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Mini-review

Recent advances in natural products from plants for treatment of liver diseases

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ABSTRACT

Liver disease is any condition that may cause liver inflammation or tissue damage and affects liver function. Natural products that are found in vegetables, fruits, plant extracts, herbs, insects, and animals, have been traditionally used for treating liver diseases. They are chemical compounds that usually have biological activities for use in drug discovery and design. Many natural products have been clinically available as potent hepatoprotective agents against commonly occurring liver diseases. This review summarizes the current progress in the basic, clinical, and translational research on natural products in treatment of various liver diseases. Furthermore, we will focus on the discovery and biological evaluation of the natural products, which shows potential as a new therapeutic agent of liver diseases.

1. Introduction

Liver disease afflicts over 10% of the world population [1]. This includes chronic hepatitis, alcoholic steatosis, fibrosis, cirrhosis and hepatocellular carcinoma (HCC), which are the most health-threatening conditions drawing considerable attention from medical professionals and scientists. Patients with alcoholism or viral hepatitis are much more likely to have liver cell damage and cirrhosis, and some may eventually develop HCC, which is unfortunately, and very often, a fatal malignancy without cure. Although treatment options exist for most of the liver diseases, many types remain incurable and the emergence of drug resistance is pervasive [2]. Thus, novel treatment approaches are essential to improve outcome. Nearly half of the agents used in liver therapy today are either natural products or derivatives of natural products [4–6]. The term "natural products" is usually associated with secondary metabolites produced by an organism, which in most cases function as defense mechanisms against herbivores, microorganisms, insects and competing plants. A variety of natural products, mostly from plant sources, contain several active components and have been used for thousands of years by a significant fraction of the population, and are still used in healthcare in many countries or regions of the world [7]. Natural products have generated a rich source of structurally diverse substances with a wide range of biological activities, which could be useful for the development of alternative or adjunctive therapies.

The use of natural products to prevent and/or treat various liver diseases dates back several thousand years in many countries. Natural products have begun to gain popularity worldwide for promoting healthcare as well as disease prevention, and been used as conventional or complementary medicines for both treatable and incurable diseases [8]. Global analysis of natural products is an important issue in developing new therapeutic managements for liver disease. Approximately 25% of the drugs prescribed worldwide at present come from plants and 60% of anti-infectious drugs already on the market or under clinical investigations are of natural origin [9]. In the US and Europe, about 65% of patients with liver disease take herbal preparations; the cost of the use of silymarin reaches $180 million in Germany alone [10]. The effectiveness of natural products has inspired pharmaceutical scientists to search for new directions in drug discovery and development. The easy accessibility without the need for laborious pharmaceutical synthesis has drawn increased attention toward herbal medicines. Natural products that are increasingly used, and have been used to treat liver disorders and become a promising therapy internationally for pathological liver conditions [11]. Several phytochemicals that have been identified and showed promising activity, are glycyrrhizin to treat chronic viral hepatitis, ellagic acid for antifibrotic treatment, and phyllanthin for treating chronic hepatitis B [12]. These compounds has specific characteristics and actions, with an

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intrinsic beneficial or toxic effect and especially used as antioxidants or hepatoprotective agents. Experimental studies have clearly demonstrated these compounds, which have proven antioxidant, antiviral or anticarcinogenic properties and have significant hepatoprotective activity with minimal systemic adverse effects, can serve as primary compounds for further development as hepatoprotective drugs [13].

Plants produce a diverse array of more than 100,000 secondary metabolites, and can be classified on the basis of composition, the pathway by which they are synthesized, or chemical structure [14]. A simple classification includes three main groups: (i) phenolic compounds, which are made from simple sugars, containing benzene rings, hydrogen and oxygen; (ii) terpenoids, which are made from mevalonic acid and composed almost entirely of carbon and hydrogen; and (iii) alkaloids, which are nitrogen-containing compounds [15,16]. However, it is a challenging approach owing to complex chemistry and isolation procedures to derive active compounds from natural products. The true value of natural products in liver diseases prevention and/or their exact mechanisms of action remain largely unknown. Thus, some promising plant compounds for liver diseases were chosen and analyzed critically from the basic to the clinical and provides the chemistry, pharmacology and future aspects, focus on hepatoprotective properties. Following this, it is hoped that as a result of this review, readers will have a greater awareness of the excellent promise that plant-derived natural products and their derivatives show for use in the therapy of liver diseases.

2. Basic aspects

Liver diseases, a major problem of worldwide proportions, incorporate several maladies, which can range from benign histological changes to serious life-threatening conditions. These may include inborn metabolic disease, primary and metastatic cancers, alcoholic cirrhosis, viral hepatitis and drug-induced hepatotoxicity [17]. It remains a major cause of morbidity and mortality with significant economic and social costs. The use of natural phytochemicals, some of them obtained from dietary sources, in the amelioration of illness have recently gained considerable popularity [18]. These phytochemicals can provide a safe and effective means of ameliorating liver disease. Scientists are looking for lead compounds with specific structures and pharmacological effects often from natural sources. Many drugs presently prescribed by physicians are either directly isolated from plants or are artificially modified versions of natural products [19]. The compounds described herein are: wogonin, curcumin, glycyrrhizin, resveratrol, silymarin, naringenin, geniposide, rhein, 6,7-dimethylesculetin, matrine, ellagic acid, mellein, artemisinin *etc.*

2.1. Wogonin

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections remain a major threat worldwide. Chronic hepatitis B and C together with alcoholic and non-alcoholic fatty liver diseases represent the major causes of progressive liver disease that can eventually evolve into cirrhosis and its end-stage complications, including decompensation, bleeding and liver cancer [20–23]. Although several antiviral drugs have been approved for hepatitis B, they cause significant drug resistance and adverse side effects. Safe and potent new anti-HBV drugs are mandatory and urgently needed. Numerous natural alternatives for treating HBV have been suggested. Wogonin (Fig. 1) is a monoflavonoid isolated from *Scutellaria radix* which has been used for thousands of years in Asia for inflammatory diseases and also for hepatitis [24]. The anti-HBV activity of wogonin demonstrates its ability to suppress hepatitis B surface antigen (HBsAg)

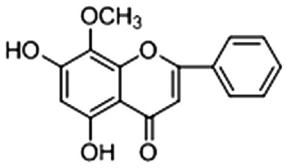

Fig. 1. Chemical structure of various natural product: wogonin from *Scutellaria radix*.

secretion in cell culture. Plasma HBsAg level was significantly reduced in ducks treated with wogonin, and an additional histopathological evaluation of their liver showed considerable improvement. Wogonin had effective cytotoxic effects through apoptosis induction in hepatocellular carcinoma cells SK-HEP-1; activation of caspase-3 cascade, induction of p53 protein and alternative expression of p21 protein were involved [25]. Furthermore, immunohistological staining of human HBV-transgenic mouse livers confirmed the potential of wogonin in HBsAg reduction. Therefore, it is currently under early development as anti-HBV drug.

2.2. Curcumin

Curcumin (Fig. 2), one of the main active compound obtained from the plant *Curcuma longa*, was first isolated two centuries ago. It was used in ancient times on the Indian subcontinent to treat various illnesses such as rheumatism, body ache, skin diseases, intestinal worms, diarrhea, intermittent fevers, hepatic disorders, biliousness, urinary discharges, dyspepsia, inflammations, constipation, leukoderma, amenorrhea, and colic. In recent years, considerable interest has been focused on curcumin due to its use to treat a wide variety of disorders without any side effects. Curcumin has the potential to treat a wide variety of inflammatory diseases including cancer, diabetes, cardiovascular diseases, arthritis, Alzheimer's disease, psoriasis, *etc*, through modulation of numerous molecular targets [26]. Its ability to inhibit several factors like nuclear factor-kappaB, which modulates several pro-inflammatory and profibrotic cytokines as well as its antioxidant properties, provide a rational molecular basis to use it in hepatic disorders. Curcumin could attenuate liver injury induced by ethanol, thioacetamide, iron overdose, cholestasis and acute, subchronic and chronic carbon tetrachloride (CCl_4) intoxication; moreover, it can reverse CCl_4 cirrhosis to some extent [27].

2.3. Glycyrrhizin

HCV is a major cause of chronic liver diseases which can lead to permanent liver damage, hepatocellular carcinoma and death. The presently available treatment with interferon plus ribavirin, has limited benefits due to adverse side effects such as anemia, depression, and fatigue [28]. Glycyrrhizin (Fig. 3), a major biological active constituent of licorice (*Glycyrrhiza glabra*) root, has various pharmacological effects and been used as a treatment for chronic hepatitis. It is a natural anti-inflammatory and antiviral triterpene and is ancillary drugs used clinically in China for protection of liver function and treatment of tumors. Glycyrrhizin had a protective effect on immunosuppression, a strong non-specific anti-inflammatory effect,

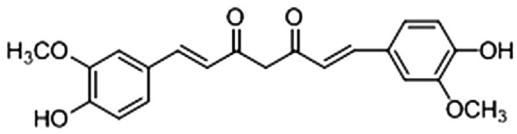

Fig. 2. Chemical structure of various natural product: curcumin from the plant *Curcuma longa*.

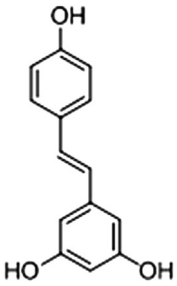

Fig. 3. Chemical structure of various natural product: glycyrrhizin from *Glycyrrhiza glabra*.

and an effect of reducing the incidence of sodium and water retention [29]. The effect of glycyrrhizin on expression of MMP-9 have examined [30]. Results indicated that MMP-9 played a role in the development of LPS/GalN-induced mouse liver injury, and suggested that an inhibition by glycyrrhizin of the acute liver injury may have been due to a downregulation of MMP-9. Glycyrrhizin also significantly inhibited hepatocyte apoptosis by down-regulating the expression of caspase-3 and inhibiting the release of cytochrome C from mitochondria into the cytoplasm [31]. The anti-inflammatory activity of glycyrrhizin may rely on the inhibition of release of tumor necrosis factor-a, myeloperoxidase activity, and translocation of nuclear factor-kappaB into the nuclei. Glycyrrhizin can up-regulate the expression of proliferating cell nuclear antigen, implying that it might be able to promote regeneration of livers harmed by LPS. It is noteworthy that glycyrrhizin has the therapeutic potential to prevent liver injury during hepato-biliary surgery [32]. The prevention by Glycyrrhizin of Con A-induced hepatitis is due partly to the modulation of hepatic iNOS induction and of degeneration of hepatocytes [33]. As one of the most widely used herbal preparations for the treatment of liver disorders, the potential beneficial effect of glycyrrhizin in a mouse model of CCl_4-induced liver injury was evaluated [34]. The mRNA expression of heme oxygenase-1 was augmented by the glycyrrhizin treatment, while glycyrrhizin attenuated the increase in tumor necrosis factor-alpha, inducible nitric oxide synthase, and cyclooxygenase-2 mRNA expressions. These results suggest that glycyrrhizin alleviates CCl_4-induced liver injury, and this protection is likely due to the induction of heme oxygenase-1 and the downregulation of pro-inflammatory mediators and may represent a potent drug protecting the liver injury.

2.4. Resveratrol

Resveratrol (Fig. 4), a polyphenolic phytochemical present in berries, grapes and wine, has shown considerable promise as a

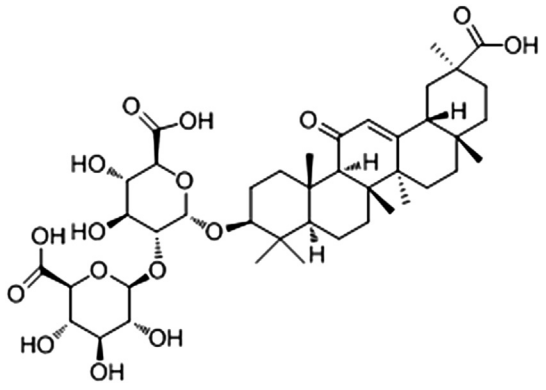

Fig. 4. Chemical structure of various natural product: resveratrol from *Polygonum cuspidatum* Sieb. et Zucc.

therapeutic agent in the treatment of the liver ailments. Several studies have highlighted the hepatoprotective properties of resveratrol. Resveratrol could prevent hepatic damage because of free radicals and inflammatory cytokines, induce antioxidant enzymes and elevate glutathione content, and also shown to modulate varied signal transduction pathways of liver diseases. Studies using purified enzymes, cultured cells, and laboratory animals have suggested that resveratrol has anti-aging, anticarcinogenic, anti-inflammatory, and antioxidant properties that might be relevant to chronic diseases and/or longevity in humans [35]. Resveratrol could significantly reduced TNF-α and IL-6 mRNA and decreased the number of Kupffer cells recruited in the injured liver. It decreased fibrosis and promoted hepatocyte regeneration, which increased the survival of BDL mice. Resveratrol was beneficial for the treatment of cholestatic liver injury [36]. The histopathological, immunohistochemical, and apoptotic analysis were used to assess the effect of resveratrol on morphological, oxidative status in CCl_4-challenged liver tissue [37]. It indicated that the inflammatory cytokines TNF-α and IL-6 were profoundly expressed in experimental rats, whereas resveratrol decreases the immunopositivity of TNF-α and IL-6 and restored the altered architectural structure of challenged hepatic tissue. Resveratrol also protects liver cells by suppressing oxidative stress and apoptosis. The administration of resveratrol either at the early or advanced stages of hepatocarcinogenesis is equally effective and involves the activation of the apoptotic pathway in male Wistar rats [38]. The inhibitory effect of resveratrol on vascular endothelial growth factor activity and angiogenesis in hepatocellular carcinoma may occur partly through suppression of the activation of NF-kappa B in HepG2 cells [39]. It significantly inhibited liver tumor growth and angiogenesis. Resveratrol protects against methotrexate-induced hepatic injury and may be of therapeutic potential in alleviating the systemic side effects of chemotherapeutics [40]. Oral administration of resveratrol (20 mg/kg daily for 4 weeks) remarkably prevented the DMN-induced loss in body and liver weight, and inhibited the elevation of serum alanine transaminase, aspartate transaminase, alkaline phosphatase and bilirubin levels [41]. Resveratrol showed not only reduced mRNA expression of fibrosis-related genes such as transforming growth factor beta1, collagen type I, and alpha-smooth muscle actin, but also a significant decrease of hydroxyproline in rats with DMN-induced liver fibrosis [42]. Resveratrol exhibited *in vivo* hepatoprotective and anti-fibrogenic effects against DMN-induced liver injury, suggesting that resveratrol could be used to treat liver injury and fibrosis and be useful in preventing the development of liver fibrosis and cirrhosis.

2.5. Silymarin

Milk thistle (*Silybum marianum*) is the most well-researched plant in the treatment of liver disease. Extracts of milk thistle have been recognized for centuries as 'liver tonics' and are well-known to prevent or reverse hepatotoxicity of reactive drug metabolites or naturally occurring toxins [43]. Silymarin, a flavonolignan from milk thistle plant, is used for the protection against various liver conditions in both clinical settings and experimental models [44]. It acts as an antioxidant by reducing free radical production and lipid peroxidation, has antifibrotic activity and may act as a toxin blockade agent by inhibiting binding of toxins to the hepatocyte cell membrane receptors [45]. In animals, silymarin reduces liver injury caused by acetaminophen, carbon tetrachloride, radiation, iron overload, phenylhydrazine, alcohol, cold ischemia and *Amanita phalloides* [46]. Number of studies has established to treat alcoholic liver disease, acute and chronic viral hepatitis and toxin-induced liver diseases. Silymarin exerts membrane-stabilizing and antioxidant activity, it promotes hepatocyte regeneration; furthermore it reduces the inflammatory reaction, and inhibits the fibrogenesis in

the liver [47]. According to open studies the long-term administration of silymarin significantly increased survival time of patients with alcohol induced liver cirrhosis. Based on the methods of molecular biology, silymarin can significantly reduce tumor cell proliferation, angiogenesis as well as insulin resistance. Liver cirrhosis, non-alcoholic fatty liver and steatohepatitis are risk factors for HCC. The chemopreventive effect of silymarin on HCC has been established in several studies using *in vitro* and *in vivo* methods; it can exert a beneficial effect on the balance of cell survival and apoptosis by interfering cytokines. These results have been established by experimental and clinical trials.

2.6. Naringenin

Naringenin (Fig. 5), a naturally occurring citrus flavanone, found in grapefruits and tomatoes, has been reported to have a wide range of pharmacological properties. Oral administration of naringenin (20 and 50 mg/kg daily) remarkably prevented the DMN-induced loss in body and liver weights and inhibited the elevation of serum alanine transaminase, aspartate transaminase, alkaline phosphatase, and bilirubin levels [48]. It demonstrated that naringenin exhibited *in vivo* hepatoprotective and antifibrogenic effects against DMN-induced liver injury. It also exhibited antioxidant property and decrease the lipid peroxidation against oxytetracycline-induced oxidative stress in liver [49]. These results suggest that naringenin may be useful in preventing the development of hepatic fibrosis. Cadmium is a major environmental pollutant and is known for its wide toxic manifestations. A study suggested that naringenin may be beneficial in ameliorating the cadmium-induced oxidative damage in the rat liver [50]. Administration of naringenin to rats with ethanol-induced liver injury significantly decreased the levels of serum aspartate and alanine transaminases, gamma-glutamyl transpeptidase, tissue thiobarbituric acid reactive substances, conjugated dienes, lipid hydroperoxides and protein carbonyl content and significantly elevated the activities of superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and glutathione-S-transferase [51]. Histological changes observed in the liver correlated with the biochemical findings. Taken together these findings suggest that naringenin has a therapeutic potential in the abatement of ethanol-induced hepatotoxicity.

2.7. Geniposide

Geniposide (Fig. 6) that is iridoid glycoside from the fruit of *Gardenia jasminoides* Ellis, is recognized as being useful against hyperlipidemia and fatty liver [52]. Recent studies have suggested that geniposide can effectively inhibit liver fibrosis [53]. In addition, geniposide suppressed expression of CYP2E1 and increased peroxisome proliferator-activated receptor-α (PPARα) expression. These benefits may be associated with increased superoxide dismutase and decreased malondialdehyde in liver. Geniposide exerts protective effects against hepatic steatosis in rats fed with a high fat diet; the underlying mechanism may be associated with its antioxidant actions or regulation of adipocytokine release and expression of PPARα. Genipin, the aglycone of geniposide, exhibits anti-inflammatory and anti-angiogenic activities. Genipin could induces apoptotic cell death in rat hepatoma cells and human hepatocarcinoma Hep3B cells [54].

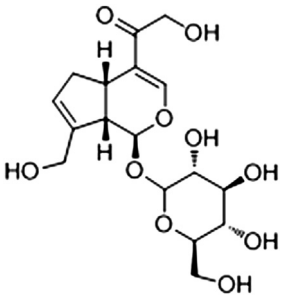

Fig. 6. Chemical structure of various natural product: geniposide from *Gardenia jasminoides* Ellis.

2.8. Rhein

Rhein (Fig. 7), an anthraquinone derivative of rhubarb, inhibits the proliferation of various human cancer cells. It plays role by inducing cell cycle arrest via downregulation of oncogene c-Myc and apoptosis through the caspase-dependent pathway [55]. Rhein ameliorates fatty liver disease through negative energy balance, hepatic lipogenic regulation, and immunomodulation in diet-induced obese mice [56]. The protective effects of rhein against APAP-induced liver and kidney injuries might result from the amelioration of Acetaminophen-induced oxidative stress [57]. Rhein can protect hepatocyte from injury and prevent the progress of hepatic fibrosis in rats, which may associate with that rhein plays a role in antioxidation, anti-inflammation, inhibiting the expression of TGF-beta1 and suppressing the activation of hepatic stellate cells [58]. It has protective effect on liver injury and can inhibit liver fibrosis induced by CCl_4/ethanol in rats [59]. The mechanisms possibly contribute to its action of antioxidant and anti-inflammatory activity, also associated with its effect of inhibiting TGF-beta1 and suppressing the activation of hepatic stellate cells. It is expected that rhein will be effective and useful as a new agent in hepatocellular carcinoma treatment in the future.

2.9. Others

Traditional medicine is a very complex mixture containing hundreds or thousands of different components and has played an indispensable role in the prevention and treatment of diseases, especially the complicated and chronic liver ones. A selective and sensitive method of UPLC-ESI-Q-TOF-MS/MS had been developed to screen the potentially bioactive components *in vivo*, using the semi-quantitative determination of multicomponents in the rat plasma after a single oral administration of Yin-Chen-Hao-Tang, a famous formula for liver disorders [60]. Comparing the body dynamics of each composition, the initial choice of the compounds as the candidate components was 6,7-dimethylesculetin (Fig. 8). Matrine (Fig. 9) is the major active component of the traditional

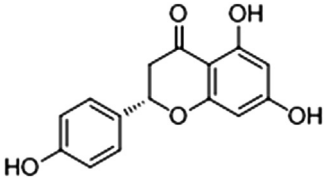

Fig. 5. Chemical structure of various natural product: naringenin.

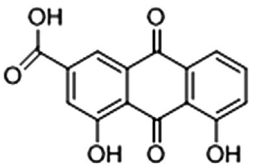

Fig. 7. Chemical structure of various natural product: rhein from *Rheum palmatum* L.

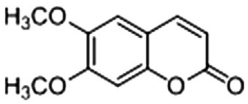

Fig. 8. Chemical structure of various natural product: 6,7-dimethylesculetin from *Artemisia annua* L.

medicine *Sophora flavescens* Ait, has a wide spectrum of pharmacological effects. It attenuates endotoxin-induced acute liver injury after hepatic ischemia/reperfusion mainly by its anti-inflammatory and antioxidative activities, and has little inhibitory effect on cell apoptosis [61]. Matrine significantly inhibited MMP-9 expression of SMMC-7721 cells [62]. The inhibitory effects are partly associated with the downregulation of the NF-kappa B signaling pathway. Another flavonoid molecule, ellagic acid (Fig. 10), isolated from *Phyllanthus urinaria* exhibits a rather peculiar anti-HBV function. Ellagic acid administration orally can circumvent the CCL_4 toxicity and subsequent fibrosis [63]. To further explore that hepatic stellate cell (HSC) activation results in physiological protection against environmental insult, the profile of differentiation of HSC has been examined upon treatment with ellagic acid [64]. Mellein (Fig. 11), a compound isolated from the fungus *Aspergillus ochraceus*, exhibits anti-HCV protease activity with an IC_{50} value of 35 μmol/L. Derived from *Artemisia annua* and mainly known for its antimalarial activity, artemisinin (Fig. 12)was also found out to have anti-HBV activity. Deoxynojirimycin is iminosugar which exerts anti-HCV activity by inhibiting alpha-glucosidases. Other natural products with promising anti-HCV activity are mellein and pseudoguaianolides. Saikosaponin C, chrysophanol 8-O-beta-D-glucoside, and protostane triterpenes are available and active against HBV [23].

3. Clinical studies

The hepatoprotective potential of several natural products has been clinically evaluated [65–67]. Significant efficacy has been seen with glycyrrhizin, matrine and silymarin in treatment of hepatitis, alcoholic liver disease and liver cirrhosis [68]. In Japan, glycyrrhizin injection has been used as a therapeutic drug for chronic hepatitis since 1979 [69]. Because administering glycyrrhizin by injection has some disadvantages, many researchers have systematically searched for novel glycyrrhizin formulation that can be administered through oral, rectal, intranasal, and subcutaneous routes. In the near future, convenient pharmaceutical preparations of glycyrrhizin will be developed for chronic hepatitis patients who require glycyrrhizin therapy. Liver function and cellular immunity of children with infectious mononucleosis complicated liver impairment (IM-LI) were explored the clinical therapeutic effects of compound glycyrrhizin [70]. Forty-two patients with IM-LI were randomly assigned. All the patients were treated with conventional treatment, and glycyrrhizin was given additionally once a day in the treated group. The improvement in the treated group was better than that in the control group. Cellular immunity dysfunction often occurs in patients with IM-LI, and glycyrrhizin treatment can not only obviously promote the recovery of liver function, but also

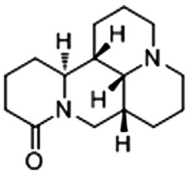

Fig. 9. Chemical structure of various natural product: matrine from *Sophora flavescens* Ait.

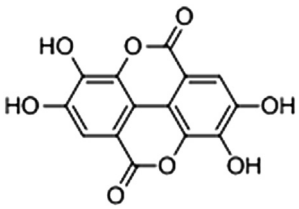

Fig. 10. Chemical structure of various natural product: ellagic acid from *Phyllanthus urinaria*.

regulate the immune function in organism. Glycyrrhizin injection therapy could significantly decrease the incidence of hepatocellular carcinoma in patients with IFN-resistant active chronic hepatitis C, whose average aminotransferase value was twice or more of upper limit of normal after interferon [71].

Natural products seem to be promising targets and may offer a cost effective protective alternative to individuals known to have a high risk for liver diseases [72]. HBV infection, a global public health problem, is the leading cause of cirrhosis and HCC worldwide. There are more than 350 million HBV carriers in the world and up to one million die annually due to hepatitis B associated liver disease. So far no optimal treatment is available for patients with chronic hepatitis B. In a study, the efficacy of intramuscular matrine in the treatment of chronic hepatitis B was investigated. The chronic hepatitis B patients of the matrine group were given intramuscularly with matrine of 100 mg daily for 90 days [73]. Significant differences were seen in terms of improvement of clinical symptoms and signs, recovery of liver functions. Serious side effects were not observed except mild pain at the site of injection of matrine in a few patients. These results indicate that intramuscular matrine may be an economical, efficacious, safe drug for the treatment of chronic hepatitis B. The effect of matrine could prevent the liver function of patients with primary hepatic carcinoma (PHC) after trans-artery chemo-embolization [74]. In therapy group, matrine injection may be used to protect the liver function for patients with primary hepatic carcinoma, to relieve the liver cells damage. *In vivo* matrine (50 mg/kg and 100 mg/kg) significantly decreased serum hyaluronic acid levels and hepatic hydroxyproline contents in rats treated with CCl_4 [75]. Inhibition actions on hepatic stellate cell by matrine might provide a possible mechanism of its antifibrotic activities. Interest in and use of natural products in the treatment of liver diseases has increased in the past decade. However, this has not been supported by a significant increase in sound clinical research evidence for their efficacy. The efficacy of these natural products need to be evaluated in rigorously designed, larger randomized, double-blind, placebo-controlled multicenter trials.

4. Translational research

Natural product compound that has no known primary biochemical role in an organism. Such compounds are also called secondary metabolites, and apparently are produced by the organism for ecological or defensive purposes, thus promoting its

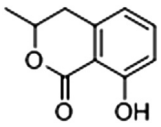

Fig. 11. Chemical structure of various natural product: mellein from the fungus *Aspergillus ochraceus*.

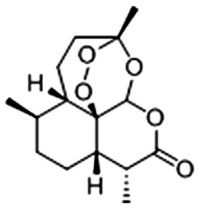

Fig. 12. Chemical structure of various natural product: artemisinin from *Artemisia annua*.

survival [76]. There remains a great interest in the search for natural products from plants, terrestrial and marine animals, and microorganisms as potential drug chemical leads for the treatment of a wide range of disease. Natural products, obtained to date mainly from fungi, higher plants, and soil microorganisms, have a long history of beneficial use by mankind for the treatment of disease. There is an especially strong interest in developing new hepatoprotective agents from natural sources, because of the many past successes in this endeavor [77]. These substances may be useful in their structurally unmodified or biotransformation form to enhance potency or pharmacologic properties such as water-solubility or thermostability [78]. Discovery of a new drug is time consuming and laborious process. Natural products have long been a thriving source for the discovery of new drugs due to their chemical diversity and ability to act on various biological targets. The phytochemical exploration of translational research has contributed to some extent in this race for the discovery of new drugs [79,80]. Natural products arising from their biotransformation into reactive chemical intermediates is an important reason for high attrition rates in early drug discovery efforts. Certain natural compounds that are difficult to isolate and purify, and synthesize. The biotransformation will certainly increase the probability of discovering new leads and drug candidates from natural products. Clearly, it may be particularly beneficial for new discoveries to be made of natural products from plants and other organisms with promising hepatoprotective activities. Once an effective molecule is identified, the mode of action can be investigated and can be translational research. Thus even when an active natural product does not reach clinical use, its investigation can provide critical clues for the development of new targeted drugs.

5. Development strategy and future directions

Natural products from plant-derived foods or traditional medicine may be lead compounds, or more likely may serve as hits that may be useful in providing templates that can guide the design of potentially superior compounds. Interest in natural products research is strong and can be attributed to several factors, including therapeutic needs, the remarkable diversity of chemical structures, biological activities of naturally secondary metabolites, the utility of bioactive natural products as biochemical and molecular probes. The potential of natural products to provide or inspire the development of anti-liver diseases lead compounds is, therefore, really quite evident [81]. However, to raise the chances of the actual realization of this potential, it has become necessary to think beyond the confines of conventional natural-product drug discovery. Natural products has not yet become a widely acceptable treatment modality for liver disease around the world. This eventuality is held back by the lack of the following factors: standardization of natural products and identification of its active ingredients, randomized controlled clinical trials, and toxicological evaluation. Recently, enormous efforts have been directed toward the scientific basis and clinical evaluation as a result of a growing interest in therapeutic agents derived from natural products [82]. The application of a wide variety of scientific tools and the interactive collaboration of experts in diverse scientific disciplines (such as phytochemistry, pharmacognosy, phytotherapy, molecular biology and genetics) has become truly and practically obligatory [83]. Some advanced and interdisciplinary technology and methodology can facilitate standardization of natural products and identification of its active ingredients. The emergence of powerful new analytical technologies and advances in 'omics' knowledge has opened the door to a new era in the development of novel therapies using natural agents [84–89]. Furthermore, new separation and structure determination technologies have increased the plausibility of screening mixtures of structurally complex molecules. More importantly, advances in plant genomics, metabolic engineering and biosynthetic chemistry can now provide reproducible and optimized sources for the isolation and/or production of bioactive agents [90]. It can also be used as a template for the generation of biotransformation agents. In addition, natural agents can be used alone as single molecules and/or in combination with other agents for enhanced therapeutic effects [91]. Clearly, there is great potential for the discovery of therapeutically relevant compounds from nature. However, careful experimental designs using multidisciplinary approaches in conjunction with the standardization and characterization of natural products are critical for the successful development of novel and promising therapies. Advancing in the novel and sensitive techniques is to detect biologically active natural products, and to isolate, purify, and structurally characterize the active constituents, solving the demand for supply of natural products.

6. Summary

In this article, we discuss the laboratory findings and clinical trial studies of herbal medicines for the treatment of liver disease, highlight on natural products that harbor bioactive molecules, which may exert hepatoprotective properties. Selected examples of important natural product-derived drugs are cited, focusing on some of the most recent introductions to the recent developments, clinical setting, and remaining challenges in the discovering and developing process. Natural products have been used to treat liver disorders for thousands of years and have now become a promising therapy for pathological liver conditions. There are many plants and their extracts that have been shown to possess hepatoprotective activities. Natural products have been used as a major source of innovative and effective therapeutic agents, offering a diverse range of structurally distinctive bioactive molecules that are known to play a major role in the management of liver diseases. The active phytochemicals that imparts hepatoprotective activity has been identified in many plants. These phytochemicals can be isolated and developed as single-ingredient drugs, with quality and standards of modern medicine. The pharmaceutical industry is facing serious challenges as the drug discovery process is becoming extremely expensive, riskier and critically inefficient. Natural products have served as a major source of drugs for centuries, and about half of the pharmaceuticals in use today are derived from natural products. The 21st century has seen a paradigm shift toward therapeutic evaluation of herbal products in liver diseases by carefully synergizing the strengths of the traditional systems of medicine with that of the modern concept of evidence-based medicinal evaluation, standardization of herbal products and randomized placebo-controlled clinical trials to support clinical efficacy. Natural products have potentially served as materia medica a part of our lifestyle, and have now become a promising therapy internationally for pathological liver conditions.

Authors' contribution

Aihua Zhang, Hui Sun and Xijun Wang have equally contributed to this work. Xijun Wang designed the project. Aihua Zhang wrote the manuscript. Hui Sun supervised the project.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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