactions among the 3 treatment groups ($p>0.05$).

In the present study, the double and triple combinations of DG had significant efficacy in the treatment of DILI, while the quadruple combination had no clinical significance. DG injection, reduced glutathione injection and Kuhuang injection are commonly used liver protective drugs. It is reported that DG can effectively improve two molecular mechanisms of liver injury, that is glycyrrhizic acid can inhibit the production of high mobility group box 1 (HMGB1)[8,9] and other related inflammatory factors such as IL-6 and TNF-α, thereby relieving liver inflammation[10,11]. Reduced glutathione is the most important antioxidant in hepatocytes, the decline in its level can alter the cell redox environment and increase the production of reactive oxygen species in cells[12], and supplementing it can resist the damage of oxidants to the liver. Kuhuang injection is derived from the Yinchenhao Decoction of Treatise on Febrile Diseases, which possesses the effects of removing jaundice and reducing enzymes, benefitting gallbladder and protecting liver, and it is also rich in amino acids

TABLE 1: TREATMENT RESPONSE RATES

Group	n	Efficacy at 1 w		Efficacy at 2 w	
		Effective	Ineffective	Effective	Ineffective
Treatment group A	34	26 (76.47 %)	8 (33.53 %)	29 (85.29 %)#	5 (14.71 %)
Control group A	37	22 (59.46 %)	15 (40.54 %)	14 (37.84 %)	23 (62.16 %)
Treatment group B	45	30 (66.67 %)	15 (33.33 %)	41 (91.11 %)*□#	4 (8.89 %)
Control group B	55	28 (50.91 %)	27 (49.09 %)	24 (43.64 %)	31 (56.36 %)
Treatment group C	31	19 (61.29 %)	12 (38.71 %)	15 (48.39 %)#	16 (51.61 %)
Control group C	32	23 (71.88 %)	9 (28.12 %)	24 (75.00 %)	8 (25.00 %)

*p<0.05 vs. at 1 w after treatment, #p<0.05 vs. control group

TABLE 2: BIOCHEMICAL INDICES BEFORE AND AFTER TREATMENT

Group	n	ALP (IU/l)			GPT (IU/l)			TB (μmol/l)			GGT (IU/l)		
		Before treatment	At 1 w after treatment	At 2 w after treatment	Before treatment	At 1 w after treatment	At 2 w after treatment	Before treatment	At 1 w after treatment	At 2 w after treatment	Before treatment	At 1 w after treatment	At 2 w after treatment
Treatment group A	34	153.49 ±14.39	138.28 ±10.29	128.39 ±9.12*	574.32 ±55.43	234.11 ±21.42	148.98 ±18.27*	105.29 ±24.38	91.21 ±16.31	66.87 ±5.48*	178.87 ±11.29	117.81 ±10.45	114.38 ±23.12
Control group A	37	155.78 ±15.62	150.89 ±15.18	152.35 ±14.32	578.38 ±34.23	261.31 ±21.45	244.38 ±22.31	104.32 ±17.34	104.88 ±15.13	105.49 ±18.19	178.29 ±24.38	177.56 ±21.45	177.68 ±22.37
Treatment group B	45	128.37 ±8.29	116.37 ±11.34	102.28 ±10.23*	419.28 ±32.32	178.28 ±21.23	82.19 ±7.27*	99.09 ±21.23	88.02 ±20.21	81.20 ±5.43*	143.27 ±18.29	113.36 ±14.31	96.37 ±11.23*
Control group B	55	127.46 ±7.94	125.38 ±9.28	135.37 ±11.24	419.19 ±28.32	311.25 ±21.25	320.18 ±34.29	99.09 ±6.37	95.01 ±6.24	91.28 ±8.27	142.36 ±27.38	167.31 ±25.32	189.09 ±34.28
Treatment group C	31	179.27 ±21.29	143.21 ±20.21	129.38 ±12.35*	178.22 ±15.48	118.28 ±11.23	83.28 ±7.82*	127.38 ±8.29	129.67 ±8.21	136.34 ±24.32	147.28 ±26.34	105.21 ±16.31	86.37 ±15.34*
Control group C	32	180.94 ±22.35	158.29 ±19.28	141.27 ±13.29	178.42 ±4.38	198.27 ±23.23	211.37 ±25.49*	126.38 ±9.02	112.31 ±9.43	82.34 ±9.29*	146.28 ±27.38	151.11 ±25.31	155.92 ±24.39

*p<0.05 vs. control group

TABLE 3: INFLAMMATORY FACTORS BEFORE AND AFTER TREATMENT

Group	n	TNF-α (pg/mL)			IL-6 (pg/mL)		
		Before treatment	At 1 w after treatment	At 2 w after treatment	Before treatment	At 1 w after treatment	At 2 w after treatment
Treatment group A	34	24.11±1.31	15.28±1.22*	11.39±1.12*	14.32±1.22	9.11±1.12*	6.98±0.27*
Control group A	37	24.22±1.27	15.89±1.18*	11.35±1.22*	14.38±1.23	9.31±1.42*	6.38±0.31*
Treatment group B	45	24.31±1.23	15.37±1.32*	11.28±1.22*	14.28±1.23	9.24±1.24*	6.19±0.27*
Control group B	55	24.46±1.24	15.38±1.24*	11.37±1.23*	14.19±1.31	9.24±1.26*	6.18±0.29*
Treatment group C	31	24.27±1.25	15.21±1.21*	11.18±1.32*	14.22±1.23	9.25±1.24*	6.28±0.32*
Control group C	32	24.44±1.31	159.29±1.22*	11.21±1.29*	14.42±1.21	9.21±1.23*	6.37±0.29*

*p<0.05 vs. control group

and trace elements required by the human body, thus promoting the recovery of hepatitis patients[13]. Therefore, these three kinds of liver protective drugs exert complementary therapeutic effects from different mechanisms of action. In this study, the results showed that compared with control group, the double combination of DG (DG+reduced glutathione) could greatly reduce TB, and the triple combination of DG (DG+reduced glutathione+Kuhuang) could greatly reduce ALP, GPT and GGT. Moreover, with the prolongation of treatment time, the response rates of double and triple combinations of DG rose at 2 w compared with those at 1 w, which had statistical significance in the triple combination. It can be seen that the combination of DG injection, reduced glutathione and Kuhuang injection has a synergistic liver protective effect. The liver is an important immune organ of the human body. During the onset of DILI, the specific immune response involving inflammatory factors is an important cause of liver injury and also an important mechanism of DILI. Kupffer's cells and intrahepatic monocytes produce and release inflammatory factors such as TNF-α and IL-6. TNF-α has direct hepatotoxicity and can directly cause damage to hepatocytes, resulting in hepatocyte necrosis. Besides, it can induce the production of IL-6 and other cytokines, and then these mediators promote the production of TNF-α, worsening liver injury. Therefore, DILI is a complex process involving multiple factors and mechanisms and inflammatory factors play important roles in the occurrence, progression and prognosis of DILI. In this study, the levels of inflammatory factors in each treatment group and control group were lower than those before treatment, and they had no statistically significant differences between treatment groups and control groups ($p>0.05$).

Ursodeoxycholic acid is a kind of hydrophilic bile acid, and it is currently the only drug approved by the Food and Drug Administration (FDA) for the treatment of cholestatic liver disease, which has been widely applied in the clinical treatment of various liver diseases, also obtaining good effects[14]. However, it has been found that ursodeoxycholic acid prevents hydroperoxide induced oxidative damage of hepatocytes through inducing reduced glutathione[15], and it can also interact with DG to induce cytochrome P450[16,17]. The quadruple combination already contains reduced glutathione and DG, so the effect of ursodeoxycholic acid fails to be fully exhibited, but it increases the metabolic stress of the liver. In this study, the results also manifested that the quadruple combination could raise the level of TB. Therefore, the combination of DG injection, reduced glutathione, Kuhuang injection and ursodeoxycholic acid had no obvious clinical significance compared with control group in the treatment of DILI. In this study, it was found that the double (DG+reduced glutathione) and triple combinations of DG (DG+reduced glutathione+Kuhuang) had a higher response rate than the quadruple combination of DG (DG+reduced glutathione+Kuhuang+ursodeoxycholic acid) in the treatment of DILI, while the response rate had no statistically significant difference between the double combination and the triple combination. Consistent with the research results of Long *et al.*[18], the results in this study manifested the response rates of the double and triple combinations of DG were 75.00 % and 64.40 % at 1 w, and 83.33 % and 91.11 % at 2 w, respectively. Whether the double combination of DG has a faster effect than its triple combination in the short term, and whether its triple combination has more advantages when the treatment time extends remain to be observed through more samples. In addition, the decline in biochemical indices was not significant compared with those before treatment in control group A (reduced glutathione alone) and control group B (reduced glutathione+Kuhuang) in the treatment of DILI, so the sample size needs expanding for further observation.

In the double, triple and quadruple combinations of DG in this study, no serious adverse reactions occurred, and stomach discomfort, constipation and skin pruritus with mild symptoms were observed occasionally. Therefore, the drug combination of DG has good safety in the treatment of DILI. However, it is reported that DG injection has severe allergic reactions such as laryngeal edema and anaphylactic shock[19], but they rarely occur. Therefore, it is necessary to ask patients about the allergic history in clinical use of DG preparations, and avoid using in allergic patients. If allergic reactions occur, the drug should be promptly withdrawn, and oxygen inhalation and intravenous injection of dexamethasone should be performed to promote the recovery. In this retrospective real world study, the grouping method did not conform to the principle of random medication, so there may be some biases. Moreover, the applicability of the results is limited, the sample size remains to be expanded and more high quality randomized controlled trials are needed.

In conclusion, compared with reduced glutathione alone and reduced glutathione+Kuhuang, the double combination (reduced glutathione+DG) and triple combination (reduced glutathione+Kuhuang+DG)

can improve the biochemical indices of liver function and increase the response rate, with a higher response rate than quadruple combination (reduced glutathione+Kuhuang+ursodeoxycholic acid+DG). The quadruple combination of DG has no clinical significance compared with the combination without DG, and may cause the waste of medical resources. At the same time, the double, triple and quadruple combinations of DG all have good safety. The conclusion in this study provides guidance for the reasonable and effective combination of DG in clinic.

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Conflict of Interests:

The authors declared no conflict of interest..

REFERENCES

1. Leise MD, Poterucha JJ, Talwalkar JA. Drug induced liver injury. In Mayo clinic proceedings 2014;89;95-106.
2. Chalasani NP, Hayashi PH, Bonkovsky HL, Navarro VJ, Lee WM, Fontana RJ. Practice Parameters Committee of the American College of Gastroenterology. ACG Clinical Guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol 2014;109:950-66.
3. Cheng X, Hu W, Dang X, Feng Q. Effects of diammonium glycyrrhizinate on serum inflammatory factors and peripheral blood T lymphocytes in patients with s chronic obstructive pulmonary disease. Rev Argentina de Clin Psicol 2020;29:376.
4. Yu YC, Mao YM, Chen CW, Chen JJ, Chen J, Cong WM *et al*. CSH guidelines for the diagnosis and treatment of drug-induced liver injury. Hepatol Int 2017;11:221-41.
5. Li QZ, Li DJ, Zhi LQ. Systematic review of diammonium glycyrrhizinate in the treatment of drug-induced liver injury. China Pharm 2010;21:1100-5.
6. Shi L, Hao Z, Zhang S, Wei M, Lu B, Wang Z, *et al*. Baicalein and baicalin alleviate acetaminophen induced liver injury by activating Nrf2 antioxidative pathway: The involvement of ERK1/2 and PKC. Biochem Pharmacol 2018;150:9-23.
7. Chen K, Yang R, Shen FQ, Zhu HL. Advances in pharmacological activities and mechanisms of glycyrrhizic acid. Curr Med Chem 2020;27:6219-43.
8. Mollica L, De Marchis F, Spitaleri A, Dallacosta C, Pennacchini D, Zamai M, *et al*. Glycyrrhizin binds to high-mobility group box 1 protein and inhibits its cytokine activities. Chem Biol 2007;14:431-41.
9. Brisby H, Olmarker K, Larsson K, Nutu M, Rydevik B. Proinflammatory cytokines in cerebrospinal fluid and serum in patients with disc herniation and sciatica. Eur Spine J 2002;11:62-6.
10. Wang CY, Kao TC, Lo WH, Yen GC. Glycyrrhizic acid and 18β-glycyrrhetinic acid modulate lipopolysaccharide-induced inflammatory response by suppression of NF-κB through PI3K p110δ and p110γ inhibitions. J Agric Food Chem 2011;59:7726-33.
11. Mahmoud AM, Al Dera HS. 18β-Glycyrrhetinic acid exerts protective effects against cyclophosphamide-induced hepatotoxicity: potential role of PPARγ and Nrf2 upregulation. Genes Nutr 2015;10:1-3.
12. Schafer FQ, Buettner GR. Redox environment of the cell as viewed through the redox state of the glutathione disulfide/glutathione couple. Free Radic Biol Med 2001;30:1191-212.
13. Fan Y, Ma Z, Zhao L, Wang W, Gao M, Jia X, *et al*. Anti-tumor activities and mechanisms of Traditional Chinese medicines formulas: A review. Biomed Pharmacother 2020;132:110820.
14. Alaca N, Ozbeyli D, Uslu S, Şahin HH, Yigitturk G, Kurtel H, *et al*. Treatment with milk thistle extract (Silybum marianum), ursodeoxycholic acid, or their combination attenuates cholestatic liver injury in rats: Role of the hepatic stem cells. Turk J Gastroenterol 2017;28:476-84.
15. Mitsuyoshi H, Nakashima T, Sumida Y, Yoh T, Nakajima Y, Ishikawa H, *et al*. Ursodeoxycholic acid protects hepatocytes against oxidative injury via induction of antioxidants. Biochem Biophys Res Commun 1999;263:537-42.
16. Zha J, Badri PS, Ding B, Uchiyama N, Alves K, Rodrigues-Jr L, *et al*. Drug interactions between hepatoprotective agents ursodeoxycholic acid or glycyrrhizin and ombitasvir/paritaprevir/ritonavir in healthy Japanese subjects. Clin Ther 2015;37:2560-71.
17. Han L, Wang R, Wu B, Gu Y, Yuan Y. Effect of diammonium glycyrrhizinate on pharmacokinetics of omeprazole by regulating cytochrome P450 enzymes and plasma protein binding rate. Xenobiotica 2019;49:975-80.
18. Long LH, Zeng ZL, Niu CY, Shi JF, Mao JJ, Yan J. Drug utilization review and drug utilization evaluation for evaluation of usage of hepatoprotective drugs in patients with hepatitis: Analysis of 129 cases. World Chin J Digestol 2014;22:4140-5.
19. Wang F, Weng Z, Li C, Peng G. A reliable method for the evaluation of the anaphylactoid reaction caused by injec drugs. Molecules 2016;21:1352.

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