Jurnal Farmasi dan Ilmu Kefarmasian Indonesia
Pharmacy and Pharmaceutical Sciences Journal
Published by Faculty of Pharmacy Universitas Airlangga
OPEN ACCESS
E-ISSN 2580-8303
P-ISSN 2406-9388

Jurnal Farmasi dan Ilmu Kefarmasian Indonesia Vol. 10 No. 1 April 2023, 126-140
DOI: 10.20473/jfiki.v10i12023. 126-140
Available online at https://e-journal.unair.ac.id/JFIKI/

Pharmacological Effects of *Glycyrrhiza glabra* L. as Antihepatitis and Hepatoprotective for Children

Faisal Akhmal Muslikh[1], Puja Adi Priatna[1], Wiwied Ekasari[2*]
[1]Master Program of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia
[2]Department of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia

*Corresponding author: wiwied-e@ff.unair.ac.id

Submitted: 21 November 2022
Accepted: 1 March 2023
Published: 30 April 2023

Abstract

Background: *The incidence of hepatitis in children has grown from the normal number of hepatitis cases since January 2022, and it will continue to rise since the etiology and pathophysiology are unknown. This case is distinct from those caused by the hepatitis A, B, C, D, and E viruses. Glycyrrhiza glabra L. is a medicinal herb that has long been used in medicine to treat respiratory, digestive, and immune system problems, but it is also known to have an inhibitory impact on the virus. Coronavirus-associated acute respiratory syndrome, hepatitis, herpes simplex virus, influenza virus.* ***Objective:*** *This article will look at Glycyrrhiza glabra L.'s antihepatitis and hepatoprotective properties.* ***Methods:*** *The Pubmed, Sage Journal, and Sciencedirect databases were searched using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards and the keywords "Glycyrrhiza glabra for hepatitis." The inclusion and exclusion criteria were followed.* ***Results:*** *From the search results, 17 publications were discovered that explain how Glycyrrhiza glabra L. can operate as an antihepatitis agent through anti-inflammatory, antiapoptotic, and hepatoprotective mechanisms.* ***Conclusion:*** *Glycyrrhiza glabra L. can be used as an anti-hepatitis and hepatoprotective in children at doses ranging from 240-480mg/kg/day.*

Keywords*: Glycyrrhiza glabra, Licorine, Pediatric Hepatitis, Hepatoprotective, Toxicity.*

How to cite this article:
Muslikh, F. A., Priatna, P. A. & Ekasari, W. (2023). Pharmacological Effects of *Glycyrrhiza glabra* L. as Antihepatitis and Hepatoprotective for children. *Jurnal Farmasi dan Ilmu Kefarmasian Indonesia,* 10(1), 126-140. http://doi.org/10.20473/jfiki.v10i12023.126-140

P-ISSN: 2406-9388
E-ISSN: 2580-8303

INTRODUCTION

Investigations into cases of pediatric hepatitis have been ongoing since January 2022 due to an increase in pediatric hepatitis cases, most of which are found in the United States. Through the end of April 2022, instances were reported on all three continents (North America, Asia, and Europe), with a pronounced concentration in Europe. As of May 11, approximately 450 suspected instances of acute hepatitis of unknown etiology had been documented. The ages of the affected children range from one month to sixteen. Of 31 known children with the syndrome, 15 in the US, 5 in Europe, and 11 in the UK required liver transplants (Branwell, 2022; WHO, 2022).

Due to a lack of data on the causative agent, method of transmission (including silent infection), and risk factors, the rise in severe acute hepatitis of unknown origin in children so cannot be estimated. The absence of a connection between these cases of "acute non-HepA-E hepatitis" and the recognized viral hepatitis agents (HAV (hepatitis A virus), HBV (hepatitis B virus), HCV (hepatitis C virus), HDV (hepatitis D virus), HEV(hepatitis E virus)) stimulated research into this growing disease to determine its aetiology and pathogenesis (ECDC, 2022; WHO, 2022). Other causes of hepatitis in children may be unknown autoimmune diseases, drug toxicity or specific drug reactions, and hidden metabolic or genetic disorders (Alexander and Deep, 2022; Ng *et al*., 2022).

Frequent gastrointestinal effects such as jaundice (71%), respiratory distress (19%), pale stools (50%), fever (31%), diarrhoea (45%), and vomiting (63%) were noted as symptoms (UKHSA, 2022). Concerning acute hepatitis in children is the high frequency of severe cases demanding liver transplantation in a few affected youngsters. The theory is that cofactors make kids more likely to get a mild adenovirus infection, leading to a more serious infection or liver damage caused by the immune system (ECDC, 2022).

The main challenge in combating diseases, particularly viral infections, is their fast adaptation and development of treatment resistance, along with introducing new hybrid viruses, which pose the greatest threat. Common medications are frequently insufficient and have a variety of negative effects. Natural medicines have grown in popularity in recent years (Cecilia and Thomas, 2012).Liquorice, or *Glycyrrhiza glabra* L., has been used for thousands of years as a herbal cure and is described in ancient Chinese, Indian, and Greek medical writings. It is predominantly employed in clinics to medicate respiratory and gastrointestinal disorders and increase immunity (Huan *et al*., 2021). Glycyrrhiza has been used to medicate chronic hepatitis for more than 50 years, with improved histology in the liver and decreased serum aminotransferases compared to placebo. For seven days, Glycyrrhiza hydromethanolic root extract at dosages of 300 and 600 mg/kg showed a hepatoprotective effect (Sharma and Agrawal, 2014). Glycyrrhizin has been shown to inhibit viral hepatitis, influenza virus, herpes simplex virus, and coronavirus-associated acute respiratory syndrome (Huan *et al*., 2021). Glycyrrhizin has been used as a treatment for chronic hepatitis under the brand name SNMC (stronger neo minophagen-C) for more than six decades (Clercq, 2000). It is utilized to treat hepatitis and allergies.

This study will look at hepatitis in children, the active chemicals in the plant, *in vitro*, *in vivo*, and clinical trials of the plant to see how well it fights hepatitis and hepatoprotective.

MATERIALS AND METHODS

This literature review meets the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. This article looks at hepatitis in children and the benefits of *Glycyrrhiza glabra* as an antihepatitis and hepatoprotective, from pre-clinical trials to clinical trials using *Glycyrrhiza glabra*'s way of working.

Search Methodology

Articles were found using the keywords "*Glycyrrhiza glabra* for hepatitis" and "*Glycyrrhiza glabra* for hepatoprotective" in the Pubmed, Sage Journal, and ScienceDirect databases. The language is English, and the article exploration spans the last ten years (2012-2022). The publications used on the potential of *Glycyrrhiza glabra* as an antihepatitis treatment ranged from preclinical trials to clinical trials, as well as additional liver functions such as hepatoprotective. Two writers each did their own search, using the criteria in table 1 for what to include and what to leave out.

Data extraction

The data was collected and checked by the authors using standard procedures. Information from selected articles on hepatitis in general, hepatitis in children, *Glycyrrhiza glabra*, pre-clinical studies, clinical studies, mechanism of action of *Glycyrrhiza glabra* as antihepatitis and hepatoprotective. There are 17 articles used in this literature review, which can be seen in Figure 1.

Table 1. Inclusion and exclusion criteria in journal searches

Criteria	Inclusion	Exclusion
Plant	*Glycyrrhiza glabra*; Licorine; the active compound of *Glycyrrhiza glabra*	Outside the plant *Glycyrrhiza glabra*
Year	2012-2022	Excluding 2012-2022
Biological activity	Antiviral activity in hepatitis	In addition to antiviral activity in hepatitis
Language	Articles in English	Apart from articles in English

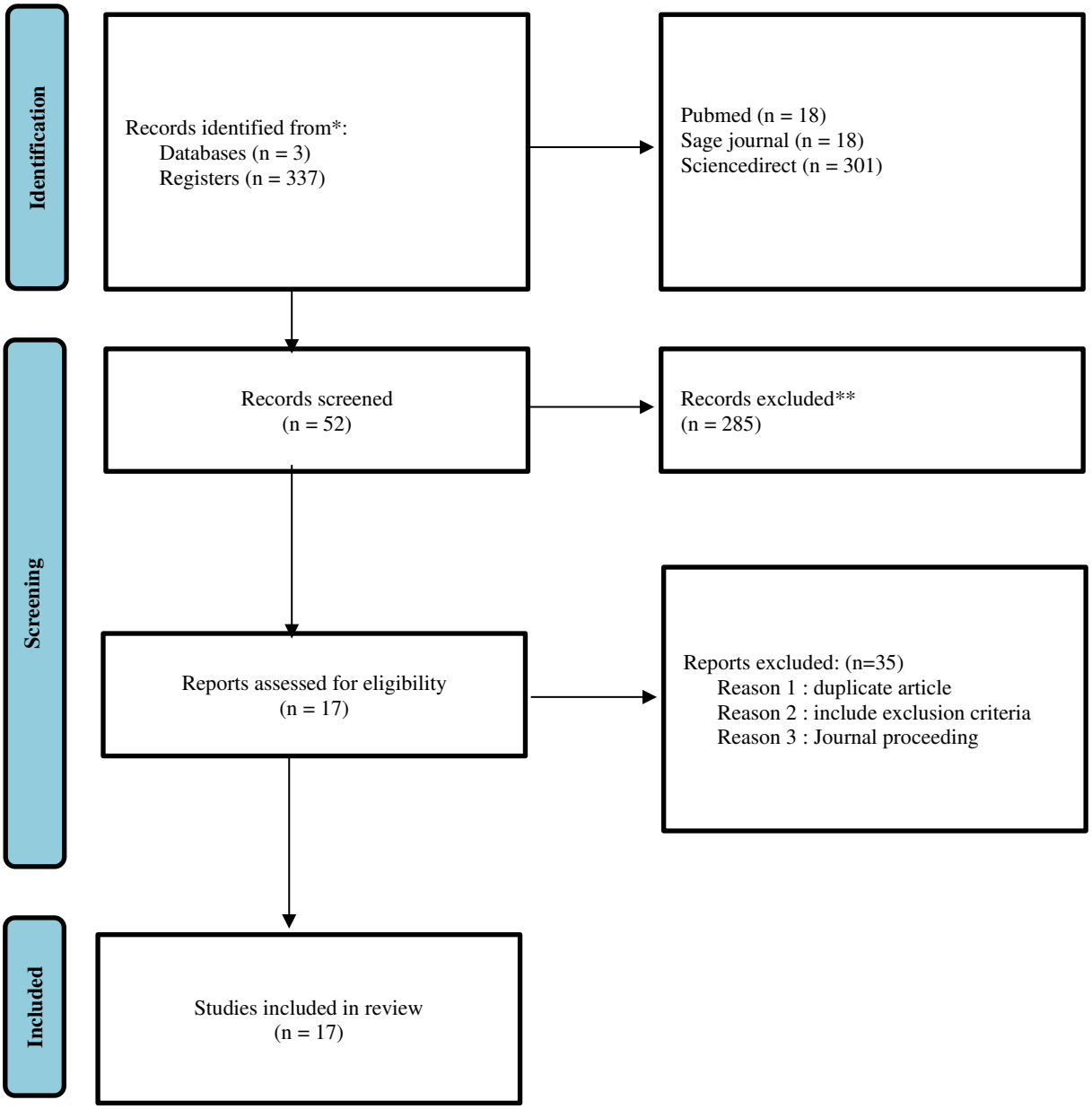


Figure 1. PRISMA guidelines flow chart in article search

Table 2. Systematic review data table

Source	Research results		
	In vitro	***In vivo***	**Clinical Trial**
Wang *et al*., 2013	√		
Adianti *et al*., 2014	√		
Sharma and Agrawal, 2014		√	
Yang *et al*., 2016		√	
Chen *et al*., 2017			√
Ali *et al*., 2018	√	√	
Lin *et al*., 2018			√
Maksoud *et al*., 2018		√	
Cao *et al*., 2019		√	
Polansky and Lori, 2020	√		√
Shi *et al*., 2020	√	√	
Zang, 2020	√		
Bell *et al*., 2021			√
Rad *et al*., 2021			√
Richard, 2021		√	
Tan *et al*., 2021	√	√	
Bisht *et al*., 2022	√		

RESULTS AND DISCUSSION

Children's Hepatitis Research

Hepatitis is a condition that causes parenchymal inflammation of the liver. Hepatitis is a disease that causes liver inflammation caused by poisons such as chemicals or medicines, as well as and infectious agents such as viruses. It is possible for inflammation to be either transient, lasting less than six months and resulting in normal liver function, or persistent (Chugh *et al*., 2016).

Children's non-infectious hepatitis can be brought on by chemical or drug exposure, immune system issues (such as autoimmune diseases), metabolic issues (such as Wilson disease and tyrosinemia), and abnormal metabolism (e.g., acetaminophen). Primary hepatotropic viruses cause the majority of infectious diseases. Acute hepatitis can be brought on by the cytomegalovirus (CMV), rubella virus, Epstein-Barr virus (EBV), parvovirus, adenovirus, enterovirus, human immunodeficiency virus (HIV) and herpes virus (HHV-7, HHV-6, HHV-2, HHV-1). *Leptospira*, *Coxiella burnetii*, and other pathogenic organisms that can cause hepatitis include the *Brucella* spp. (ECDC, 2022).

Due to a lack of knowledge regarding the etiologic agent, transmission route (including asymptomatic infection), and risk factors, it is impossible to assess the increase in children with severe acute hepatitis of unclear cause. Current consensus holds that cofactors that predispose children to adenovirus infection, which is generally mild, cause a more severe illness or immune-mediated liver damage (ECDC, 2022).

In the United Kingdom, a rise in the diagnosis of severe hepatitis in young children has been linked to an increase in the prevalence of adenovirus in young children. If adenovirus is found to be the cause or a contributing factor in these instances, an increase in circulating adenovirus could lead to a rise in severe hepatitis in children in other European nations. Although few cases requiring liver transplantation have been reported, they are considered to have a significant potential influence on the affected pediatric population. The ability to transplant and support pediatric liver failure patients differs significantly across EU/EEA nations. Hence, access to highly specialized pediatric intensive care and transplant facilities may influence outcomes, especially as the number of cases rises (ECDC, 2022).

Myalgia, nausea, vomiting, lethargy, tiredness, stomach discomfort, fever, and diarrhoea are some signs and symptoms of acute hepatitis. These signs and symptoms may last for several weeks. A significant fraction of acute viral hepatitis infections are asymptomatic, and children are far more prone than adults to develop mild or silent disease from hepatitis A or B infection (Reider and Beckingham, 2001).

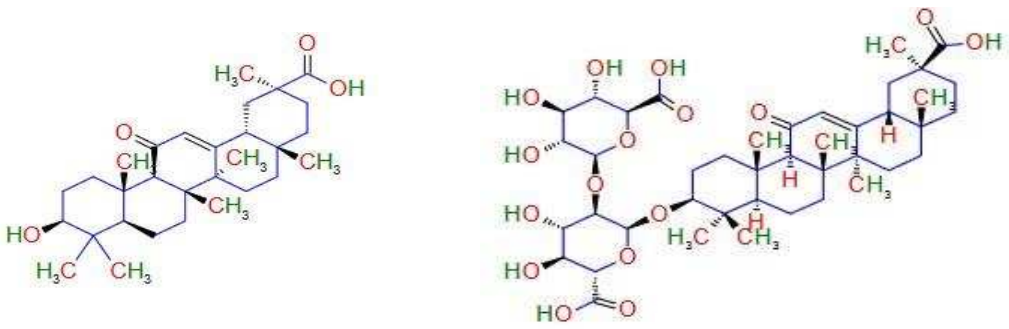
Figure 2. *Glycyrrhiza glabra* L (Sharma and agrawal, 2013; Zadeh *et al*., 2013)

Glycyrrhiza glabra L. (Fabaceae) is one of the plants that can be used as medicine (IT IS, 2022). Glycyrrhiza is derived from the Greek words glykos, sweet, and rhiza, root. This plant is native to parts of Asia and the Mediterranean (Sharma and Agrawal, 2013; Sharma *et al*., 2018). Ancient Egypt, Rome, East China, Greece, and the West all used the herbal remedy licorice, since the 16th century has been cultivated in Europe. Different species types of liquorice are grown in Europe, the United States, the Middle East, Southwest Asia, Central Africa, Afghanistan, and northern India (Wahab *et al*., 2021).

Licorice is a plant that grows to a height of ± 2.5 meters, around 7-15 cm for bearing pinnate leaves, with 9-17 leaves with a yellow-green oval/ellipse shape. The length of the flowers is between 0.8-1.2 cm with purple to pale whitish blue, spiny armpits. The petals are short, and conical in shape. The fruit is pod-shaped with a length of 2-3 cm and contains 3-5 brown seeds. Roots are ± 1 meter long, and usually harvested after 3-4 years (Zadeh *et al*., 2013; Sharma *et al*., 2018; Mamedoy and Egamberdieva, 2019).

Licorine has various health benefits, such as anti-tussive, expectorant, antibacterial, antioxidant, anticoagulant, antiviral, antiulcer, hepatoprotective, antitumor, antidiabetic (Sharma and Agrawal, 2013); treatment of chronic hepatitis (Zadeh *et al*., 2013); anticarcinogenic, antimutagenic (Sharma *et al*., 2018); dermatological effects, antidepressants, and memory enhancing activities (Mamedoy and Egamberdieva, 2019). This is due to the chemical compounds contained in licorine.

Glycyrrhiza glabra contains greater than 20 triterpenoids and almost 300 flavonoids. Figure 3 displays the primary, secondary metabolites of *Glycyrrhiza glabra*. The secondary metabolites include triterpenoid saponins, glycyrrhizin, glycosides, 4-methyl coumarin, prenylated biaurone, isoliquiritigenin, 7-acetoxy-2-methyl-isoflavone, licoagrone, 7-methoxy-2-methylisoflavone, glyzaglabrin, 7-hydroxy-2 methyl isoflavone, quercetin-3-glucoside, quercetin, liquiritigenin, and liqcoumarin. Other reported ingredients include vanone rhamnoglucoside, 18α-hydroxy glycyrrhetic acid, isoliquiritin, liquiritoside, liquiritin, licuraside, liquiritic acid, liquoric acid, isoglabrolide, glabrolide glabridin, glabrol, glyzarin, glycyrrhetinic acid, glyzaglabrin, licoisoflavones, licoflavonol, licoisoflavones A, B and glycyrrhizic acid. The primary ingredients in *Glycyrrhiza glabra* are glycyrrhizin and glycyrrhetinic acid. Glycyrrhizin can be transformed into glycyrrhetinic acid in humans through metabolic mechanisms. As a result, glycyrrhizin's pharmacological effects are comparable to those of glycyrrhetinic acid. (Thakur and Raj, 2017; Wahab *et al*., 2021).



Glycyrrhetinic acid Glycyrrhizin

Figure 3. Chemical content of *Glycyrrhiza glabra* (Thakur and Raj, 2017; Wahab *et al*., 2021).

Potential Chemical Content of *Glycyrrhiza glabra* as Hepatitis and Hepatoprotective Antivirus

Since 60 years ago, Glycyrrhizin has been used clinically as an antiallergic and antihepatitic drug under the brand name stronger neo minophagen-C (SNMC) to medicate chronic hepatitis. Due to its ability to prevent viral cells from adhering, glycyrrhizin possesses strong antiviral properties. The antiviral efficacy of ribavirin, mycophenolic acid, pyraziofurin, glycyrrhizin and 6-azauridine against the severe acute respiratory syndrome (SARS) virus's FFM-1 and FFM-2 clinical isolates was recently assessed. Glycyrrhizin was demonstrated to be the most efficient agent for inhibiting viral replication and might be used as a preventive measure. Patients with chronic HCV and HIV-1 have previously received treatment with glycyrrhizin. (Clercq, 2000).

Compared to placebo, glycyrrhizin significantly reduced serum aminotransferase and enhanced liver histology. Additionally, long-term glycyrrhizin use has been linked to reducing the risk of hepatocellular carcinoma in people with chronic HCV. Studies conducted *in vitro* (Ali *et al*., 2018; Sato *et al*., 1996) have demonstrated that glycyrrhizin alters cells' internal movement and can inhibit the HBV surface antigen.

An aglycone of glycyrrhizin called glycyrrhetinic acid (GA) lowers the expression of the P450 E1, sparing the liver. By enhancing GST (glutathione-S-transferase) and CYP1A1 activity, GA can help reduce the liver damage and oxidative brought on by aflatoxins. It may also contribute to anticarcinogenic effects by metabolically inactivating hepatotoxins (Chan *et al*., 2003). Glycyrrhizin and its analogues stimulate the synthesis and proliferation of hepatocyte DNA *in vitro* via activating epidermal growth factor receptors, activating the mitogen activated protein kinase (MAP kinase) pathway (Kimara *et al*, 2001).

Hepatoprotective and Antihepatitis Activities: from Non-Clinical to Clinical Trials

Glycyrrhizin is a primary compound of the Glycyrrhiza family and is reported to have antiviral activity. Glycyrrhizin inhibited HCV infection in Huh-7.5 cells. According to research, glycyrrhizin has receptor ligand binding activity triggered by peroxisome proliferators and has antibacterial activity against *Moraxella catarrhalis*, *Haemophilus influenzae*, and *Streptococcus pyogenes*. According to reports, glycyrol inhibits the function of calcineurin by binding to it and having an anti-inflammatory impact. The following Glycyrrhiza species have substances with anti-HCV action (Adianti *et al*., 2014).

Table 3. Compounds from Glycyrrhiza spp have anti-HCV activity (Adianti *et al*., 2014)

Compounds	IC_{50} (µg/mL)	Concentration (mg/mL)	Anti HCV Activity (% inhibition)		
			During (a)	After (b)	During and after (c)
Glycycoumarin	8,8	20	16,7	100	100
Glycyrin	7,2	15	18,4	98,3	99,6
Glycyrol	4,6	10	21,3	100	100
Liquiritigenin	16,4	30	15,5	90	87,2
Isoliquiritigenin	3,7	8	14,1	91	82,5
Licochalcone A	2,5	5	0	94,4	93,8
Glabridin	6,2	12	0	91	93,8

NB: Treatment is given only during, only after, or during and after virus inoculation. The concentration was determined from the results of $2xIC_{50}$. (a) sampling during virus inoculation; (b) sampling after virus inoculation; and (c) sampling both during and after virus inoculation.

The primary bioactive component of *G. glabra*, glycyrrhizin, also known as glycyrrhizic acid, has several pharmacological effects, including the prevention of viral replication in various DNA and RNA viruses, including HAV, HCV, herpes zoster, herpes simplex, HIV, cytomegalovirus and varicella. Glycyrrhizic acid blocks the production of prostaglandins, cyclooxygenase activity, and platelet aggregation, among other components of the inflammatory process (Basar et al., 2015). Glycyrrhizin inhibits aldosterone metabolism in the liver, and has mineralocorticoid and glucocorticoid activity. Other G. glabra secondary metabolites, like hydrocortisone, also have anti-inflammatory properties. The suppression of phospholipase A2, which is implicated in a number of inflammatory processes, may be the cause ofseveral inflammatory processes, may cause the anti-inflammatory activity.

Table 4. *Glycyrrhiza glabra* has the potential as a hepatoprotector and anti-hepatitis *in vitro*.

Source	Sample	Effect	*In vitro* research results
Wang *et al*., 2013	Glycyrrhizic acid	Antiviral	CVA16 inactivates and inhibits EV71 infection via post-viral cell entry.
Adianti *et al*., 2014; Zang, 2020	Glycycoumarin	Antiviral	Decreased translation of the HCV nonstructural protein, NS5A, from HCV replication.
Ali *et al*., 2018	Glycyrrhizin	Hepatitis B Antiviral	The administration of glycyrrhizin to PLC/PRF/5 cells decreased HBsAg generation into the culture medium, leading researchers to believe that glycyrrhizin alters hepatocyte surface characteristics and intracellular transport.
Cheel *et al*., 2010; Polansky and Lori, 2020	Infusion *G. glabra*	Antiviral	Proliferation of human lymphocytes should be activated.
Shi *et al*., 2020	Glycyrrhetinic acid	Antiviral	Repairs liver inflammatory damage via the HMGB1-TLR4 signaling pathway, leading to the release of TNF-α and IL-6.
Tan *et al*., 2021	Licorice root extract and Magnesium isoglycyrrhizinate	Hepatotoxicity	Activates the Nrf2 pathway, increases protein expression of Nrf2 target genes, mRNA and reduces triptolide-induced hepatotoxicity (TP).
Bisht *et al*., 2022	Glycyrrhizin	Hepatitis C Antiviral	When coupled with interferon α 2a, glycyrrhizin lowers HCV titers by resulting in a 50% decrease in HCV at a concentration of 14 ± 2 µg. Glycyrrhizin inhibits the expression of the core HCV 3a gene at the mRNA level.

Glycyrrhizin inhibited HBsAg secretion into culture media in PLC/PRF/5 cells, indicating that glycyrrhizin can decrease HBsAg secretion and exert its effect in hepatocytes chronically infected with HBV (Ali *et al*., 2018). Glycyrrhizin can stop HAV from sticking to and getting into PLC/PRF/5 cells. This means that hepatocytes treated with glycyrrhizin change how they move inside the cells and how they look on the outside (Sato *et al*., 1996).

Using interferon with ribavirin to treat HCV remains with issues, including being expensive, still having significant side effects, and reportedly failing to cure approximately fifty percent of illnesses (Moore *et al*., 2004). Therefore, a combination of interferon with glycyrrhizin was developed, which is cost effective, more efficacious and less toxic. Both its ability to stabilize membranes and its stimulation of endogenous interferon synthesis. When coupled with interferon 2a, glycyrrhizin has a synergistic impact that inhibits the production of the HCV 3a core gene at the mRNA level (Ashfq *et al* 2011; Bisht *et al*., 2022).

Damage generated by reactive oxygen species (ROS) as an effect of oxidative stress is the cause of TP-induced hepatotoxicity (Tan *et al*., 2018). The physiological response to oxidative stress is controlled by the nuclear factor erythroid 2-related factor 2 (Nrf2). Cytosolic Nrf2 is destroyed under physiologically normal conditions by binding to the Kelch-like ECH 1 and the proteasome (Keap1). When under oxidative and electrophilic stress, Nrf2 separates from Keap1, enters the nucleus, dimerizes with Maf-binding protein, and then interacts with the response element antioxidant (ARE) (Tan *et al*., 2018). Then, Nrf2 activates numerous cytoprotective proteins and drug efflux transporters, including hemeoxygenase 1 (HO-1), uridine diphosphate glucuronosyl transferase (UGT), and multidrug resistance-associated protein 2 (MRP2) (Yuan-Jing *et al*., 2016). The Nrf2/ARE signalling

pathway, particularly Nrf2, is thought to be a promising therapeutic target to stop oxidative stress-induced liver damage because it is the most important mechanism underlying cellular defence against oxidative stress (Tan *et al*., 2018).

EV71 and CVA16 are RNA viruses belonging to the genus Enterovirus. The virus can be spread by direct contact with a patient's blisters and other surfaces that can be contaminated with the virus in liquid form, such as by the faecal-oral route. Glycyrrhizic acid can inactivate CVA16 and inhibit EV71 infection through post-virus cell entry so that it can act as an antiviral (Wang *et al*., 2013)

Licorice can stimulate the activation and proliferation of human lymphocytes (B cells, NK cells, CD+, and CD8+). Participation of this type of immune cell, which confers an excess of innate immune cells such as neutrophils and macrophages at the site of infection, is linked to severe death and cases. So, licorice may help the adaptive immune system get rid of viruses early and stop inflammation from getting too bad (Polansky and Lori, 2020).

Table 5. *Glycyrrhiza glabra* has the potential as a hepatoprotector and anti-hepatitis *in vivo*.

Source	Sample	Effect	*In vivo* research results
Sharma and Agrawal, 2014	Glycyrrhiza hidro hydromethanolic root extract	Hepatoprotector	May improve liver histology and decrease serum aminotransferase, rat liver tissue exhibited a effect of hepatoprotective against CCl4-induced oxidative stress at dosages of 300 and 600 mg/kg for 7 days.
Yang *et al*., 2016	Magnesium isoglycyrrhizinate	Hepatoprotector	Capable of eliminating the proliferation of CD25, CD69+ subsets in primary CD4+ T-cells, administration caused a decrease in the expression of NALP3, NLRP6, and caspase-3.
Ali *et al*., 2018	Glycyrrhizin	Hepatoprotector	Intraperitoneally giving mice glycyrrhizin stops liver damage caused by lipopolysaccharide and D-galactosamine by stopping inflammation and the production of IL-18.
	Glycyrrhizin and glycyrrhetinic acid	Hepatoprotector	Administration markedly inhibited α2 (I) activation of the progression of liver fibrosis and the collagen gene promoter in transgenic mice produced by repeated CCl4 injections.
	Glycyrrhizin	Hepatoprotector	Glycyrrhizin stops mice from getting hepatitis caused by anti-Fas antibodies by working before proteases like CPP32.
Maksoud *et al*., 2018	Licorice root extract	Hepatoprotector	Hepatoprotective effect of ethanolic extract of liquorice, 400 mg/kg BW rats, against chronic hepatitis and silymarin through anti-inflammatory and antioxidant mechanisms.
Cao *et al*., 2019	Magnesium isoglycyrrhizinate	Hepatotoxicity	MgIG exerts beneficial effects on intestinal damage and MTX-induced hepatotoxicity.
Shi *et al*., 2020	Glycyrrhetinic acid	Antiviral	Inhibit activation of the hepatic inflammatory response by blocking HMGB1 cytokine activity and suppressing HMGB1 release in mice induced by murine hepatitis virus.
Richard, 2021	Glycyrrhizin	Antiviral	Mice that were given Glycyrrhizin were able to make IFN-γ. This was done by stimulating macrophages, such as by making NK activity go up.
Tan *et al*., 2021	Licorice root extract and Magnesium isoglycyrrhizinate	Hepatotoxicity	Increases protein expression of Nrf2 target and mRNA genes and decreases triptolide-induced hepatotoxicity through activating the Nrf2 pathway (TP).

Another study found that intraperitoneal treatment of glycyrrhizin plus epidermal growth factor (EGF) dramatically promoted liver regeneration and restoration of liver function in rats, which was feasible due to EGF receptor stimulation. Furthermore, glycyrrhizin and EGF stimulated hepatic DNA proliferation and synthesis while decreasing serum aspartate transaminase (AST) and alanine aminotransaminase (ALT) activity. This means that liver function will return quickly after a surgeon

removes a part of the liver. This gives doctors a new way to treat people with acute or chronic hepatitis C or after a live liver transplant (Ali *et al*., 2018).

Serum glutamic oxaloacetic transaminase (SGOT), also known as aspartate aminotransferase (AST), and serum glutamic pyruvic transaminase (SGPT), also known as alanine aminotransferase (ALT), are intracellular enzymes found primarily in the heart, liver, and skeletal tissue that are released from damaged tissue (necrosis) or changes in cell permeability). The normal range for SGOT and SGPT is 5-35 units/ml (Price and Wilson, 2005). Levels will rise if liver cells are damaged or in other conditions, such as a myocardial infarction.

Plasma aminotransferase enzymes might be used to make a diagnosis. Aminotransferases are generally intracellular enzymes, with low plasma levels signifying cellular content release during normal cell turnover. Elevated levels of aminotransferase enzymes may suggest damage to enzyme-rich cells caused by physical trauma or a disease condition that results in cell lysis and the release of intracellular enzymes into the blood. When present in plasma, aminotransferase enzymes such as AST and ALT can be used to make a diagnosis. Plasma AST and ALT levels are raised in practically all liver illnesses, but they are particularly high in situations that cause necrosis, such as severe viral hepatitis, toxic damage, and persistent bleeding. Aminotransferases can be raised in diseases other than the liver, such as myocardial infarction and muscular problems. These illnesses, however, are frequently clinically indistinguishable from liver disease (Champe *et al*., 2009).

A hepatoprotector is a medication that can protect the liver against the harmful effects of endogenous or exogenous causes by reducing inflammation and disease progression (Sulaiman, 2012). Chronic hepatitis is a chronic liver condition that can progress to cirrhosis, hepatocellular cancer, and potentially liver failure. Glycyrrhiza has been used to treat chronic hepatitis for over 50 years, with improved liver histology and decreased serum aminotransferases compared to placebo. In Swiss albino rat liver tissue, Glycyrrhiza hydromethanolic root extract at dosages of 300 and 600 mg/kg/day for seven days was hepatoprotective against CCl4-induced oxidative stress (Sharma and Agrawal, 2014). As shown by a rapid rise in liver function measurements and the formation of toxic compounds from the peroxidation of polyunsaturated fatty acids (MDA) in biological membranes (Maksoud *et al*., 2018), CCl4 damages liver tissue. It causes oxidative stress similar to that seen in humans with chronic hepatitis.

Magnesium isoglycyrrhizinate (MIG) is a novel glycyrrhizic acid stereoisomer that is clinically employed as a hepatoprotective medication with a stronger effect and fewer adverse effects than glycyrrhizic acid. Furthermore, MGL can protect against hepatotoxicity caused by free fatty acid exposure, ischemia/reperfusion-induced liver injury, and decrease ethanol-induced lipid peroxidation (Yang *et al*., 2016; Tan *et al*., 2018).

Interferon (IFN) can cure hepatitis B patients with or without adenine arabinoside. IFNs can reduce hepatitis B and DNA polymerase surface antigen levels in hepatic patients. GL also increased IFN-γ synthesis in human T cells and promoted IFN production in mice, which was produced by stimulation of macrophages and increased natural killer (NK) activity. After GA therapy, spleen IFN-α, IFN-γ, and IL-12 expression increased. Through IFN, GL significantly lowers inflammation. They came to the conclusion that GL's anti-inflammatory effect in enteritis may be linked to its ability to block the IFN signalling pathway (Richard, 2021).

Methotrexate (MTX) was first used to treat juvenile acute leukaemia, and it is now used to treat psoriasis and rheumatoid arthritis worldwide (Jenko *et al*., 2018). However, it has a hazard profile similar to hepatotoxicity (Conway and Carey, 2017). MTX has been linked to an increase in liver transaminases, changes in liver histology, and the development of cirrhosis and fibrosis (Conway and Carey, 2017). Due to hepatotoxicity, MTX's clinical applicability is limited. Aminopterin, the first folate antimetabolite that may prevent the synthesis of purines and pyrimidines and DNA synthesis, repair, and replication, has a stable derivative called MTX. Also, MTX affects the intestinal mucosa, which changes the way the intestinal barrier works and lets bacteria move into the liver (Cao *et al*., 2019). This is called hepatotoxicity.

Table 6. *Glycyrrhiza glabra* has clinical potential as hepatoprotective and antihepatitic.

Source	Sample	Effect	Clinical Trial Research Results
Subrat *et al*., 2012	Interferon (I) α-2b 3 MU/day + Ribavirin (R)	Hepatitis C Antiviral	Ninety-nine patients were given six months of treatment, where the sustained viral response (SVR)

	1000mg/ day (I+R) and Interferon (I) α-2b 3 MU/ day + glycyrrhizin (G) 250 mg (I+G)		was much higher in group I + R than in group I + G (65.7% vs 46.9%, OR = 2.2, P = 0, 03).
Chen *et al*., 2017	Long-Dan-Xie-Gan-Tang Products (*Glycyrrhiza glabra, Gentiana scabra, Scutellaria baicalensis, Gardenia jasminoides, Plantago asiatica, Alisma orientalis, Clematis montana, Angelica sinensis, Rehmannia glutinosa, and Bupleurum chinense*)	Hepatitis C Antiviral	The 36 chronic hepatitis C patients who received RYJGT treatment for 12 weeks had a significantly higher HCVRNA reduction ratio and better symptoms than those who received placebo.
Lin *et al*., 2018	Glycyrrhizin 100 mL (200 mg) i.v/day for five days oral entecavir	Hepatitis B Antiviral	A trial in 10 chronic hepatitis B patients with acute-chronic liver failure resulted in ALT levels halving after two days of treatment. Liver compensatory return within 30 days was achieved in 8 patients (80%).
Cheel *et al*., 2010; Polansky and Lori, 2020	Tincture of *G. glabra*	Antiviral	At 24 hours, 16 people who took the placebo said CD69 expression went up in CD8, CD4+, and NK cells.
Bell *et al*., 2021	Glycyrrhizin	Hepatoprotector	After 12 weeks of therapy, ALT levels dropped more with glycyrrhizin than with placebo, and necroinflammation and fibrosis got better after 52 weeks of treatment.
	Glycyrrhizin and ursodeoxycholic acid	Hepatitis C Antiviral	The medication is effective and safe in raising specific liver enzyme abnormalities and can be used as an alternative to interferon in chronic HCV infection, particularly for interferon-resistant patients, according to clinical trials involving 170 participants.
Rad *et al*., 2021	Stronger Neo-Minophagen C (SNMC)	Hepatitis C Antiviral	Giving SNMC to patients can improve liver pathology in chronic hepatitis patients. Besides that, SNMC can inhibit inflammation and liver necrosis in chronic hepatitis C patients.

Compared to the placebo group, using a Long-Dan-Xie-Gan-Tang product, including a wide variety of herbs including *Glycyrrhiza glabra* resulted in a substantially higher reduction in the blood HCV RNA ratio and a better TCM pattern, particularly "Wet Heat" and "Heart Qi Depression." When administered to patients with chronic HCV, this medication is also relatively safe. Only four patients suffered adverse effects (for example, diarrhoea and gastrointestinal problems), which were moderate and resolved spontaneously or with extra therapy (Chen *et al*., 2017). In a randomized, double-blind study, we provide scientific proof that herbal regimens of this product can be utilized as an alternative therapy option for individuals who do not respond to or are not suitable for ribavirin/interferon treatment in the treatment of patients with chronic HCV (Tang, 2006).

Overall, IFN, in conjunction with ribavirin demonstrated considerably greater SVR than IFN alone. IFN coupled with glycyrrhizin, on the other hand, was found to be less hazardous than ribavirin. As a result, glycyrrhizin may be used instead of ribavirin in combination with IFN as an HCV therapy regimen if ribavirin causes negative effects in the patient (Subrat *et al*., 2012).

Studies that combined glycyrrhizin and entecavir showed that the combination treatment was safe and effective for about five days. This could mean chronic HBV with acute-chronic liver failure could stay in the hospital less and live longer (Lin *et al*., 2018).

SNMC is an injectable medication comprising the active component glycyrrhizin, L-cysteine, and glycine. It has been used in Japan for more than 30 years to treat chronic hepatitis and has been demonstrated to be beneficial in preventing the development of

hepatocellular carcinoma in HCV patients. Since 1948, SNMC has been utilized to treat allergy illnesses and chronic liver disease in Japan. SNMC has been shown to dramatically lower serum levels of AST, ALT, and -GTP. Since 1979, SNMC has been approved to treat chronic liver disease in Japan, where there are problems with how the liver works (Saito *et al*., 2016).

Toxicity study on Glycyrrhiza glabra

A single oral dose of 1000 mg/kg BW female albino rats in an acute toxicity test with aqueous and ethanol extracts of *Glycyrrhiza glabra* did not result in death. A single dose of 1500 mg/kg BW of *Glycyrrhiza glabra* aqueous extract orally administered to Swiss albino mice did not result in mortality after 14 days, but there were physical changes in Swiss albino mice (Chowdhury *et al*., 2013; Gupta *et al*., 2016; Nazari *et al*., 2017). Because of the influence of first-pass metabolism and limited oral absorption, acute toxicity by IV/IP has a considerable variance in LD_{50} values (Nazari *et al*., 2017).

Subacute toxicity testing of *Glycyrrhiza glabra* aqueous extract (100; 200; 500 mg/kg BW male Wistar rats) revealed a dose-dependent inhibitory effect on the adrenal-pituitary axis, resulting in a hyper mineralocorticoid state with decreased levels of adrenocorticotropic, potassium, aldosterone, and cortisol, as well as increased concentrations of ren (Al-Qawari *et al*., 2002; Nazari *et al*., 2017).

Subchronic toxicity experiments on *Glycyrrhiza glabra* aqueous extracts (500; 1000; 2000 mg/kg BW, orally, for nine weeks) revealed no long-term effect in experimental animals. Furthermore, it demonstrates that it has no major harmful effect on reproductive organs (Shin *et al*., 2008; Nazari *et al*., 2017). Meanwhile, testing of 12 weeks of subchronic glycyrrhizin (0.1-1mg/mL in drinking water) revealed cardiovascular adverse effects in Sprague-Dawley male rats. This leads to an overabundance of mineralocorticoids, water retention, systemic hypertension, hypokalemia and hypernatremia. This demonstrates glycyrrhizic acid's beneficial effect on boosting right atrial and pulmonary artery pressure. Histological tests (Ruszymah *et al*., 1995; Nazari *et al*., 2017) show that pulmonary hypertension is real.

In male and female rats, chronic toxicity tests on Licorine flavonoid oil (400; 600; 800; 1600 mg/kg, orally, for 90 days) revealed a decrease in hematocrit, erythrocytes, and haemoglobin. Furthermore, there was an increase in mean corpuscular haemoglobin (MCH), white blood cell count (WBC) and mean corpuscular haemoglobin concentration (MCHC), a delay in prothrombin time (PT) and activated partial thromboplastin time (APTT), an increase in Na+ levels in urine and an increase in urine volume (Nakagawa *et al*., 2008; Nazari *et al*., 2017). A 45-day chronic toxicity test of G. glabra propylene glycol root extract (1; 2; 4 mg/L) on male black molly fish revealed 100% mortality for 4 mg/L on day 7, 34% mortality for 2 mg/L on day 15, and 17% mortality for 1 mg/L on day 25, followed by a decreased appetite on day 3, weight loss, and liver damage that increased with increasing dose (Radhakrishnan *et al*., 2005).

Because of the effect of first-pass metabolism and the decreased absorption of oral administration compared to IV/IP administration, *G. glabra* can be administered orally as a therapy. In individuals with hypertension and hypokalemic diseases, long-term therapy of *G. glabra* should be considered. Furthermore, it is contraindicated in pregnant women and neonates since licorine intake during pregnancy might cause premature birth, alterations in the hypothalamic-pituitary-adrenocortical axis, and cognitive impairment in newborns. It should also be taken with caution in women who have a family history of preeclampsia (Nazari *et al*., 2017).

G. glabra extracts at doses of 300, 400, and 600 mg/kg BW rats per day demonstrated hepatoprotective effects by improving liver histology, lowering serum aminotransferases, and anti-inflammatory and antioxidant activity (Sharma and Agrawal, 2014; Maksound, 2014). To convert a safe dose for children from a rat dose to a human dose, the dose for children per day ranges from 240 mg/kg/BW (equal to a rat dose of 300 mg/kg BW) to 480 mg/kg BW (corresponding to a rat dose of 600 mg).

CONCLUSION

Glycyrrhiza glabra is a medicinal plant with over 20 triterpenoids and over 300 flavonoids. Glycyrrhizin and glycyrrhetinic acid are the primary, secondary metabolites of *Glycyrrhiza glabra*. According to the findings of this study, *Glycyrrhiza glabra* exhibits antihepatitis and hepatoprotective activity with multiple mechanisms, such as anti-inflammatory, antiapoptotic, and hepatoprotective activity in clinical trials, *in vivo*, and *in vitro*. The dose that can be applied to children from the research results described is between 240 and 480 mg/kg/day.

REFERENCES

Adianti, M., Aoki, C., Komoto, M., Deng, L., Shoji, I., Wahyuni, T.S., ... & Hotta, H. (2014). Anti-

hepatitis C virus compounds obtained from *Glycyrrhiza uralensis* and other Glycyrrhiza species. *Microbiology and immunology*; 58(3): 180-187.

Al-Qarawi, A.A., Abdel-Rahman, H.A., Ali, B.H., & El Mougy, S.A. (2002). Liquorice (*Glycyrrhiza glabra*) and the adrenal-kidney-pituitary axis in rats. *Food and chemical toxicology*; 40(10); 1525-1527.

Alexander, E. C., & Deep, A. (2022). Characterization of a Hepatitis Outbreak in Children, 2021 to 2022. *JAMA Network Open*, 5(10), e2237091-e2237091.

Ali, M., Khan, T., Fatima, K., Ali, Q.U.A., Ovais, M., Khalil, A.T., Ullah, I., Raza, A., Shinwari, Z.K., Idrees, M. (2018). Selected hepatoprotective herbal medicines: Evidence from ethnomedicinal applications, animal models, and possible mechanism of actions. *Phytother Res*; 32(2); 199-215. doi: 10.1002/ptr.5957.

Al-Razzuqi, R., Al-Jawad, F., Al- Hussaini, J., Al-Jeboori, A. (2012). Hepatoprotective effect of *Glycyrrhiza glabra* in carbon tetrachloride-induced model of acute liver injury. *J Phys Pharm Adv*; 2; 259-63

Anagha, K., Manasi, D., Priya, L., Meera, M. (2014). Scope of *Glycyrrhiza glabra* (Yashtimadhu) as an Antiviral agent: A Review. *Int.J.Curr.Microbiol.App.Sci*; 3(12); 657-665

Ashfaq, U.A., Masoud, M.S., Nawaz, Z. (2011). Glycyrrhizin as antiviral agent against Hepatitis C Virus. *J Transl Med*; 9; 112. doi:10.1186/1479-5876-9-112

Baker JM, Buchfellner M, Britt W, Sanchez V, Potter JL, Ingram LA, Shiau H, Gutierrez Sanchez LH, Saaybi S, Kelly D, Lu X, Vega EM, Ayers-Millsap S, Willeford WG, Rassaei N, Bullock H, Reagan-Steiner S, Martin A, Moulton EA, Lamson DM, St George K, Parashar UD, Hall AJ, MacNeil A, Tate JE, Kirking HL. 2022. Acute Hepatitis and Adenovirus Infection Among Children – Alabama. *MMWR Morb Mortal Wkly Rep*; 6(18); 638-640. doi: 10.15585/mmwr.mm7118e1.

Basar, N., Oridupa, O. A., Ritchie, K. J., Nahar, L., Osman, N. M. M., Stafford, A., ... & Sarker, S. D. (2015). Comparative cytotoxicity of *Glycyrrhiza glabra* roots from different geographical origins against immortal human keratinocyte (HaCaT), lung adenocarcinoma (A549) and liver carcinoma (HepG2) cells. *Phytotherapy Research*; 29(6); 944-948.

Bell, R. F., Moreira, V. M., Kalso, E. A., & Yli-Kauhaluoma, J. (2021). Liquorice for pain?. *Therapeutic advances in psychopharmacology*; 11; 20451253211024873.

Bisht, D., Rashid, M., Arya, R.K.K., Kumar, D., Chaudhary, S.K., Rana, V.S., Sethiya, N.K. (2022). Revisiting liquorice (Glycyrrhiza glabra L.) as anti-inflammatory, antivirals and immunomodulators: Potential pharmacological applications with mechanistic insight. *Phytomed Plus*; 2(1);100206. doi: 10.1016/j.phyplu.2021.100206.

Branswell, H. (2022). CDC investigating 109 unusual hepatitis cases in kids in outbreak. https://www.statnews.com/2022/05/06/cdc-looking-at-cases-of-109-children-in-suspected-hepatitis-outbreak/

Cao, Y., Shi, H., Sun, Z., Wu, J., Xia, Y., Wang, Y., ... & Lu, Y. 2019. Protective effects of magnesium glycyrrhizinate on methotrexate-induced hepatotoxicity and intestinal toxicity may be by reducing COX-2. *Frontiers in pharmacology*; 10; 119.

Cecilia, P., Thomas, E., (2012). Antiviral Medicinal Herbs and Phytochemicals. *Journal of Pharmacognosy*; 3(1); 45-48

Chan, H.T., Chan, C., Ho, J.W. (2003). Inhibition of glycyrrhizic acid on alfatoxin B1-induced cytotoxicity of hepatoma cells. *Toxicology*; 188:211–217

Champe PC, Harvey RA, Ferrier DR. *Biochemistry. Edisi ke-4. Philadelphia*: Lippincott Williams & Wilkins; 2009

Cheel, J., Onofre, G., Vokurkova, D., Tůmová, L., & Neugebauerova, J. 2010. Licorice infusion: Chemical profile and effects on the activation and the cell cycle progression of human lymphocytes. *Pharmacognosy Magazine*; 6(21); 26.

Chen, F.P., Chang, C.M., Wu, T.P., Yang, J.L., Kung, Y.Y., Huang, Y.H., Su, C.W., Lan, K.H., Chiang, S.C., Hwang, S.J. (2017). Clinical efficacy of Rong-Yang-Jyh-Gan-Tang on patients with chronic hepatitis C: A double-blinded randomized placebo-controlled crossover study. *J Ethnopharmacol*; 196;1-8. doi: 10.1016/j.jep.2016.12.013.

Chowdhury, B., Bhattamisra, S. K., & Das, M. C. (2013). Anti-convulsant action and

amelioration of oxidative stress by *Glycyrrhiza glabra* root extract in pentylenetetrazole-induced seizure in albino rats. *Indian journal of pharmacology*; 45(1); 40.

Chugh, A., Maximos, M., Perlman, M., Gonzalez-Peralta, R.P. (2016). Viral Hepatitis in Children: A Through E. *Pediatric Annals*; 45(12); e420-e6.

Clercq, E. (2000). Current lead natural products for the chemotherapy of human immunodeficiency virus (HIV) infection. *Med Res Rev*;20;323–349

Conway, R., & Carey, J. J. 2017. Risk of liver disease in methotrexate treated patients. *World Journal of Hepatology*; 9(26);1092.

ECDC (European Centre for Disease Prevention and Control). (2001). *Increase in severe acute hepatitis cases of unknown aetiology in children*, ECDC: Stockholm.

Gupta, M., Sasmal, S. K., Karmakar, N., Sasmal, S., & Chowdhury, S. (2016). Experimental evaluation of antioxidant action of aqueous extract of Glycyrrhiza glabra Linn. roots in potassium dichromate induced oxidative stress by assessment of reactive oxygen species levels. *Inter. J. Pharmacognosy and Phytochem. Res*; 8(8); 1325-1333.

Huan, C., Xu, Y., Zhang, W., Guo, T., Pan, H. and Gao, S. (2021). Research Progress on the Antiviral Activity of Glycyrrhizin and its Derivatives in Liquorice. *Front. Pharmacol*; 12;680674. doi: 10.3389/fphar.2021.680674

ITIS. Accessed on 7 june 2022. https://www.itis.gov/servlet/SingleRpt/SingleRpt?search_topic=TSN&search_value=26718#null . diakses pada 7 juni 2022

Jenko, B., Tomšič, M., Jekić, B., Milić, V., Dolžan, V., & Praprotnik, S. (2018). Clinical pharmacogenetic models of treatment response to methotrexate monotherapy in Slovenian and Serbian rheumatoid arthritis patients: differences in patient's management may preclude generalization of the models. *Frontiers in pharmacology*; 9; 20.

Kimura, M., Inoue, H., Hirabayahi, K., Natsume, H., Ogihara, M. (2001). Glycyrrhizin and some analogues induce growth of primary cultured adult rat hepatocytes via epidermal growth factor receptors. *Eur J Pharmacol*; 431;151–161

Korenaga, M., Hidaka, I., Nishina, S., Sakai, A., Shinozaki, A., Gondo, T., (2011). A Glycyrrhizin-Containing Preparation Reduces Hepatic Steatosis Induced by Hepatitis C Virus Protein and Iron in Mice. *Liver Int*; 31(4); 552–560. doi:10.1111/j.1478-3231.2011.02469.x

Lin, Chien-Chu; Weng, Meng-Tzu; Chung, Chen-Shuan; Liang, Cheng-Chao. (2019). The dramatic effect of intravenous glycyrrhizin on acute-on-chronic hepatic failure in chronic hepatitis B patients without liver cirrhosis. *Advances in Digestive Medicine*; 6;153–157. doi:10.1002/aid2.13131

Mamedov, N. A., & Egamberdieva, D. (2019). Phytochemical constituents and pharmacological effects of licorice: a review. *Plant and Human Health*; 3; 1-21.

Maksoud, H.A., Magid, A., Mostafa, Y.M., Elharrif, M., Sorour, R., & Sorour, M. (2018). Ameliorative Effect of Liquorice Extract Versus Silymarin in Experimentally Induced Chronic Hepatitis: A Biochemical and Genetical Study. *Clinical Nutrition Experimental*; 23. doi: 10.1016/j.yclnex.2018.10.005.

Matsumoto, Y., Matsuura, T., Aoyagi, H., Matsuda, M., Hmwe, S.S., Date, T., (2013). Antiviral Activity of Glycyrrhizin against Hepatitis C Virus In Vitro. *PLoS One*; 8(7); e68992. doi:10.1371/journal.pone.0068992

Matsuo, K., Takenaka, K., Shimomura, H., Fujii, N., Shinagawa, K., Kiura, K., 2001. Lamivudine and Glycyrrhizin for Treatment of Chemotherapy-Induced Hepatitis B Virus (HBV) Hepatitis in a Chronic HBV Carrier with NonHodgkin Lymphoma. *Leuk. Lymphoma*; 41(1-2);191–195. doi:10.3109/10428190109057970

Moore, M.M., Elpern, D.J., Carter, D.J. (2004). Generalized nummular eczema secondary to interferon alfa-2b plus ribavirin combination therapy in a patient with chronic hepatitis C virus infection. *Arch Dermatol*; 140;215-217.

Nakagawa, K., Kitano, M., Kishida, H., Hidaka, T., Nabae, K., Kawabe, M., & Hosoe, K. (2008). 90-Day repeated-dose toxicity study of licorice flavonoid oil (LFO) in rats. *Food and chemical toxicology*; 46(7); 2349-2357.

Nazari, S., Rameshrad, M., & Hosseinzadeh, H. (2017). Toxicological effects of Glycyrrhiza glabra (licorice): a review. *Phytotherapy research*; 31(11); 1635-1650.

P-ISSN: 2406-9388
E-ISSN: 2580-8303

Ng, V., Science, M., Feld, J., *et al*. (2022). Severe acute hepatitis in children of unknown etiology. *Science Briefs of the Ontario COVID-19 Science Advisory Table*. https://doi.org/10.47326/ocsat.2022.03.63.1.0

Polansky, H., & Lori, G. (2020). Effects of Gene-Eden-VIR and Novirin on SARS-CoV: Implications for COVID-19. *Journal of Evidence-Based Integrative Medicine*; 25; 2515690X20932523.

Rad, S.J., Quispe, C., Herrera-Bravo, J., Belén, L.H., Kaur, R., Kregiel, D., ... & Suleria, H.A.R. (2021). Glycyrrhiza Genus: Enlightening Phytochemical Components for pharmacological and health-promoting abilities. *Oxidative medicine and cellular longevity*. 2021.

Radhakrishnan, N., Gnanamani, A., & Sadulla, S. (2005). Effect of licorice (*Glycyhrriza glabra* Linn.), a skin-whitening agent on Black molly (*Poecilia latipinnaa*). *Journal of applied cosmetology*; 23(4); 149.

Richard, S.A. (2021). Exploring the pivotal immunomodulatory and anti-inflammatory potentials of glycyrrhizic and glycyrrhetinic acids. *Mediators of Inflammation*. 2021.

Romero, M.R., Efferth, T., Serrano, M.A., Castaño, B., Macias, R.I.R., Briz, O., (2005). Effect of Artemisinin/artesunate as Inhibitors of Hepatitis B Virus Production in an "In Vitro" Replicative System. *Antiviral Res*; 68(2); 75–83. doi:10.1016/j.antiviral.2005.07.005

Ruszymah, B.H.I., Nabishah, B.M., Aminuddin, S., & Khalid, B.A.K. (1995). Effects of glycyrrhizic acid on right atrial pressure and pulmonary vasculature in rats. *Clinical and Experimental Hypertension*; 17(3); 575-591.

Ryder S, Beckingham I. 2001. Acute hepatitis. BMJ.322(7279):151-3.

Sato, H., Goto, W., Yamamura, J., Kurokawa, M., Kageyama, S., Takahara, T. Shiraki, K. (1996). Therapeutic basis of glycyrrhizin on chronic hepatitis B. *Antiviral Research*; 30(2–3); 171–177.

Saito, Z., Kaneko, Y., Kinoshita, A., Kurita, Y., Odashima, K., Horikiri, T., ... & Kuwano, K. (2016). Effectiveness of hepatoprotective drugs for anti-tuberculosis drug-induced hepatotoxicity: a retrospective analysis. *BMC Infectious Diseases*; 16(1); 1-6.

Sharma, V.A.R.S.H.A., & Agrawal, R.C. (2013). *Glycyrrhiza glabra*-a plant for the future. *Mintage J Pharm Med Sci*; 2(3); 15-20.

Sharma, V., Agrawal, A. (2014). In vivo antioxidant and hepatoprotective potential of *Glycyrrhiza glabra* extract on carbon tetra chloride (CCl 4) induced oxidative-stress mediated hepatotoxicity. *Int. J. Res. Med. Sci*; 2(1);314-320

Sharma, V., Katiyar, A., & Agrawal, R.C. (2018). *Glycyrrhiza glabra*: chemistry and pharmacological activity. Sweeteners, 87.

Shi, X., Yu, L., Zhang, Y., Liu, Z., Zhang, H., Zhang, Y., Liu, P., Du, P. (2020). Glycyrrhetinic acid alleviates hepatic inflammation injury in viral hepatitis disease via a HMGB1-TLR4 signaling pathway. *Int Immunopharmacol*; 84;106578. doi: 10.1016/j.intimp.2020.106578.

Shin, S., Jang, J.Y., Choi, B.I., Baek, I.J., Yon, J.M., Hwang, B.Y., ... & Kim, Y.B. (2008). Licorice extract does not impair the male reproductive function of rats. *Experimental animals*; 57(1);11-17.

Subrat, K.A., Sreenivas, V., Siddharth, D.G., Shakti, K., Yogesh, K.C., Anurag, T., Aejaz, H., Premashish, K., Abhijit, C., Gourdas, C., Shiv, K.S., Amarapurkar, D.N., Vidya, A., Mohan, D.G., Sushma, G., Deepali, M., Divya, S., Rohit, G., Badri, N.T. (2012). Treatment of Chronic Hepatitis due to Hepatitis C Virus (CH-C) in India: A Randomized Controlled Trial Comparing Daily Interferon-alfa-2b and Ribavirin with Daily Interferon-alfa-2b and Glycyrrhizin A Multicenter Study. *Journal of Clinical and Experimental Hepatology*; 2(1); 10-18.

Sulaiman, H.A., Sulaiman, A.S. (2012). *Obat herbal pada penyakit hati. Buku Ajar Ilmu Penyakit Hati*. 1 st ed. Jakarta: Sagung Seto, p:639-45.

Takahara, T., Watanabe, A., and Shiraki, K. (1994). Effects of Glycyrrhizin on Hepatitis B Surface Antigen: a Biochemical and Morphological Study. *J. Hepatol*; 21(4); 601–609. doi:10.1016/s0168-8278(94)80108-8

Tan, Q.Y., Hu, Q., Zhu, S.N., Jia, L.L., Xiao, J., Su, H.Z., ... & Jin, J. (2018). Licorice root extract and magnesium isoglycyrrhizinate protect against triptolide-induced hepatotoxicity via up-regulation of the Nrf2 pathway. *Drug delivery*; 25(1); 1213-1223.

Tang, J.L., 2006. Research priorities in traditional Chinese medicine. *BMJ*; 333(7564); 391–394.

Tang, B., Qiao, H., Meng, F., Sun, X. (2007). Glycyrrhizin attenuates endotoxin-induced acute liver injury after partial hepatectomy inrats. *Braz. J. Med Biol. Res*; 40; 1637–1646.

Thakur, A.K., & Raj, P. (2017). Pharmacological perspective of *Glycyrrhiza glabra* Linn: A mini-review. *J. Anal. Pharm. Res;* 5(5); 00156.

UKHSA. (2022). Investigation into acute hepatitis of unknown aetiology in children in England, technical briefing, https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1073704/acute-hepatitis-technical-briefing-2.pdf

Wahab, S., Annadurai, S., Abullais, S.S., Das, G., Ahmad, W., Ahmad, M.F., ... & Amir, M. (2021). *Glycyrrhiza glabra* (Licorice): A Comprehensive Review on Its Phytochemistry, Biological Activities, Clinical Evidence and Toxicology. *Plants*; 10(12); 2751.

Wang, J., Chen, X., Wang, W., Zhang, Y., Yang, Z., Jin, Y., ... & Yang, G. (2013). Glycyrrhizic acid as the antiviral component of Glycyrrhiza uralensis Fisch. against coxsackievirus A16 and enterovirus 71 of hand foot and mouth disease. *Journal of ethnopharmacology*; 147(1); 114-121.

WHO. 2022. COVID-19, Ukraine and other global health issues. Virtual press conference transcript. World Health Organization.

WHO. (2022). Multi-Country—Acute, Severe Hepatitis of Unknown Origin in Children. Available online: https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON376 (accessed on 28 April 2022)

Xi, C., Peng, S., Wu, Z., Zhou, Q., & Zhou, J. (2017). Toxicity of triptolide and the molecular mechanisms involved. *Biomedicine & Pharmacotherapy*; 90; 531-541.

Yang, Q., Wang, J., Liu, R., Wang, Z., Li, Y., Zhang, Y., Hao, X., Huang, Y., Xie, W., Wei, H. (2016). Amelioration of concanavalin A-induced autoimmune hepatitis by magnesium isoglycyrrhizinate through inhibition of CD4+CD25-CD69+ subset proliferation. *Drug Des Devel Ther*; 10;443-453. doi:10.2147/DDDT.S92440.

Zadeh, J.B., Kor, Z.M., & Goftar, M.K. (2013). Licorice (*Glycyrrhiza glabra* Linn) as a valuable medicinal plant. *International journal of Advanced Biological and Biomedical Research*; 1(10); 1281-1288.

Zhang, H., Ya, G., & Rui, H. (2017). Inhibitory effects of triptolide on human liver cytochrome P450 enzymes and P-glycoprotein. *European journal of drug metabolism and pharmacokinetics*; 42(1); 89-98.

Ziaei, S., & Halaby, R. (2016). Immunosuppressive, anti-inflammatory and anti-cancer properties of triptolide: A mini review. *Avicenna journal of phytomedicine*; 6(2); 149.

P-ISSN: 2406-9388
E-ISSN: 2580-8303