HERBAL MEDICINE FOR THE TREATMENT OF LIVER DISEASES: A REVIEW OF EVIDENCE AND CONCERNS

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Abstract

Liver diseases, including cirrhosis and liver cancer, are a major global public health problem. Natural products have long been investigated as a source for discovering new drug candidates to treat various liver diseases, including hepatitis, inflammation, and cirrhosis. Herbal products and their essential ingredients have been found to be useful means for the treatment of liver diseases. This review examines the evidence from case reports on the effectiveness of natural herbal products in treating liver diseases and protecting the liver. The transforming growth factor-β1 (TGF-β1) pathway has been identified as a key molecular pathway in the development of liver fibrosis and cirrhosis, and several herbal medicines have been found to target this pathway. However, concerns remain regarding the effectiveness and potential side effects of these herbal products. Thus, further research is needed to fully understand the effectiveness and safety of herbal medicines in treating liver diseases.

Keywords: *Herbal medicine, the transforming growth factor-β1 (TGF-β1) pathway, liver diseases, inflammation, and cirrhosis.*

Điều trị bệnh xơ gan bằng thảo dược và các thuốc thảo dược

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Tóm tắt

Các bệnh gan, bao gồm xơ gan và ung thư gan, là một vấn đề sức khỏe công cộng toàn cầu nghiêm trọng. Sản phẩm tự nhiên đã được nghiên cứu từ lâu như một nguồn tài nguyên để tìm ra các ứng cử viên thuốc mới để điều trị các bệnh gan khác nhau, bao gồm viêm gan và xơ gan. Sản phẩm thảo dược và các thành phần cần thiết của chúng đã được tìm thấy là phương tiện hữu ích trong điều trị các bệnh gan. Bài báo này đánh giá các bằng chứng từ các báo cáo trường hợp về hiệu quả của các sản phẩm thảo dược tự nhiên trong điều trị các bệnh gan và bảo vệ gan. Con đường tăng trưởng chuyển hóa tổng hợp beta-1 (TGF-β1) đã được xác định là con đường phân tử chính trong quá trình phát triển xơ gan và ung thư gan, và một số loại thuốc thảo dược đã được tìm thấy để tác động vào con đường này. Tuy nhiên, vẫn còn những lo ngại về hiệu quả và tác dụng phụ tiềm năng của các sản phẩm thảo dược này. Do đó, cần thêm nghiên cứu để hiểu rõ hơn về hiệu quả và an toàn của các loại thuốc thảo dược trong điều trị các bệnh gan.

Từ khóa: *Thuốc thảo dược, con đường tăng trưởng chuyển hóa tổng hợp beta-1, bệnh gan, xơ gan, viêm gan.*

Introduction

Chronic liver diseases are characterized by inflammation and injury to hepatocytes, which can lead to the development of liver fibrosis, cirrhosis, and hepatocellular carcinoma. Liver fibrosis is a condition

where excessive deposition of extracellular matrix proteins (EMP) replaces hepatocytes, leading to the formation of fibrous scars that can cause liver dysfunction. These conditions represent a significant global health burden, with liver cirrhosis ranking as the 6th leading cause of death from non-communicable diseases worldwide according to a 2015 study on the global burden of disease (GBD). Chronic liver diseases have become a major cause of illness and death globally, with cirrhosis alone carrying a substantial national economic burden of over $14 million yearly for patient treatment and an additional $2 billion in indirect costs due to loss of labor and reduced quality of life.

Hepatic fibrosis occurs when the liver undergoes a wound-healing response to repeated injury. Following an acute liver injury, the necrotic or apoptotic cells are replaced by regenerated parenchymal cells. Chronic liver disease is most commonly caused by chronic viral infections such as hepatitis B and C, excessive alcohol consumption, non-alcoholic fatty liver disease, and cholestatic diseases like primary biliary cholangitis and primary sclerosing cholangitis. [3-5].

Diagnosing and treating liver functions and disorders, including liver fibrosis, typically involves a two-stage approach. The primary stage involves identifying and removing the causative agent responsible for the cirrhosis, while the secondary stage involves addressing the fibrogenic process itself. It is noteworthy that many patients in developing countries have traditionally relied on herbal products and formulations for treating their liver fibrotic damage. [6-9].

This review article aims to examine the pathophysiology of liver fibrosis and its progression to cirrhosis and hepatocellular carcinoma, as well as current therapeutic options available for treating these diseases. Furthermore, the potential use of herbal medicine and herbal products with hepatoprotective properties in treating cirrhosis will be discussed. The efficacy and potential side effects of these herbal products will also be considered.

Riview liturature

1. Liver fibrosis and cirrhosis, and their causes

Liver fibrosis and cirrhosis are significant global health concerns resulting from long-standing liver injury or repeated damage. Chronic viral infections, excessive alcohol consumption, fatty liver disease, autoimmune liver diseases, and metabolic diseases such as diabetes and obesity are common underlying causes of liver fibrosis. It is crucial to establish the severity of liver fibrosis, as it can predict liver-related morbidity and mortality, and the emergence of complications of portal hypertension. Liver fibrosis is classified into a 5-point scale consisting of stages F0-F4, with F0 indicating no fibrosis and F4 indicating cirrhosis. Patients in stages F2 or F3 are considered to have "significant fibrosis" or "advanced fibrosis," respectively. In stage F4, fibrosis progresses to cirrhosis and liver failure, and complications of liver disease can arise, including appetite loss, unexplained weight loss, difficulty thinking clearly, jaundice, nausea, and weakness.

- Lower body edema or ascites (severe accumulation of fluid in the abdomen and legs).

- Hepatic encephalopathy: buildup of waste product ammonia in brain, that destroys brain functions, causes confusion, fatigue, memory loss, and diminishes mental abilities.

- Variceal bleeding (high-pressure in portal veins causes a backup into esophageal varices (varicose veins), which can then burst and bleed), blood leaks (present in vomit or bowel motions) and/or hepatocellular carcinoma (liver cancer), etc. Liver fibrosis can be staged using different methods including composite scoring systems, direct serum biomarkers, liver imaging techniques or liver biopsy. Liver markers like albumin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) and gamma glutamyltransferase (GGT) which reflect the synthetic function and evidence of

liver cell damage are routinely measured in blood and considered as liver function tests (LFTs). The ALT (with plasma half-life of approximately 36–48 h) level is specifically raised when hepatocyte damaged. And AST (plasma half-life of 12– 24 hours) is released by hepatocytes after damage. When AST : ALT ratio >1 indicates is predictive of substantial fibrosis [2-4,7].

2. The treatment of liver fibrisis with herbs and hebral medicine

Hepatocytes, the major parenchymal cells in the liver, are responsible for a variety of cellular functions including carbohydrate, lipid and protein metabolism, detoxification and immune cell activation to maintain liver homeotasis. With pivotal roles in various biochemical and metabolic functions, thepersistent damage or injury of hepatocytes can lead to fibrogenesis in liver.

By exposure to hepatotoxic or harmful chemicals like poisonous toxins or chlorinated compounds, drug overdose as well to stimuli like reactive oxygen species (ROS), viruses (e.g., viral hepatitis) the hepatic cells lead to damage and death (necrosis and apoptosis). The hepatocyte injury leads to Kupffer cells and subsequently stellate cell activation [8,9]. Chronic inflammatory hepatocyte regenerate nodules, fibrosis, and cirrhosis. So that, the removal of the causative agent turns out to be the most effective intervention for the treatment of liver fibrosis. Stop drug overdose, stop abuse liver damaged drugs (like acetaminophen), and neutralize the toxins are necessary to reverse liver fibrosis. One of the most possible ways to prevent liver injury and reduce long-term health risk is to limit alcohol consumption to a recommended standard amount of drink per day [10]. The inhibition of liver cell apoptosis can also attenuate liver injury and fibrosis. Based on these analyses, therapeutic agents for this process are defined to compounds or plant extracts with toxic removal activity as (i) hepato anti-toxic agents (antidote); (ii) anti-hepatitic substances, (iii) antioxidant compounds, and (iv) hepatoprotective compounds.

2.1. Anti-toxic agents (antidote)

The decondary acute or chronic liver injury are caused by hepatotoxic agents originated from drugs or herbal compounds. Some typical of them are listed in table 1 below

Table 1. Several hepatotoxic agents and their origins

Hepatotoxic compounds	Origin	Examples	Ref.
Metals	Soil, tin canned-food, drinking water	Arsenic, beryllium, copper, iron, manganese	(8)
Endocrine disruptors	Foods, toys, plastic bottles and containers, liners of metal food cans, flame retardants, cosmetics, and pesticides.	Perchlorate, Perfluoroalkyl and Polyfluoroalkyl Substances (PFAS), phthalates, Polybrominated diphenyl ethers (PBDE), Polychlorinated biphenyls (PCB), Triclosan	(8)
Endogenous compounds	plastic containers	Androgens, estrogens, glucocorticoids	(8)
Drugs	Anti-pyretic drugs	Acetaminophen	(9)
	Antibiotics	amoxicillin, tetracycline	(8)
	Drugs that lower cholesterol	Statins	(9)
	Anesthetic	Halothane	(9)
	Anti-seizure medications	phenobarbital, valproate	(9)
	Antidepressant	SSRI antidepressants include citalopram, escitalopram SNRI antidepressants include desvenlafaxine, duloxetine	(9)
	Anti-rheumatic drugs	including sulfasalazine and methotrexate	(9)
	Anti-tubercular drugs	ethambutol, rifampicin, isoniazid (especially when used in combination)	(9)
	Vitamin, mineral or herbal supplements	Oil-soluble vitamins (A, E) Zn, Fe, Cu, Mn	(9)
Biological factors	Virus, bacteria, parasites	Viral Hepatitis	(10)
		Syphilitic hepatitis	(11)
		Plasmodum falciparum, P. vivax	(12)
Xenobiotics	Foods, environment, industrial factory, manufacturing plants,	Allyl alcohol, bromobenzene, carbon tetrachloride, hexachlorobenzene, PFOA, polychlorinated dibenzodioxins (PCDD or dioxin), vinyl chloride	(8)
Toxins	Toxic fungi, toxic animals	Mycotoxins (aflatoxin B_1, fumonisins, sporidesmin), amatoxins, phalloidin (*Amanita phalloides*))	(9)
		Rugulosin A, luteoskyrin (*Penicillium rugulosum*)	(13)
	Toxic plants	Plant toxins (lantadene)	(9)
		pyrrolizidine alkaloids (*Crotalaria senecio doronicum* and *S. jacobea*, *Heliotropium lasocarpium*)	(14)
		Podophyllotoxin (Bajiaolian (*Dysosma pleianthum*, Mayapple family)	(15)

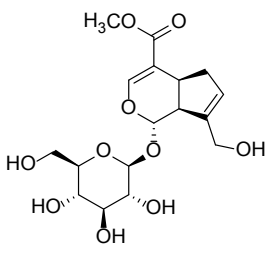
To treat the liver hepatotoxicity caused by the compounds mentioned in tablle 1 or others, liver antitoxic agents or/and natural compounds have been used to date to mitigate the toxicity and to detoxify, finally to clean toxic compounds out of the liver. Geniposide (**1**) is a bioactive iridoid glycoside that found in numerous medicinal herbs, including Gardenia jasminoides (fruits, Rubiaceae family) [19], Eucommia ulmoides Oliv. (Eucommiaceae), Rehmannia glutinosa Libosch. (Scrophulariaceae), and Achyranthes bidentata Bl. (Amarathaceae) [20]. Geniposide seems to detoxify the liver by affecting the activity of

liver enzymes to lessen oxidative stress and increase mitochondrial function. It elevates the activities of glutathione S-transferase (GST) and gamma-glutamylcysteine synthetase (γ-GC), these enzymes are key factors for glutathione (GSH) biosynthesis. GSH involve in the enzymatic and non-enzymatic reactions of hepatic tissues defense mechanism plays an extremely important role in protecting hepatocytes against toxic injury [21].

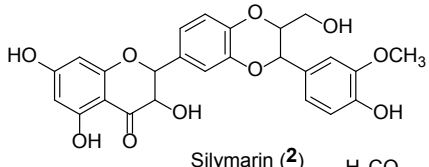
Geniposide (**1**) up-regulated expression of main hepatic antioxidant enzymes, therefore reduced oxidative stress, mitigated disorders that affect the metabolism of amino acids and protected liver from injury in alcohol-induced liver injury model mice [22,23].

Silymarin (**2**), a mixture of isomer flavonolignans isolated from Silybum marianum (milk thistle) can prevent toxins binding to hepatocyte cell membrane receptors and block their toxicity to the liver. It can reduce liver injury caused by chemicals like acetaminophen (paracetamol), CCl_4, iron overload, phenylhydrazine, alcohols and amatoxins from Amanita phalloides [24].

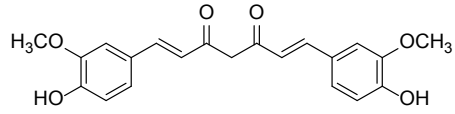
Similarly, aγβ-diketone curcumin (**3**) abundant in the rhizome of *Curcuma longa* (Zingiberaceae), had been reported to possess a significant hepatoprotective activity against liver damages induced by toxic agents including mycotoxins (aflatoxin B1), halides (chloroform, CCl_4), pyrethroids insecticides (lambda-cyhalothrin), and heavy metals (mercury, iron) in adult rats (100 or 200 mg/kg/day, i.p.) [25].



Geniposide (**1**)



Silymarin (**2**)



Curcumin (**3**)

2.2. Anti-viral hepatitis agents

Eliminating the stimuli responsible for liver fibrogenesis can reverse the fibrosis process in affected patients. Corticosteroids are commonly used to treat autoimmune hepatitis and halt the progressive inflammation that leads to fibrosis. Chronic hepatitis B (HBV) and hepatitis C (HCV) are prevalent causes of fibrosis/cirrhosis, as well as morbidity and mortality worldwide. Studies have shown that successful anti-viral therapy for HBV and HCV can reverse advanced fibrosis and even early-stage cirrhosis. However, the increasing resistance of these viruses to currently approved therapeutic drugs like interferon-alpha (IFN-α) and nucleoside analogues has limited their use in HBV treatment. Therefore, there is a need to develop novel anti-hepatitis drugs with various mechanisms of action, which can overcome viral resistance and be made available to more patients in developing countries through reasonably priced antiviral combination therapy[26].

It is reported that there are numbers of medicinal plants and their produced secondary metabolites with anti-viral effects, such as crude extracts of many medicinal plants such as Phyllanthus sp., Glycyrrhiza sp. [27], Pulicaria crispa, Fumaria parviflora, Guiera senegalensis, Artemisia capillaris, Boehmeria nivea, etc. with their antiviral substances attracted much attentions for the development of novel anti-HBV drug candidates [28].

Characteristically, the crude extract of Cananga odorata (commonly called ylang-ylang, family Annonaceae) exhibited the highest inhibitory activity to HBV production and may exert anti-HBV activity at both viral entry and post-entry steps [28].

In the same vein, a crude extract derived from the leaves of Dimocarpus longan (from the Sapindaceae family) has shown significant inhibition of the HCV virus, blocking both viral entry and post-entry stages via direct virucidal activity. When used in combination with other approved anti-HCV drugs such as cyclosporine A or telaprevir, it demonstrated additive and synergistic antiviral effects, making it a promising supplementary therapy for treating HCV infections. [29].

Solanum procumbens Lour. (Solanaceae family) is known by its antiviral HBV property. In folk medicine, the whole plant is used for treatment of HBV infection in liver [30]. Clinical studies of liver detoxification showed the high efficiency of treatment in patients suffered from hepatitis B, liver injury (for example, due to paracetamol overdose abuse) and inflammation caused by carragenin.

Schisandra is an herb known by its liver protective activity. Its constituent lignans have been described to possess anti-hepatitis activity in a clinical trial, where 76% cases were noted with successful and no side effects hepatitis treatment. Schisandra has been usually used in the treatment of hepatitis and poor liver function [31].

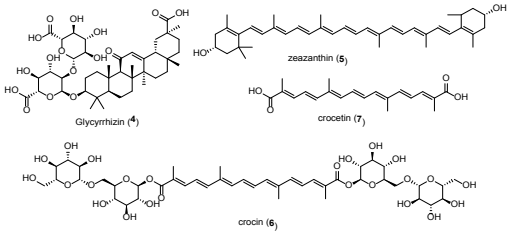
Many phytochemicals, including terpenoids (artemisinin), lignans (helioxanthin), coumarins (esculetin), polyphenols (geraniin), flavonoids (wogonin), saponins (astragaloside IV), lactones, and alkaloids (oxymatrine), have been described to possess anti-proliferative activity against various viruses including HBV in vitro and in vivo [32]. Removing the viral fibrogenic stimulus, the liver can get remarkable reversal of fibrosis and the scar tissue might be disappeared.

Glycyrrhizin (4) (or glycyrrhizic acid (GA)), a triterpene isolated from licorice (Glycyrrhiza glabra (Fabaceae), roots and rhizomes) can reduce liver damage in HBV/HCV-induced cirrhosis and hepatocellular carcinoma [33]. The antiviral mechanism of glycyrrhizin can be listed as following:

Binding to hepatocytes and suppressing the secretion of hepatitis B surface antigen (HBsAg) and its transport in the cell [34 - 35]. It also improved the immune status of chronic HBV patients [36].

Inhibiting the expression of the hepatitis A virus (HAV) antigen in a concentration-dependent manner through altering negative charge potential on the cell surface and membrane fluidic capacity and therefore inhibition of viral-entry and endocytosis of the virus in liver cells [37].

Showing additive effect with lamivudine when given intravenously for the treatment of subacute hepatitis caused by hepatitis B [38, 39].



2.3. Antioxidant agents

Oxidative stress (OS) of hepatocyte indicates an unbalanced state between antioxidant ability and the levels of free radicals in cells. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) derived from molecular oxygen and the oxidants from $NO^{\bullet}$, respectively are among the most common free radicals. The generation and accumulation of these ROS cause lipids peroxidation of cellular membranes and DNA damage leading to hepatocellular injury [40] and the progression of liver disease [41]. In addition, OS can cause related diseases like brain impairment (hepatic encephalopathy), cardiovascular disorders (hypertension) and kidney failure (hepatorenal syndrome).

Carotenoids, divided into carotenes,

xanthophylls and lycopene, are colorful natural fat-soluble pigments and present in many fruits or vegetables like tomatoes (*Lycopersicum esculentum* Mill.), carrots (*Daucus carota* L.), peppers (*Piper nigrum* L.), algae (*Dunaliella salina)* [42], gac (*Momordica cochinchinensis* (Lour.) Spreng.) [19]. The occurrence of conjugated double bonds enables these compounds to scavenge ROS and then neutralize free radicals [43]. A combination of carotenoids with lipophilic antioxidants (e.g. vitamins E, C) can contribute additive antioxidant effects against ROS/RNS and inhibition of lipid peroxidation [44]. In addition, zeaxanthin (**5)**, one of the most common carotenoids in nature, found in paprika (*Capsicum annuum,* Solanaceae), corn (*Zea mays*, Poaceae), saffron (*Crocus sativus*, Iridaceae), goji berries (*Lycium barbarum*, Solanaceae) and many other colorful fruits or plants, can effectively scavenge both water- and lipid-soluble peroxyl radicals [45].

Carotenoids also contribute to the defense against lipid peroxidation [46]. The polar carotenoids can extend and fit the phospholipid bilayer of the cellular membrane, therefore they rigidify the fluid phase of the membranes and prevent oxygen penetration into the hydrophobic membrane to promote oxidative degradation [47].

Crocin (**6**) and crocetin (**7**), carotenoids derived from Saffron (*Crocus sativus,* stigma) [48] had been known to be powerful antioxidants, stronger than α-tocopherol [49]. Both crocin (**6**) and crocetin (**7**) showed their hepatoprotective efficacy through the induction of different antioxidant pathways [19].

*Crocetin (**7**) inhibited mRNA expression of pro-inflammatory biomarkers as TNF-α, IL-1β and iNOS in the liver and protects the liver cells from apoptotic activation [50].

*Crocetin reduced hepatic apoptosis probably by depressing hepatic ATP, prevention of mitochondrial membrane damage, increasing oxygen transport in the plasma and thereby enhancing oxygen supply at the cellular level in the mitochondrial [51].

*Crocetin acted as an anti-inflammatory or as an antioxidant agent and protect against hepatotoxic effects of aflatoxin B1 in animal model [52]. Crocetin triggered the protection mechanisms of liver tissues, increased the activity of Phase II detoxification enzymes (GSH S-transferase), decreased the formation of adducts between aflatoxin and hepatic DNA so that reduced the hepatotoxicity induced by aflatoxin B1 [53].

*Crocetin reduced the lipid peroxidation of cellular membrane (therefore reduced the malondialdehyde (MDA) level) via inhibition of the formation of ROS (superoxide anion) and quenching the free radical 1, 1-diphenyl-2- picrylhydrazyl (DPPH) [53].

*Curcumin (**3**), a bright yellow compound isolated from the rhizome of turmeric *Cucurma longa* (Zingiberaceae), is soluble in lipid and containing a variety of functional antioxidant groups, including the β-diketo group, carbon-carbon double bonds, methoxy groups and phenyl rings. Cucurmin itself acts as a free radical scavenger and can eradicate lipid radicals in the cell membrane [54].

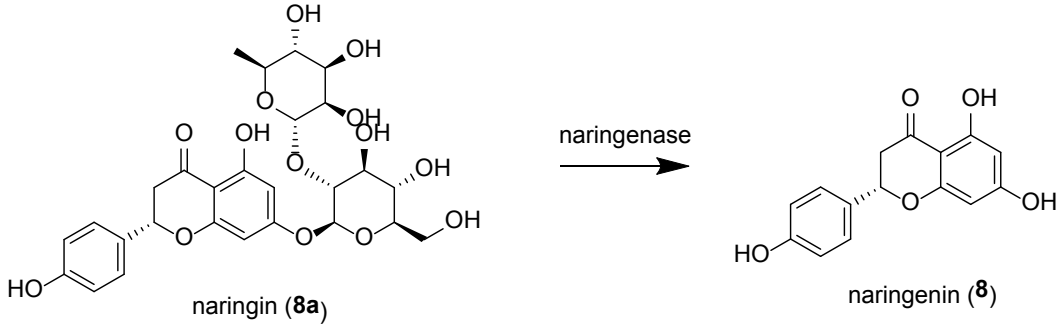
*Flavonoids and their glycosides, including quercetin, quercetin-3-O-β-D-glucoside, quercetin-3-O-α-L-rhamnoside, quercetin-3-O-rutinoside, kaempferol-3-O-rutinoside, kaempferol-3-O-β-D-glucoside, myricetin-3-O-rutinoside, rutin, hesperitin, as well as vitamins C and E, possess strong antioxidant properties. These compounds are believed to be responsible for the liver-protective activity of their original extracts, such as the leaf extract of Azadirachta indica (Meliaceae family) and the fruit extracts of Phyllanthus emblica (Phyllanthaceae), Citrus sinensis (Rutaceae), among others.

2.4. Hepatoprotective agents

As earlier mentioned, hepatic disease caused from the chronic injury of hepatic cells, that account for more than 80% of the total liver cell population and carry out most of the metabolic liver function. The hepatocytes express a number of hepatic

enzymes like phase I enzymes involved in drug metabolism (P450 cytochromes) and phase II enzymes catalyzing the metabolic processes that convert various xenobiotics into less active but more water solubility forms to effectively excrete through the bile or urine such as glutathione S-transferases (GSTs), UDP-glucuronyl transferases (UGTs), etc. [56]. These detoxification processes might produce more reactive and toxic molecules than their parents. They might accumulate and harm the cells and then the whole liver tissue. Normally, an anti-oxidant enzymic systems composed of enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GRx) etc. play a significant role in scavenging ROS, preventing the lipid peroxidation of cellular membranes and are sustained in the cells to keep their redox status homeostasis [57]. So that plants or compounds can protect the liver cells from apoptosis, support the cells survive, reverse the liver damage and recover the liver function are worthy as hepatoprotective agents. Generally, these liver-protective plants contain many different phytoconstituents, such as polyphenols (coumarins, flavonoids, lignans, glycosides), monoterpenes, alkaloids, carotenoids, organic acids, and xanthines, which can induce hepatic antioxidant enzymes to efficiently detoxify and remove xenobiotics and therefore inhibit the liver damage processes.

Typically, naringin (**8a**) is a flavonoid disaccharide occurring naturally in citrus fruits, especially in grapefruit. Its aglycon naringenin (**8**) (4',5,7-trihydroxyflavanone) is the main product metabolized from naringin by enzyme naringenase present in the human gut [57]. As naringenin is free from the steric hindrance provided by the two sugar moieties, it seems to be more potent than its parent molecule naringin in quenching the free radicals and ROS damaged the liver cells. So, it helps to increase the levels of anti-oxidant enzymes SOD, CAT, GPx, GRx, GST (glutathione-*S*-transferase) and phase II enzymes, modulate circulatory lipid peroxidation and improve antioxidant status of alcoholic-induced toxicity in the liver [57, 58].



naringin (**8a**) naringenin (**8**)

The extract of the milk thistle *Silybum marianum* (seeds) with the naturally occurring flavonoid silymarin (**2**), which is a mixture of three flavonolignan isomers silibinin, silidianin, and silichristin was found to prevent liver lipid peroxidation of the membranes, reduce hepatic glutathione depletion and improve the liver damage [59]. Silymarin (**2**) is capable to support liver cells through multiple action, including inhibiting toxin diffusion into hepatic cells by binding to cell membranes and increasing the activity of SOD and CAT antioxidant enzymes [58].

Curcumin (**3**) is a potential compound that is not only an antioxidant but also a hepatoprotective compound due to its ROS/RNS neutralization capability and inhibitory activity against lipid peroxidation [60]. Curcumin ameliorates antioxidant enzymes, including GST, GR, SOD and CAT (25), which inhibit ROS production and prevent OS in liver diseases. Its ability to participate to various cellular and molecular

mechanisms like inhibition of pro-inflammatory cytokines and hepatic stellate cells activation lead to its outstanding protective and therapeutic effects for liver diseases [54].

Overall, polyphenol phytochemicals including flavonoids, tannins, stilbenes and phenolic acids in fresh / dried fruit or juice and/or wines, with antioxidant activity are potential hepatoprotective agents because they effectively eradicate the toxic effects of reactive metabolites. They also improve the protective system by increasing protective antioxidant enzymes represented by SOD, glutathione (GST, GPx, GRs), peroxidase, catalase (CAT) etc., which remarkably reduce lipid peroxidation of hepatocytic membrane and conversely elevate the levels of liver injured biochemical markers like ALT, AST, ALP and bilirubin (BIL) [58].

Conclusion

The aforementioned findings demonstrate that numerous medicinal plants, fruits, and herbal products contain natural bioactive compounds with diverse pharmacological properties that may have potential benefits in reversing liver fibrosis and treating affected patients. Certain compounds, such as geniposide, crotins, and baicalin, have exhibited promising anti-fibrotic activities and could be suitable candidates for further development as potential therapeutics for treatment of other liver diseases, such as fatty liver, NAFLD, or liver carcinoma.

Acknowledgments

This study received partial support from the Basic Science Research Program, which was conducted as a joint research project between the Slovak Academy of Sciences (SAS) and the Vietnam Academy of Science and Technology (VAST). The project, entitled "Anti-inflammatory Effects of Natural Compounds Isolated from Vietnam Medicinal Plants," was led by Pham Ngoc Khanh and Katarina Bauerova, who served as principal investigators. The grant was identified as QTSK01.03/21/22.

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