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Herbal remedies for liver fibrosis: A review on the mode of action of fifty herbs

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ABSTRACT

Liver fibrosis is a dynamic pathological condition which can be slowed down in its initial phases. Without proper clinical management of fibrosis, progressive liver damage may lead to cirrhosis and ultimately to liver failure or primary liver cancer, which are irreversible conditions. Therefore, in order to cure fibrotic damage to liver, its early stages should be the centre of attention. In this context, some supplements and 'complementary and alternative medicine (CAM)' deserve specific mention, because of their already recognized natural way of healing and long lasting curative effects. Moreover, CAM display negligible side effects and hence it is gaining worldwide importance in clinical practices. In particular, herbal medicines are now replacing synthetic pharmaceuticals and looked upon as the sources of novel bioactive substances. To develop satisfactory herbal combinations for treating liver fibrosis, phyto-products need to be systematically evaluated for their potency as anti-fibrotic, anti-hepatotoxic and antioxidant agents. More importantly, the identified herb/agent should have the remarkable tendency to stimulate hepatocytes regeneration. The present review is a systematic account of at least fifty medicinal herbs and their products which in experimental models have demonstrated antifibrotic activity and thus, most likely candidates to offer therapeutic protection to liver. Nevertheless, much additional work is still needed to explore molecular pathways to discover potential applications of these medicines so as to open up new vistas in biomedical research.

1. Introduction

Liver is one of the most important organs that plays crucial roles in the physiological functions of our body.[1,2] In human body liver is the site of regulation of glycogen storage, decomposition of RBCs, hormone and plasma protein production and detoxification.[3] Since liver also plays a central role in detoxifying and transforming chemicals, it is in a way exposed to their harmful effects increasing its susceptibility to diseases. Therefore, it may not be surprising that over 10% of the world population suffers from liver diseases. Most common of these conditions are hepatitis, hepatic steatosis (fatty liver), fibrosis, cirrhosis, alcoholic and drug induced diseases.[4] Synthetic drugs used to treat liver ailments have often proved life threatening and therefore, the preference is being shifted to complementary and alternative medicines (CAM), which are either natural products or their derivatives. The very basis of this preference is their safety and long lasting therapeutic potential. As a result, the source of nearly half of the agents used to treat liver diseases now come from natural products. Available evidence further indicates that bioactive compounds derived from medicinal herbs may be potential hepatoprotective agents. Out of the broad range of natural products, herbal medication plays a fundamental role, since 65% of patients in Europe and US depend on herbal remedies for the treatment of liver diseases.[4] However, their preparation, search and extraction is an exhaustive procedure. (see Figs. 1–3)

Of all liver ailments, fibrosis has emerged as a major health concern. It is the consequences of sustained wound healing response to a chronic liver injury from a variety of causes including viral, autoimmune, drug induced, cholestatic and metabolic diseases. Hepatic fibrosis is characterized by immoderate production and deposition of extracellular matrix (ECM).[5–8] Activated hepatic stellate cells (HSCs), portal fibroblasts and myofibroblasts of bone

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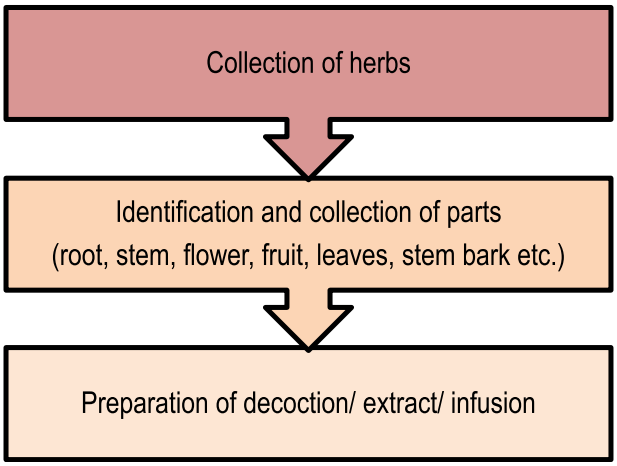

Fig. 1. Flow chart representing the general process of preparation of plant extract.

marrow origin have been identified as the major collagen producing cells.[9] If left uncured, fibrosis can lead to cirrhosis and ultimately to hepatocellular carcinoma which are irreversible. Mortality statistics raises the level of concern further, since as compared to 0.8 million deaths in 1990[10], cirrhosis resulted in 1.2 million deaths in 2013. Hepatocellular carcinoma (HCC) is the fifth most common cancer with more than 1 million annual mortality worldwide.[11] Hepatocellular carcinoma is less common in most parts of the developed western world but appears to be markedly increasing in Asian countries.[12] Thus, there is an urgent need to investigate the causes and remedies for hepatic fibrosis so as to procure normal liver function.

Complementary and alternative medicine (CAM) is used in medical treatment but it is not the component of mainstream medicine system. Extensive use of CAM is highlighted among people with chronic diseases, since it helps to avoid malaise often associated with conventional health care and empower people to manage their chronic condition.[13] Complementary and alternative medicine is classified by National Center for Complementary and Alternative Medicine (NCCAM), USA into five categories: whole medical system, mind body medicine, manipulative and body based practices, energy medicine and biologically based practices. On record, biologically-based practices such as herbal remedies continue to play highly significant role in health care. About 80% of the world's population relies mainly on CAM, especially herbal medication, for their primary health care.[14] The use of phytomedicine perhaps began in China at the time of Xia dynasty and in India during Vedic times. Herbal remedies are rejoicing growing popularity throughout the world because of many reasons like long lasting curative effects, efficacy, safety, natural way of healing and lesser side effects.[15,16] Treatment with medicinal herbal-concentrates fortifies natural healing process and adds to feeling of wellness.[17]A number of herbal derivatives show promising effects against hepatic fibrosis either experimentally in cell culture (*in vitro*), in animals models (*in vivo*) or even in clinical trials. In this review, we have systematically presented published information that describes the mechanism of attenuation of liver fibrosis in experimental models. The compilation is an exhaustive effort on fifty herbs or their ingredients used globally and known to possess antifibrotic properties.

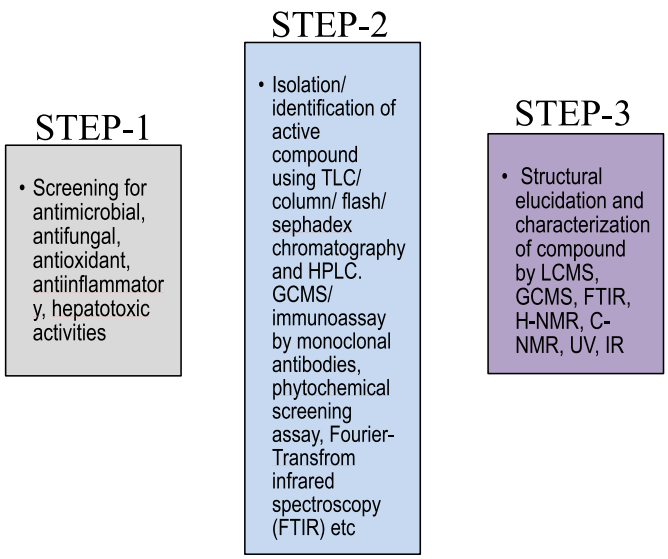

Fig. 2. Representation of the systematic process followed to search a bioactive compound from herb.

2. Methodology

Relevant published reports on liver fibrosis were collected since 1998 to 2015 by direct search on popular search engines for scientific literature retrieval, such as Elsevier-Science direct, Google Scholar, PubMed and Science Research. It is during the last 20 years that liver fibrosis has gained importance as a reversible stage of liver damage. The following key words phytoremediation, phytomedicine, plant, plant extracts, herbs, botanicals, alternative medicine were cross-referenced with the key words: liver fibrosis, liver cirrhosis, anti-fibrotic activity, experimental model of hepatic/liver fibrosis. The report clusters were searched for the details on model organisms used in the experiment for testing the activity of phytoproducts along with their mechanism of action.

3. Molecular mechanism of liver fibrosis

Hepatic fibrosis activation comprises two primary major steps: i) initiation and ii) perpetuation. Initiation is linked with paracrine mediated changes in gene expressions as cells become receptive to cytokines and other stimuli. Perpetuation is the result of maintenance of these signals which lead to further increase in cytokine secretion and progression of extracellular matrix remodeling.

Several cytokines and growth factors are crucial in the initiation of hepatic fibrogenesis. Transforming growth factor β (TGF-β) is the main fibrogenic cytokine released by kupffer cells, endothelial cells and hepatocytes in the liver and is a key mediator in human fibrogenesis.[18] It has three major isoforms: TGF-β1, TGF-β2 and TGF-β3. TGF-β1 is stored as an inactivated protein and when activated, signals through its receptors to Smad proteins, which increase the transcription of target genes such as procollagen I and III.[19] It has a role in transition of HSCs to myofibroblast like cells, triggers the synthesis of ECM proteins and retards their degradation. Platelet derived growth factor (PDGF) is potent mitogen for HSCs and is upregulated in liver fibrosis and; its inhibition alleviates hepatic fibrosis in experimental animals.[20] Endothelin-1, a powerful vasoconstrictor, stimulates fibrogenesis by its type A receptor.[21] Angiotensin-II, a vasoactive cytokine, also plays a key role in liver fibrogenesis. It induces liver inflammation and triggers a series of fibrogenic activity in activated HSCs, including secretion of proinflammatory cytokines, cell proliferation, cell migration and synthesis of collagen.[22] Adipokines are cytokines mainly secreted in adipose tissue and to a lesser extent by stromal cells. Leptin, adiponectin and ghrelin are main adipokines that contribute to liver injury.[23,24] Leptin is required for activation of HSCs and fibrosis

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