



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.

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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-dimethylscutellin, 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)

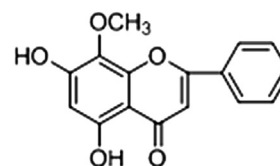


Fig. 1. Chemical structure of various natural product: wogonin from *Scutellaria radix*.

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 (CCl₄) intoxication; moreover, it can reverse CCl₄ 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,

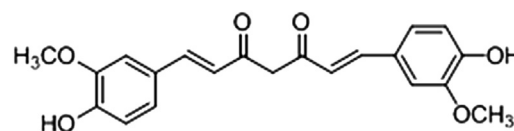


Fig. 2. Chemical structure of various natural product: curcumin from the plant *Curcuma longa*.

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