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Biological Activity of Some Herbal Medication on Liver Diseases: Article Review

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ABSTRACT: *The use of herbal medicine can be traced back to more than 4000 years ago in ancient china. Over recent decades, an increasing number of herbal products, including medicinal herbs and phytochemicals, have been used for treating chronic liver diseases worldwide due to the high abundance, long-lasting curative effects and few adverse effects. According to the previous studies, medicinal herbs and phytochemicals could protect the liver by several mechanisms such as eliminating virus, blocking fibrogenesis, inhibiting oxidative injury and suppressing tumorigenesis. Chronic liver dysfunction or injury is a serious health problem world wise. Chronic liver disease involves a wide range of liver pathologies that include fatty liver, hepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. The efficiency of current synthetic agents in treating chronic liver disease is not satisfactory and they have undesirable side effects. Thereby, numerous medicinal herbs and phytochemicals have been investigated as complementary and alternative treatments for chronic liver diseases. Since some herbal products have already been used for the management of liver diseases in some countries or regions, a systematic review on these herbal medicines for chronic liver disease is urgently needed. Herein, we conducted a review describing the potential role, pharmacological studies and molecular mechanisms of several commonly used medicinal herbs and phytochemicals for chronic liver diseases treatment. Their potential toxicity and side effects were also discussed. Several herbal formulae and their biological effects in chronic liver disease treatment are also summarized in this paper.*

Keywords: *Chronic liver disease; herbal medicine; molecular targets; Chinese medicine; herbal formulae*

1.Introduction

Chronic liver diseases represent a major health burden worldwide and remain as one of the most serious health problems, which may affect more than 10% of the world population. Among the various forms of chronic liver diseases, the most widely spread types include viral hepatitis B and C, alcoholic liver disease, non-alcoholic fatty liver disease, cirrhosis and hepatocellular carcinoma are major problems remain unsolved. Excessive alcohol consumption, virus infection, obesity, diabetes and drug-induced liver damage are the leading causes of these liver diseases [1]. Although there have been remarkable progress in discovering treatment of chronic diseases over the last several decades, most of the therapies still do not yield satisfactory outcomes in patients. In view of the scarce treatment options and significant adverse effects incurred by conventional chemical agents, novel prophylactic and therapeutic agents against chronic liver disease are urgently needed. Many recent surveys from Europe and United States have demonstrated a sharp rise in the use of botanical drugs within few years, and up to 65% patients with liver disease take herbal preparations [2-5]. According to previous studies, medicinal herbs and phytochemicals could protect the liver by several mechanisms such as eliminating virus, blocking fibrogenesis, inhibiting oxidative injury and suppressing tumorigenesis [6&7]. As a chronic disease, most liver injuries need long-term treatment, thus, reducing side- effects of the therapy is critical when developing novel hepatoprotective agents. Although most of the patients believe that medicinal herbs and phytochemicals are natural and safe to be administrated without significant toxicity or side effects, all medicinal agents including herbal medicines potentially have toxicity and side effects. For safe use of medicinal herbs and phytochemicals, the potential side effects and toxicity of these

hepatoprotective herbal medicines should be seriously taken into consideration. In this paper, we have reviewed several widely used and recognized medicinal herbs and phytochemicals in the present treatment of chronic liver diseases including but not limited to Coptis chinesis Franch (berberine), Glycyrrhiza uralensis Fisch (glycyrrhizin), Silybum marianum (L) Gaertn. (silymarine and silybinin), Bupleurum chinensis DS (saikosaponins), Salvia meltiorrhiza Bunge (salvianolic acid) and Scuttilaria baicalensis Georgi (baiclin, wogonin) [8-10]. Several recent surveys from Europe and the United states have demonstrated a sharp rise in the use of botanical drugs within a few years, and up to 65% of patients with liver disease take herbal preparations [11]. Similar figures exist for Europe where the expenses for silymarin, a herbal preparation used to treat chronic liver diseases, reaches $180 million in Germany alone .

Many factors contribute to herbal medicine's appeal Supporter of herbal medicine claim that herbs may both treat and prevent diseases. This adds to a deep belief that these treatments are safe because they are natural and fit into the image of a gentle and, therefore, harmless alternative to conventional medicine. More so since patients are often dissatisfied with the latter because of disappointing treatment success or unfavorable side effects. In addition, herbal products are often exempt from rigorous regulations, such as in the U.S., and prescriptions are usually not required for these inexpensive products [12-14]. Both clinical trials and basic research of these herbal medicines were included to review the efficacy, potential molecular mechanisms as well as the side effects or toxicity of the active ingredients. In order to retrieve more recent publications about this topics, we conducted an updated search on the following databases from 1990 (one Chinese database and four English databases): China Journals Full-Text Databases, MEDLINE, AMED (Allied and Complementary Medicine Database), EMPASE and the Cochrane Central Register of Controlled Trials (CENTRAL). Herbs and Phytochemicals for chronic liver diseases treatment will be included in this review paper. The following review describes the current scientific evidence regarding herbal drugs and the liver, especially in regards to their presumed beneficial effect, and delineates the issues that need to be addressed to incorporate herbal medicine into the arsenal of therapies in the treatment of liver diseases [15-17].

2. Therapy of liver diseases with herbal medicine

Treating liver diseases with botanical drugs has a long tradition, but evidence for efficacy is sparse. Moreover, there are concerns about the quality of studies testing herbal remedies. In spite of these limitations, a number of herbals show promising effects, either experimentally in cell culture, in animal studies, or even in clinical trials [18].

2.1. Silymarine

Silybum marianum (Milke thistle) has been used to treat liver diseases since the 16th century. Its major constituents are the flavonoids silibinin, silidianin, silichristin, and isosilibinin of which silibinin is the biologically most active compounds and used for standardization of pharmaceutical products {19}.

The pharmacological profile of silymarin has been well defined and hepatoprotective properties of silymarin were investigated both in vitro and in vivo. Experimental studies demonstrated antioxidant and free radical scavenging properties, improvement of the antioxidative defence by prevention glutathione depletion, and antifibrotic activity.

To data, a major indication for silymarin treatment is Amanita phalloides (death cup fungus) intoxification in which silymarin acts as a hepatoprotectant through several mechanisms: 1. interruption of the enterohepatic recirculation of the hepatocyte toxin α-amanitin; 2. inhibition of the binding of both phalloidin and α-amanitin for transmembrane transporters [20,21]. Amanitin toxin given to dogs resulted in lethal hepatic failure in four animals treated with supportive care compared to no fatalities in animals treated with silymarin [22]. A number of well –designed experimental studies suggest that silymarin might exert beneficial effects in chronic liver diseases through antifibrotic properties. For example,

silymarin interferes with leukotriene formation in Kupffer cell cultures and may thereby inhibit hepatic stellate cell (HSC) activation, which is crucial event in fibrogenesis [23]. In addition, silymarin at certain concentration blocked the proliferation of HSC cultures and their transformation to myofibrioblasts [24]. Mourella et al.found that silymarin dosed at 50mg/kg body weight reduced fibrosis by 30% as measured by relative collagen content(per g of liver) [25], which could not be confirmed by others [26]. Silymarin prevented further progression when fibrosis was advanced, a situation encountered in many patients. Furthermore, the number of activated HSCs was markedely reduced [27] and transcription of hepatic procollagen type 1 was decreased by 50%.

The widespread use of silymarin by patients with chronic liver disease in Europe was fueled by the results of clinical trial in which 170 patients with biopsy-proven cirrhosis of various aetiologies (92 alcohol-related,78 other causes) were treated with silymarin at 420 mg/day. The main finding was a significant survival benefit of patient treated with silymarin compared to the placebo group (77% versus 67% at 2 years, and 58% versus 39% at 4 years, respectively). More importantly, silymarin had no side effects. In a meta-analysis [28], nine trials that studied silymarine in chronic liver diseases were considered of high quality, scoring at least three points of the jaded score. The latter ranges from one to five, one or two being considered of low quality [29] . Clinical studies in acute liver diseases e.g.viral hepatitis, have produced conflicting results or failed to meet methodological requirements, since study size, duration of treatment and follow-uphave been insufficient. A major problem of most clinical trials has been the definition of end points such as progression of fibrosis case [30]. Whether higher doses of silymarin, i.e.840 mg/day, are more effective in attenuating fibrosis progression in chronic viral hepatitis C is currently tested in a randomized controlled multicenter trial but, so far, due to the lack of firm clinical evidence, silymarin cannot be recommended for the treatment of liver diseases [31].

2.2. Glycyrrhizin

Glycyrrhizin is an aqueous extract of the liquorice root (Glycyrrhiza glabra) and has been used in traditional medicine to alleviate bronchitis, gastritis and jaundice. The major constituents are glycyrrhetic acid, flavonoids and hydroxycoumarins. In Japan, a standardized extract containing glycyrhhizin, cysteine and glycine is an established treatment for chronic hepatitis as stronger Neominophagen C (SNMC). A daily dose of 80mg/day given intervenously for two weeks normalized elevated aspartate and alanine transaminase[32]. SNMC is also available over-the-counter in the United States as a liquid, powder, and tablet.

In the cell culture experiments, glycyrrhizin modifies glycosylation and blocks sialylation of hepatitis B surface antigen (HBsAg) leading to its retention in the trans-Golgi apparatus [33]. Glycyrrhizin counteracts several forms of experimental hepatic injury and partly inhibits the activity of beta-hydroxysteroid dehydrogenase prostaglandin E2 production by macrophages, and may have antioxidative properties through the induction of glutathione-s-transferases and catalases [34]. Some evidence points to an antifibrotic effect in the rat CCL4 model, possibly through inactivation of NFkB [35]. Evidence for an antiviral activity of glycytthizin is lacking and experimental evidence rather points to a membrane-stabilizing effect as proposed by a study using an in vitro hepatotoxicity model [36].

Glycyrrhizin has also been used in an open-label trial including 56 patients with subacute liver failure. Patients were treated with glycyrrhizin 100 ml daily for 30 days followed by an 8-week period with glycyrrhizin administration every other day. Survival was compared with historical controls from the previous 10 years and proved to be better in the glycyrrizin- treated group [37]. The mechanisms that lead to less tumors to occur are unclear and uneven randomization cannot be excluded.

The main characteristics of these and other clinical trials of glycyrrhizin as a treatment for chronic viral hepatitis B and C, mostly performed with SNMC. In some studies, glycyrrhizin was

administrated with interferon-alpha or ursodeoxycholic acid, while others administrated glycyrrhizin monotherapy [38].

2.3. Phyllanthus amarus

The plants of the genus Phyllanthus are found in most tropical and subtropicl countries and have long been used for treatment of chronic liver diseases. Phyllantins, hypophyllantin and several polyphenols are major constituents of which chemical and pharmacological properties are well described [39]. Experimental data indicate that some of the active compounds within Phyllanthus may exert activity against hepatitis B virus infection, possibly through interference with polymerase activity, Mrna transcription and replication [40-43].

Clinical evidence for a beneficial activity of Phyllanthus preparations in the treatment of chronic hepatitis B comes from numerous trials which were recently evaluated in a systematic review [44].

Overall, the authors conclude that Phyllanthus species may have antiviral activity, but vote for caution, since the differences between phyllanthus herb and control interventions occurred mainly in trials with lower methodological quality. In addition, the beneficial effect of Phyllanthus versus placebo or no treatment was mainly due to an Indian trial [45] which was not confirmed by the same authors in a later study [46].

2.4. Japanese traditional medicine (Kampo)

In 1976, Kampo medicines originating from Japanese medicine and Traditional Chinese Medicine (TCM) were approved for use by the National Health Insurance in Japan. In practice, the Japanese Koho-School of medicine has issued standardized formulas of traditional recipes and the often synonymously used abbreviation 'TJ' originates from a commercial classification of the main herbal drug manunfacturer in Japan who numbered Kampo-formula consecutively (TJ-1TO TJ-148.

A large series of clinical reports exist with regard to treating liver diseases with TJ-9 (sho saiko-to), a combination of seven herbals along the principles of TCM. a search in an Asian medical database revealed more than 1000 scientific articles-often with poor scientific value-on this drug which illustrates its extensive use not only for liver diseases but also for many other disorders.

Both in vitro and in vivo studies have shown that TJ-9 can exert antifibrotic activities. Kayano et al. showed that TJ-9 at 500 ug/mL or 1000ug/Ml inhibited the morphological transformation of hepatic stellate cell (HSCs) to myofibroblast-like cells, possibly by inducing an arrest of HSCs in the G0/G1 phase of the cell cycle [47]. Procollagen 1 and 111 Mrna transcription decreased simultaneously. This effect is possibly due to the flavonoids baicalin and baicalein, major constituents of TJ-9, since a cell culture study demonstrated their strong antiproliferative effect on rat HSCs [48]. The molecular mechanisms involved are only partly known. Sakaida et al. suggested that TJ-9 causes an inhibition of HSC activation as reflected by a reduced number of alfa smooth muscle actin (alfa-SMA) positive HSCs [49].In vivo studies in rats made fibrotic with the hepatotoxin dimethylnitrosamime (DMN) showed that TJ-9 reduces relative hepatic collagen content when given during injury [50}. Shimizu et al. reported suppression of lipid peroxidation in rats exposed to DMN or pig serum, which was paralleled by decreased levels of the lipid peroxidation product malondialdehyde, improved histology, reduction of relative hepatic collagen content, decreased α—SMA-staining positivity of isolated HSCs [51]. However, DMN represents a suboptimal animal model, since it rather produces a collapse of the liver and every agent that increase or maintains hepatocyte mass will decrease relative hepatic collagen content (mg/g of liver) without being necessarily antifibrotic.

Few clinical data of the efficacy of TJ-9 in human liver disease are published. In a long-term prospective, randomized, non-blinded controlled study lasting 5 years, patients positive for HBsAg received 6.5 g/daily of an aqueous TJ-9 extract with standard interferon. During follow up, the cumulative development of hepatocellular carcinoma(HCC) was significantly lower than that in controls without TJ-9 [52]. This finding was confirmed later in another prospective trial in which TJ-9 was found to the effective in preventing the development of HC, paralleled by a reduction of hepatic 8-hydroxy-2-deoxyguanosine, a marker of oxidative DNA damage [53].

2.5. Traditional Chinese Medicine (TCM)

The use of herbal medicines in China dates back as far as 2100 B.C., with comprehensive records of Chinese medical theories as early as 221 B.C . Chinese medicine comprises over 100.000 defined therapies, with about 80% being herbal combinations. Most Chinese medicines are blends of 4-5 different herbs of which 1 or 2 are the pharmacologically active ‘’King herbs’’, while the remaining constituents function as modifiers of toxicity, act synergistically with the ‘’King herbs’’improve the immune function, or strengthen certain aspects of physical well-being.

A literature searches in a traditional Oriental Medicine Database identified a number of herbal mixtures that are supposed to treat liver diseases [54]. Among these, extracts from Plantago asiatica (ribwort) appear to exert hepatoprotective activity without significant toxicity. The active component of Plantago asiatica is aucubin which was found to inhibit hepatitis B virus replication in vitro [55]. Results of a clinical trial presented in an abstract during an NIH workshop that addressed complementary and alternative medicine in liver diseases in 1999 suggested that 10mg/kg body weight administered parenterally for 4 weeks caused a 10-40% decrease in serum HBV DNA that returned to pretreatment levels after after the medication was discontinued [56].

A combination of 10 herbs termed compound 861 and which contains Saliva militriorrhiza (sage), Astragalus membranaceus, and Spatolobus suberectus as the ‘’King herbs’’ was tested in several experimental studies for antifibrotic properties. In pig-serum induced rat liver fibrosis, treatment with compound 861 was reported to lower hepatic collagen content and to decrease m RNA of procollagen type 1,111, and IV in HSC cultures, which suggested a direct antifibrotic effect [57,58}. Compound 861 was further tested in three controlled trials involving a total of 107 patients with chronic hepatitis B [59]. None of the patients cleared HBsAg, but liver enzyme levels were significantly reduced in most patients. Surrogate fibrosis markers decreased. Histologically, stages of fibrosis and grades of inflammation were improved along with a reduction in total tissue hydroxyproline. Since all clinical studies on compound 861 do not satisfy high quality criteria, further well designed trials e needed [60].

3. Adverse hepatic reactions from herbal drugs

Many herbals are on the market to support health, relieve symptoms and cure diseases. However, most of these products lack scientific evidence that supports these allegations. Experimentally, several herbals exert biological activities which justify further research and clinical testing, but so far, no herbal can be firmly recommended for the treatment of liver diseases.

Herbs are popular and many patients, particularly, those with liver diseases take them in self-medication. Therefore, once explained liver abnormalities occur, doctors are urged to ask specifically and repeatedly for ‘’herbals, health tonics, vitamins and food supplements’’ [61].

A causal relationship between an adverse hepatic reaction and the intake of herbals is usually established based on circumstantial evidence, as with most synthetic drugs. There are no specific diagnostic tests. Several Chinese herbal combinations may be useful for the treatment of chronic liver diseases, especially viral hepatitis; further more in –depth studies are necessary, since pharmacologically

active constituents are ill-defined, interactions between multiple compounds may occur, and hepatotoxicity has been observed [62,63].

4. The potential side-effects or toxicity of herbal products in chronic liver disease treatment

Although most people consider herbal products as natural and safe agents, there have been some clinical case-reports about side-effects or toxicity of herbal products in recent years. Some side effects or toxicity of herbal medicines may constitute an acute exacerbation such as allergy, while some agents may have chronic toxicity which require long-term accumulation [64,65].

4.1. Toxicity of Berberine in chronic liver disease treatment

The acute toxicity study in mice demonstrated that LD50 of berberine intervenous injection was approximately 4.9 g/Kg by oral treatment [66,67]. The most common side effects of berberine include laxative, constipation, anaphylaxis and some skin allergies. One study suggested that berberine may cause the degeneration of dopaminergic neuronal cells. Some other studies believed that berberine treatment for pregnant women may lead to hemolytic disease in newborns; berberine treatment for children may lead to sever jaundice and acute hemolysis [68--71].

4.2. Side effects or toxicity of Glycyrrhizin in chronic liver disease treatment

Previous study has proved that Glycyrrhizin can lead to pseudoaldosteronism which will cause aldosteronopenia, hypokalemia, hypertention, and inhibited plasma rennin activity [72]. Another study also found that high dose of glycyrrhizin for pregnant women will increase the premature birth rate [73].

4.3. The potential side- effects or toxicity of silymarine and silybinin in liver disease treatment

A phase 1 clinical trial in prostate cancer patients demonstrated that high dose of silybinin (13 g/day) may cause hyperbilirubinemia and increase alanine aminotransferase levels. [74].

4.4. The potential side-effects or toxicity of Saliva miltiorrhiza in chronic liver disease treatment

As a major component of Saliva miltiorrhiza Bunge, it should constitute a promising, safe a medicinal plant for liver disease treatment. However, there are still some side effects which should be paid serious attention to in clinical practice. Saliva miltiorrhiza Bunge can inhibit hemostatis through suppressing platelet aggregation, enhancing fibrinolytic activity, and inhibiting the extrinsic blood coagulation. At the same time, it could enhance the anticoagulant effect by warfarin. Thus for patients taking warfarin, Saliva miltiorrhiza Bung treatment should be avoided to decrease the risk of bleeding complications [75-77].

5. Conclusions

This review amply demonstrates that the herbal products can protect the liver from oxidative stress, inflammation and chronic liver diseases. About half of the drugs in use today are procured from plant products. However, the evidence supporting the use of herbal products for treating liver diseases is inadequate and only few of them are well standardized and also free serious side effects.

It has been clearly reported that medicinal plants and phytochemicals can treat chronic liver disease by inhibiting oxidative damage, suppressing fibrogenesis, eliminating virus infection, and preventing or inhibiting tumor growth. For some medicinal plants, the active component still need to be further confirmed. More randomized, placebo-controlled clinical trials are urgently needed to confirm the clinical efficacy of this herbal medicine in chronic liver disease treatment. For the majority of medicinal herbs and phytochemicals, the safety investigation is just as important as the efficacy

investigation. In future study, both basic research and clinical studies should be developed on the potential toxicity and side effects of these herbal medicines. More medicinal plants and phytochemicals which safe performance and significant efficacy are expected to be identified for use in chronic liver disease treatment in the future studies.

Popularity of herbal remedies is increasing and at least one quarter of patients with liver disease use botanicals. Unfortunately, well-performed clinical trials on their therapeutic value in the treatment of certain liver diseases are very rare and the frequency in which herbal drugs cause hepatic damage remains uncharted, since its use is largely uncontrolled. Further efforts will have to implement extensive methodological improvements to separate the real therapeutic value of these agents from unfounded hopes and mysteries associated with them.

Despite cumulative evidence of success in treating liver fibrosis, *in vivo* results are insufficient to confirm the clinical efficacy of natural products and herbal medicines for liver fibrosis. Therefore, successful development of novel and promising therapies for treatment requires careful designs using various experimental approaches. The identification of resources and the molecular mechanisms of action of these substances remain extremely challenging.

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