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Review article *Liver Cirrhosis*

Retrospective herbal accession on liver cirrhosis: current insights and future prospects

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ABSTRACT

Chronic liver disease encompasses a spectrum of liver conditions spanning fatty liver, hepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. Despite advancements in conventional medicine, growing emphasis is placed on phytomedicine by researchers. Herbal medicine's allure stems from its perceived potential for both treating and preventing ailments, fueled by the notion that it's a safe and "natural" alternative to conventional treatments. This review offers a thorough and systematic examination of current knowledge concerning the role of conventional medicinal herbs and phytochemicals in addressing chronic liver diseases. It also highlights the potential challenges that warrant future investigation. With chronic liver diseases being a complex and pressing health issue, this review contributes to the evolving understanding of herbal interventions and underscores the necessity for rigorous research to substantiate their effectiveness and safety.

Keywords: Liver cirrhosis, Platelet-derived growth factor, Hepatitis, Kupffer cells, matrix metalloproteinase 2

INTRODUCTION

The liver, situated in the upper abdomen, plays a vital role in digestion, waste elimination, and the removal of worn-out cells from the bloodstream. As the largest solid organ in the body, the liver weighs approximately 1.6 kilograms (3.5 pounds). It has a horizontal measurement of around 20 cm (8 inches), a vertical measurement of about 17 cm (6.5 inches), and a thickness of 12 cm (4.5 inches). The liver's tissue is composed of a cluster of cells intertwined with bile ducts and blood vessels. Roughly 60% of these are hepatic cells, distinguished by their extensive metabolic capabilities compared to other cell types. Another category, known as Kupffer cells, contributes to activities like generating blood cells, producing antibodies, and engulfing external particles and cellular remnants. Furthermore, the liver produces essential plasma proteins, notably albumin and clotting factors, and generates enzymes that alter substances like nutrients and toxins, extracted from the bloodstream. Liver disease, including instances induced by the hepatitis C virus, advances through distinct stages. This progression spans from initial inflammation to fibrosis, then to cirrhosis, ultimately culminating in end-stage liver disease or liver cancer. Ordinarily, during acute liver damage, the liver cells undergo a regenerative process that results in self-renewal without the formation of scars. Common disorders affecting the human liver encompass a spectrum of conditions, including hepatitis, liver necrosis, liver fibrosis, cirrhosis, liver cancer, liver

failure, ascites, gallstones, hemochromatosis, primary sclerosing cholangitis, and primary biliary cirrhosis.

Liver cirrhosis

Cirrhosis emerges as a consequence of chronic liver disease, distinguished by the replacement of liver tissue with fibrosis, scar tissue, and regenerative nodules—clusters that form as damaged tissue undergoes regeneration. This progression ultimately results in the impairment of liver function. The term "cirrhosis" originates from the Greek word "κίρρος," signifying the tawny hue resembling the afflicted liver's orange-yellow color. While the clinical condition was recognized earlier, it was René Laennec who bestowed the name "cirrhosis" upon it in his 1819 publication, wherein he also introduced the stethoscope [1].

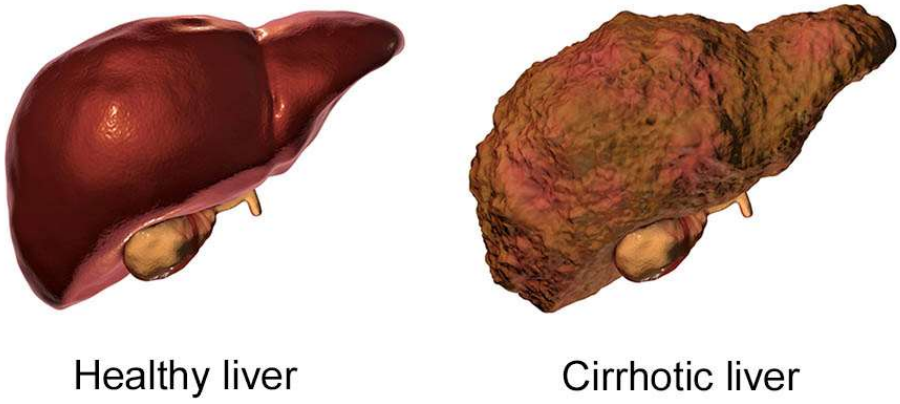

Fig 1: Difference between Normal and Cirrhotic liver

Types

- Micro-Nodular Cirrhosis
- Macro-Nodular Cirrhosis
- Mixed type

Micro-Nodular Cirrhosis

Micro-nodular cirrhosis is characterized by consistently uniform and diminutive nodules, measuring less than 3mm in diameter. This form of cirrhosis encompasses underlying causes such as alcoholic cirrhosis, nutritional cirrhosis, and Laennec's cirrhosis. It signifies a diminished ability for tissue regeneration, evident in conditions like alcoholism, malnutrition, severe anemia, and advanced age.

Macro-Nodular Cirrhosis

In this variation, the nodules exhibit diverse dimensions and typically exceed 3 mm in diameter. Macro-nodular cirrhosis corresponds to post-necrotic or post-hepatic cirrhosis within the realm of etiological classification.

Mixed Cirrhosis

In the mixed type, certain portions of the liver exhibit a micro-nodular appearance, while other sections display a macro-nodular pattern. The mixed pattern can be understood as a form of incomplete manifestation of micro-nodular cirrhosis.

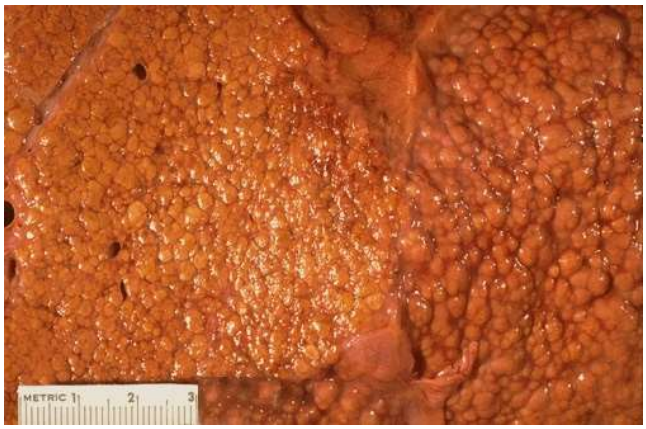

Fig 2: Micro-Nodular Cirrhosis

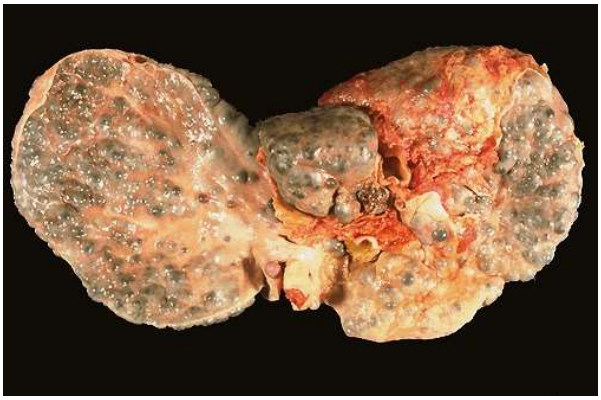

Fig 3: Macro-Nodular Cirrhosis

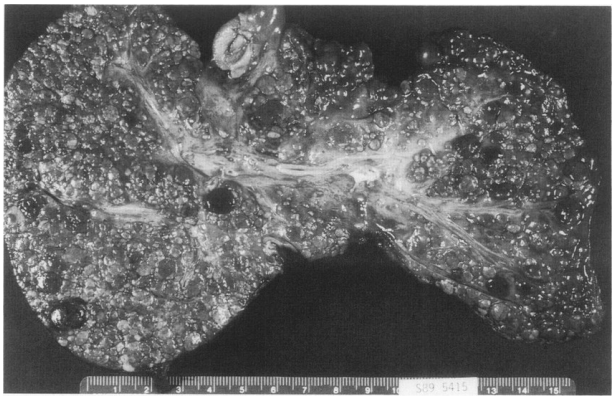

Fig 4: Mixed Cirrhosis

Modes of pathogenicity

Various liver cell types release cytokines that activate stellate cells, such as hepatocytes, Kupffer cells, platelets, and lymphocytes. In addition to transforming growth factor-beta (TGF-beta), stellate cells are capable of producing platelet-derived growth factor (PDGF). These activated stellate cells generate TGF-β1, which inhibits collagen degradation and produces collagen matrix. When collagen breaks down, matrix metalloproteinase 2 (MMP2) and matrix metalloproteinase 9 (MMP9) are deactivated by tissue inhibitors TIMP1 and TIMP2, whose levels increase during fibrosis. Fibrosis is further accelerated by cytokines produced by Th2 lymphocytes, such as interleukin-6 and 13 (IL-6 and IL-13). A further factor contributing to portal hypertension is the production of endothelin 1 by activated stellate cells.

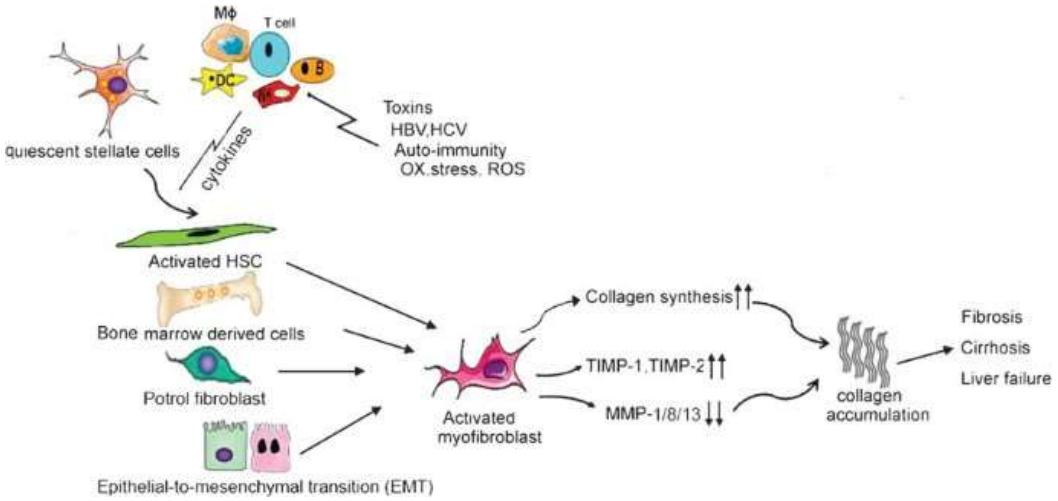

Fig 5: Pathogenesis of liver fibrosis

Etiology [2]

Cirrhosis or its complications can cause some of these signs and symptoms. Many of these symptoms are nonspecific and are not necessarily related to cirrhosis. Additionally, the absence of any of the following does not rule out the possibility of liver cirrhosis. A few complications of liver cirrhosis may cause the following symptoms. It is important to note that many of these symptoms do not necessarily point to cirrhosis and may occur in other diseases. It is also important to note that cirrhosis may exist in spite of the absence of any.

a. **Spider angiomata or Spider Nevi:** An increase in estradiol results in vascular lesions involving a central arteriole surrounding many smaller vessels. About one third of cases are affected by this [3].
b. **Palmar Erythema:** Nail changes due to altered sex hormone metabolism can cause exaggerated speckled mottling of the palm.
c. **Muehrcke's lines:** Hypoalbuminemia (insufficient production of albumin) is characterized by paired horizontal bands of normal color separated by a normal tint.
d. **Terry's nails:** There is a white appearance to the proximal two-thirds of the nail plate and a red appearance to the distal one-third, due also to hypoalbuminemia.
e. **Clubbing:** An angle of 180° or more between the nail plate and proximal nail fold
f. **Hypertrophic osteoarthropathy:** This is a chronic condition that causes intense pain in the long bones.
g. **Dupuytren's contracture:** Palmar fasciitis thickens and shortens, resulting in finger flexion deformities. This condition is thought to be caused by proliferation of fibroblasts and disorderly collagen deposition. Approximately 33% of patients suffer from it.
h. **Splenomegaly (increase in size of the spleen):** Hypertension of the portal system causes congestion of the red pulp.
i. **Caput medusa:** Umbilical veins may open as a result of portal hypertension. As a result, portal venous blood can flow into the umbilical vein and ultimately into the abdominal wall veins, resulting in caput medusa.
j. **Miscellaneous:** Autoimmune hepatitis, Primary biliary cirrhosis, Wilson disease, Alpha-1 antitrypsin deficiency, Granulomatous disease (e.g., sarcoidosis), Drug-induced liver disease (eg, methotrexate, alpha methyldopa, amiodarone) etc., [4]

Complications [5]

The disease may progress to complications as it progresses. Some people may experience these symptoms for the first time. A dysfunctional immune system can lead to infection in patients with cirrhosis.

Complications	Symptoms
Ascites	Fluid builds up in the abdomen. Symptoms include bloating, discomfort, and difficulty breathing.
Spontaneous bacterial peritonitis	The abdomen is infected with this type of infection. The condition can become serious if it's not treated immediately.
Bruising and bleeding	Blood clotting factors are being produced at a lower rate. Especially when internal bleeding is involved, it can be a serious issue.
Jaundice	There is a yellowing of the skin and eyes in this condition. As a result of bilirubin buildup, it is caused by liver damage.
Itching	Bile salts build up in the skin, resulting in this condition.
Hepatic encephalopathy	It is a brain disorder. There are a variety of symptoms associated with this condition, including confusion, drowsiness, and coma. This is a neurological condition that affects the brain. Coma, drowsiness, and confusion are some of the symptoms it can cause.
Hepatocellular carcinoma	This is a form of liver cancer. Cirrhosis patients are most likely to develop this type of cancer.
Esophageal varices	Asymptomatic esophageal vein enlargement. Ruptures and bleeding can result in life-threatening complications.
Hepatorenal syndrome	This is a condition that results in kidney failure. There is a high probability of death from this complication.
Hepatopulmonary syndrome	A condition that bypasses the normal circulation of blood through the lungs. The condition can lead to shortness of breath and cyanosis (bluish skin).
Porto-pulmonary hypertension	In this condition, the lungs' blood pressure increases. Heart failure can result from this serious complication [6].

Treatment [7,8]

a. Nutrition

- It is important that patients' diets contain enough calories and protein.
- Nutritional supplements, including liquids and powders, are frequently beneficial for patients.
- Patients who are put on low-protein diets out of fear that they will develop hepatic encephalopathy are at risk of profound muscle weakness

b. Adjunctive therapy

- Cirrhosis patients usually have zinc deficiency. The use of zinc sulfate at an oral dose of 220 mg twice daily may improve dysgeusia and stimulate appetite. Hepatic encephalopathy and muscle cramps can both be treated with zinc.
- Cirrhosis patients are more likely to develop osteoporosis. For patients with chronic cholestasis, cirrhosis with primary biliary function, and autoimmune

hepatitis treated with corticosteroids, calcium and vitamin D supplementation are crucial.

- A diet that consists of 1 gm/kg protein and 8500-12500 kJ (2000-3000 Kcal) is essential, along with abstinence.
- As part of a daily multivitamin, take 100 mg of thiamine every day.
- A dose of 1 mg of folic acid is recommended.
- Severe alcoholic hepatitis with encephalopathy may benefit from prednisone 40 mg or prednisolone 32 mg per oral (PO) dose for a month.
- Recent research suggests that pro-inflammatory cytokines may be an important factor in alcoholic liver injury and that pentoxifylline can pharmacologically inhibit TNF. This agent has been added to the treatment of severe alcoholic hepatitis as an alternative to glucocorticoids.
- If a patient has been abstinent for longer than six months, liver transplantation may be an option. As a treatment for primary biliary liver cirrhosis, cholestyramine 4 gm PO should be administered with meals.
- The use of ursodoxycholic acid 10-15 (mg/Kg) per day PO in two divided doses improves symptoms and LFTs as well as slows the progression of primary billiary liver cirrhosis. The role of laxatives in preventing encephalopathy is limited; they reduce the risk of constipation.
- As a treatment for Wilson's disease, which causes copper to build up in organs, chelation therapy (e.g., penicillamine) is used.

Herbal approaches for Cirrhosis

- Glycyrrhizin- Over 60% of patients can normalize aspartate transaminase and alanine transaminase with 80 mg given daily for two weeks.
- Daphnoretin- It has been shown that this dicoumarin drug is able to suppress HBsAg in Hep3B cells by interacting with protein kinase C.
- Silymarin- Among the main constituents of standardized milk thistle extract, silybinin, silydianin, and silychristin are flavonoids with hepatoprotective effects in the dose of 70 mg/kg.
- Picroliv- Picorhiza kurroa root extract microliv, containing the iridoid glycosides kutkoside and picroside, shows antihepatotoxic activity.
- TJ-9- In China, TJ-9 is called xiao-chai-hu-tang, and in Japan, it is called sho-saiko-to. TJ-9 is a mixture of aqueous extracts from roots of scutellaria, glycyrrhiza, bupleurum, and ginseng, in addition to pinella tubers, jujube fruit, and ginger roots. Inhibitors of lipid peroxidation include baicalin and baicalein, two major alkaloids in scutellaria.
- Compound 861- As a result of traditional Chinese medicine, cpd 861 contains an aqueous extract of ten defined herbs. Tradition Chinese medicine treats liver pathology and patient discomfort by resolving blood stasis and liver stagnation.

Strategy over current therapeutic potential over phytoconstituents of herbal therapy

Epidemiological and pathological characteristics

As a complication of chronic liver diseases, cirrhosis leads to the liver no longer functioning properly due to long-term damage. German researchers found that 52% of liver cirrhosis cases were caused by alcohol (52% by chronic Hepatitis C, 28% by Hepatitis B), and 6% by NASH. There are differences in the situation in developing countries; for example, in China, HBV accounted for 77.22% of cirrhosis cases, alcohol 5.68%, and HCV 2.80%, while the other etiologies made up 15% [9]. A total of more than 1,000,000 deaths caused by cirrhosis in 2010 were 1.95% higher than in 1980, when there were 676,000 cases, or 1.54% of total global deaths [10]. Fibrosis replaces the normal parenchyma of cirrhosis as its pathological hallmark. When a wound heals and damage is repaired, overabundant scar tissue builds up in the liver. A chronic inflammation or fatty liver may cause excessive production or inadequate degradation of extracellular matrix (ECM) proteins such as collagen [11]. It is possible to reverse fibrosis if the cause is removed, but advanced fibrosis may cause cirrhosis, which results in the loss of hepatic cells and irreversible scarring of the liver. Stellate cells play a crucial role in the development of cirrhosis, according to recent studies. Hepatic stellate cells can be activated by inflammation in the liver parenchyma, resulting in fibrosis and obstructing blood circulation. The fibrotic response is further facilitated by cytokines like TGF-β1, which promote connective tissue growth. As well as this, it secretes tissue inhibitors of metalloproteinases (TIMPs), which suppress the activity of matrix metalloproteinases (MMPs). Stellate cells are regulated by several mitogen-activated protein kinases that play a major role in fibrogenic processes. Apoptosis of hepatic cells is regulated by c-Jun N-terminal kinase, and stellate cells secrete proinflammatory cytokines [12]. Fibrinogenic actions of agonists are regulated by the focal adhesion kinase-Akt signaling pathway in stellate cells [13]. Activation of the Smad pathway by TGF-β1 modulates experimental hepatic fibrosis in vitro, which could be a potential anti-fibrotic target [14]. PPARs modulate the activation of stellate cells and the fibrosis process. PPAR-γ ligands suppress fibrogenic processes in stellate cells in vitro and in vivo [15]. Recent studies suggest that NF-κB, Toll-like receptors and β-cathepsin may be involved in fibrosis regulation [16]. In the present day, the only way to radically reverse cirrhosis is to undergo liver transplantation, but there is a shortage of liver allografts compared to those who need them. In order to prevent liver damage caused by hepatitis or fatty liver disease, the key prevention strategies for the current management of cirrhosis are prevention of liver damage caused by these diseases. Researchers have discovered that even advanced fibrosis can be cured, unlike the irreversible process of cirrhosis. In order to reduce lavish collagen deposition in the ECM without permanently damaging it, the appropriate anti-fibrosis treatment should target the reduction of collagen deposition in the ECM specifically. There have been no drugs approved in the USA for treating cirrhosis or fibrosis, but some herbal medicines have shown remarkable effectiveness in treating cirrhosis and preventing it. Numerous studies have shown that CRAE protects against chronic liver hepatotoxicity caused by CCl4 such as fibrosis [17]. In CCl4-induced rats treated with CRAE, serum ALT and AST activities were significantly reduced. CRAE recovered CCl4-induced chronic oxidative stress by antioxidant mechanisms based on the significant increase in serum SOD activity and the histological results. Berberine treatment also decreased myofibroblast proliferation and TGF-b1 and a-SMA expression, according

to another study [18]. Researchers found that CRAE and berberine were promising anti-fibrosis agents. Further mechanisms of berberine's anti-fibrosis effects include AMPK activation, Nox4 inhibition, and Akt activation [19]. Researchers found that berberine, CRAE, and bear bile all had anti-fibrotic properties on experimental liver fibrosis in rats. SOD activity was remarkably increased and peroxidative stress was reduced by all of these agents. Hepatocytes can be protected from cholestatic damage by excreting liver bilirubin products through CRAE and berberine. According to these results, CRAE and berberine might be effective alternatives to bear bile in the treatment of liver fibrosis [20]. Jaundice, gonorrhea, edema, and liver fibrosis are all treated with *Saururus chinensis* (Lour.) Baill in Chinese medicine [21]. It can also increase the activity of hepatic SOD after CCl4-treatment in hepatic fibrotic rats treated with *Saururus chinensis* (Lour.) Baill extract. CCl4-induced liver fibrosis was significantly relieved by *Saururus chinensis* (Lour.) Baill extract, according to the histopathological results. As a result of these results, *Saururus chinensis* (Lour.) Baill extract showed hepatoprotective effects against CCl4-induced liver fibrosis. Both in vitro and in vivo studies have demonstrated that glycyrrhizin protects against liver cirrhosis. Glycyrrhizin's anti-cirrhosis effect may be mediated by its inhibitory effect on NF-kB binding. Glycyrrhizin was found to have an anti-cirrhosis effect both in serum ALT detection and in histological analysis in this study. Furthermore, NF-kB binding activity in cirrhosis rats' livers was significantly decreased after treatment with glycyrrhizin. CCl4-induced liver damage in rats was also inhibited by 18alpha-glycyrrhizin, a modified derivative of glycyrrhizin. As a result of 18alpha-glycyrrhizin treatment, liver mRNA and protein levels of Smad2, Smad3, SP-1 and TGF-beta1 were decreased which in turn inhibited collagen deposition [22]. In a phase III clinical trial, 379 chronic Hepatitis C patients who failed to respond to interferon-based treatment were also shown to benefit from glycyrrhizin's antifibrosis properties. ALT levels decreased by 50% in 28.7% patients under treatment with 5x/week glycyrrhizin injections, and 29.0% in the group receiving 3x/week glycyrrhizin injections, significantly more than the placebo group (7.0%, $p < 0.0001$). After 52 weeks of treatment, 44.9% of patients with 5 sessions/week and 46.0% of patients with 3 sessions/week have reduced their levels of necro-inflammation in the liver. As compared to placebo, glycyrrhizin reduced serum ALT levels after 12 weeks of treatment and suppressed necro-inflammation and fibrosis after 52 weeks. The clinical trial also revealed no obvious side effects from glycyrrhizin [23]. The antioxidant effect of silybinin, also known as silybin, is seen in cirrhotic livers. In cirrhosis rat livers, silybinin inhibits cardiolipin oxidation and citrate carrier failure, and prevents mitochondrial reactive oxygen species (ROS) from being produced. By inhibiting lyso phosphatidylcholine acyltransferase (LPCAT) expression in cirrhotic rat livers and increasing platelet-activating factor levels, silybinin also exhibits significant anti-inflammatory effects. In a clinical survey, silymarin was found to reduce cirrhosis symptoms and quality of life. In clinical practice, the effects of silymarin on survival rates and the progression of liver cirrhosis remain controversial. An endemic Bupleurum species in Taiwan, Bupleurum kaoi Liu, C.Y. Chao & Chuang, exhibits anti-fibrotic and anti-inflammatory properties in liver cells. Glutathione expression increases in association with these effects, indicating antioxidant activity. As a result of increased expression of IL-10 and INF-gamma, it is also capable of regulating the regeneration of liver cells. The antifibrotic and hepatoprotective effects of *Bupleurum kaoi* are much greater than those of *Bupleurum chinense* DC [24]. Moreover, an associated animal research demonstrated that the application of *Salvia miltiorrhiza* Bunge to liver tissues resulted in minimal accumulation of fibrous tissue, preserved normal tissue structure, and reduced collagen buildup. The ability of *Salvia miltiorrhiza* Bunge to counteract fibrosis is further substantiated by its observed reduction in levels of tissue inhibitor of metalloproteinase (TIMP) 1 and collagen 1(alpha) proteins [25]. Animal experiments have indicated that extracts from *Salvia miltiorrhiza* Bunge possess the ability to hinder the progression of liver fibrosis and enhance liver functionality by diminishing non-functional fibrous tissue within the liver. For individuals dealing with chronic hepatitis or those who engage in excessive alcohol consumption, the utilization of *Salvia miltiorrhiza* Bunge is suggested to safeguard their liver function. In liver cell studies, it was noted that extracts from *Scutellaria baicalensis* Georgi led to an elevation in the expression of glutathione S-transferase A5 and a reduction in P450 cytochrome 3A2. The administration of methanolic extracts from *Scutellaria baicalensis* Georgi resulted in notable decreases in liver malondialdehyde and hydroxyproline levels, coupled with improvements in histological findings. These outcomes collectively underscore the anti-fibrotic potential of *Scutellaria baicalensis* Georgi [26]. The extract derived from *Scutellaria baicalensis* Georgi additionally restrains the multiplication and activation of hepatic stellate cells through the initiation of cell cycle interruption in the G2/M phase. Furthermore, it prompts apoptosis in stellate cells by engaging the caspases and Bax pathway [27]. Baicalein is potentially the primary active constituent within *Scutellaria baicalensis* Georgi that contributes to preventing cirrhosis and fibrosis. Through in vivo investigations, it has been established that baicalein holds the capacity to impede the development of hypertrophic scars by inhibiting the TGF-beta/Smad2/3 signaling pathway in mice harboring scars induced by mechanical stress. The extended usage of baicalein might effectively hinder the activation of stellate cells by diminishing the expression of PDGF-beta receptor. This mechanism consequently holds promise for curbing the progression of liver fibrosis within animal models [28].

Limitations

While many individuals perceive herbal products as inherently natural and benign substances, recent years have witnessed clinical case reports highlighting potential adverse effects or toxicity associated with their usage. These effects can encompass acute exacerbations such as allergic reactions, or they might involve chronic toxicity necessitating prolonged accumulation, as seen with certain herbs that possess nephrotoxic properties [29]. This review delves into the side effects and toxicities linked with a range of established herbal products utilized in the treatment of liver diseases. In a study involving mice, acute toxicity assessment revealed that the oral LD50 of Coptis chinensis Franch was approximately 4.9 g/kg. Furthermore, LD50 values for berberine were found to be 9.0386 mg/kg through intravenous injection and 57.6103 mg/kg through intraperitoneal injection. Berberine, while recognized for its medicinal

benefits, has been associated with a range of common side effects, including laxative effects, constipation, anaphylaxis, and various skin allergies. Research has indicated that berberine might potentially induce degeneration of dopaminergic neuronal cells in a rat model of Parkinson's disease when combined with long-term levodopa treatment. For individuals with Parkinson's disease undergoing chronic L-DOPA treatment, cautious monitoring of berberine administration is advised. Several studies have proposed potential risks of berberine treatment during pregnancy, which could lead to hemolytic disease in newborns. Similarly, administering berberine to children may result in severe jaundice and acute hemolysis [30]. Due to these concerns, some countries such as the USA and Singapore have prohibited the prescription of berberine. However, it remains legally employed for clinical purposes in China, including Hong Kong.

CONCLUSION

Liver disease, a global public health challenge, manifests diversely and is on the rise. Complementary medicine, though debated, supplements conventional approaches in treating liver ailments. Its advantages include immune regulation, disease control, enhanced quality of life, and extended survival. Herbal remedies are gaining popularity, with a quarter of liver disease patients using them. Yet, clinical trials verifying their efficacy remain scarce, and the potential for herbal drugs to harm the liver lacks proper documentation due to unregulated usage. Scientific rigor aligned with evidence-based medicine is essential to distinguish true therapeutic value from unfounded perceptions, ensuring herbal medicine's credibility beyond trendiness.

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