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, phytoproducts 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.

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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...
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. 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. 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. 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. Treatment with medicinal herbal-concentrates fortifies natural healing process and adds to feeling of wellness. 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.

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. 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. 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. Endothelin-1, a powerful vasoconstrictor, stimulates ﬁbrogenesis by its type A receptor. 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. 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. Leptin is required for activation of HSCs and ﬁbrosis
Adiponectin markedly inhibits hepatic fibrosis both in vitro and in vivo. Glucagon also attenuates liver fibrosis in experimental animals. Peroxisome proliferator-activated receptors (PPARs) regulate lipid and glucose metabolism and their expression decreases with the activation of HSCs. In contrast, PPAR-γ impedes the fibrogenic actions in HSCs and attenuates hepatic fibrosis. Toll-like receptors (TLR) are highly conserved family of receptors that help in recognition of pathogen-associated molecular patterns and assist the host cells to identify microbial infection. It has been reported that activation of TLR-4 by lipopolysaccharide upregulates chemokine secretion and sensitizes HSCs so that TGF-β can act upon. TLR-4 signalling also induces the expression of fibrogenic cytokines such as TNF-α, IL-1 and IL-2.

There are also several markers which indicate the progression of hepatic fibrosis. Alpha-smooth muscle actin (α-SMA) is a reliable marker of HSCs activation which precedes fibrous tissue deposition and is used for identification of earlier stages of liver fibrosis. Cyclooxygenases (COX) are key enzymes in the metabolism of arachidonic acid to produce prostaglandins (PGs) which are involved in the formation of tumors. It exists in two isoforms, COX-1 and COX-2. While COX-1 is expressed in wide variety of tissues, COX-2 is induced by various cytokines, growth factors, and mitogens. It has a major role in inflammation and carcinogenesis and is related with various liver diseases. It is reported that quiescent HSCs do not express COX-2 but activated HSCs in culture express COX-2, which indicates its involvement in hepatic fibrogenesis.

4. Active ingredients of plants for treatment of liver fibrosis

So far, there is no specific and effective antifibrotic therapy on record, though possible candidates might include endothelin receptor antagonists, rennin angiotensin inhibitors, PPAR-γ agonists and TGF-β signaling inhibitors. Besides, various complications are caused by synthetic drugs. Therefore, further research should focus on herbal medicine that are claimed to possess anti-hepatic fibrotic properties. Families of fabaceae, asteraceae and lamiaceae cover the largest number of anti-fibrotic plants. These plants usually contain phytochemicals such as flavonoids, alkaloids, phenols, quinones, glycosides etc. The active ingredients of each plant which fall in the category of these phytochemicals, play a key role in the treatment of hepatic fibrosis. Among many such active ingredients, silymarin, armepavine, plumbagin, rhein, glycyrrhetinic acid, ginseng, epigallocatechin-3-gallate, curcumin, salvianolic acid and osthole have been extensively studied and documented.

4.1. Silymarin

Silymarin is a flavonoid complex consisting of silybin, silydianin and silychristin and is extracted from the seeds of Silybum marianum. Silymarin is a strong antioxidant that promotes liver cell regeneration, reduces blood cholesterol, and helps in preventing cancer. It assists in combating hepatic fibrosis by restoring the level of α-SMA in CCl4 treated rats. α-SMA is a well known marker of hepatic stellate cells activation leading to fibrous tissue deposition and also a reliable marker of myofibroblast like cell recognition in both rat and man. It is reported that decrease in α-SMA level is accompanied by reduction in the number of activated HSCs. Therefore, silymarin assists in promoting apoptosis of activated HSCs. It is reported that treatment with silymarin and its constituents are safe with no adverse effects.

4.2. Arnepavine

Arnepavine is an active alkaloid compound derived from plant Nelumbo nucifera. It exerts anti-inflammatory effects on human peripheral blood mononuclear cells and immunosuppressive effects on lupus nephritic mice and on T lymphocytes. It can attenuate liver fibrosis by down-regulating the expression of TGF-β stimulated α-SMA expression in thioacetamide induced rats. TNF-α, a cytokine involved in inflammation, can also down-regulate metallothionein mRNA expression in thioacetamide induced rats. Metallothionein is reported to control intracellular redox level and regulate NF-κB and other redox-regulated transcription factors, thus, reducing fibrosis. Possibly, through anti-NF-κB activation
Table 1
Herbs along with their active ingredients demonstrating molecular mechanism against hepatic fibrosis.

| S. No. | Plant               | Family         | Part/Extract/Active ingredient                                | Experimental model | Type of study | Biomarkers/parameters affected                                      | Reference |
|--------|---------------------|----------------|--------------------------------------------------------------|--------------------|---------------|---------------------------------------------------------------------|-----------|
| 1      | Black bean          | Fabaceae       | Methanolic extract                                           | CCl4 induced       | In vivo       | ↓ liver types I and IV collagen                                       | 89        |
| 2      | Pueraria lobata     | Fabaceae       | Purerin                                                     | Alchol, CCl4 induced | In vivo       | ↓ serum AST, ALT, bcl-2 mRNA expression; ↑ apoptosis of HSCs          | 90        |
| 3      | Astragalus complanatus | Fabaceae       | Flavonoids                                                  | NDMA induced       | In vivo       | ↑ SOD, MMP-1 mRNA, ↓ MDA, serum FN, MMP and TIMP-1                   | 91        |
| 4      | Astragalus membranaceous | Fabaceae       | Root extract                                                | CCl4 induced       | In vivo       | ↓ serum transaminases, hyaluronic acid, laminin and procollagen type III levels, and contents of hydroxyproline, LPO and TGF-β; ↓ SOD and GSH-Px; ↓ thymidine and proline incorporation. | 92        |
| 5      | Glycyrrhiza glabra  | Fabaceae       | Glycyrrheticin Acid                                          | CCl4 induced       | In vivo       | ↓ ALT, AST, MDA, LPO; ↑ NF2, SOD 3, GPP2 and CAT                    | 63        |
| 6      | Cichorium glandulosum | Compositae | Root extract (petroleum ether, ethyl acetate, and n-butyl alcohol) | CCl4 induced       | In vivo       | ↑ serum AST, ALT, FN, Smard3 and TGF-β1; ↑ apoptotic index          | 93        |
| 7      | Silybum marianum    | Asteraceae     | Silymarin                                                   | CCl4 induced       | In vivo       | ↓ serum AST, ALT, ALP hepatic α-SMA; ↓ liver hydroxyproline, α-SMA, MDA and serum cholesterol | 36        |
| 8      | Artemisia iwayomogi | Asteraceae     | Plant extract (ethanol, methanol and hot water)             | CCl4 induced       | In vivo       | ↓ serum ALT, AST, hepatic α-SMA; ↓ liver hydroxyproline, α-SMA, MDA and serum cholesterol | 94        |
| 9      | Bidens pilosa       | Asteraceae     | Total flavonoids                                            | CCl4 induced       | In vivo       | ↓ serum ALT, AST levels, hepatic MDA and NF-κB; ↑ SOD and GSH-Px   | 95        |
| 10     | Vitex negundo       | Lamiaceae      | Ethanolic extract                                           | Thioacetamide induced | In vivo       | ↑ serum AST, ALT, ALP and bilirubin; ↑ serum albumin; ↑ triglyceride, LDL and total cholesterol | 96        |
| 11     | Salvia miltiorrhiza | Lamiaceae      | Salvinonolic acid                                           | CCl4 induced       | In vivo       | ↑ TGF-β1, procollagens 1 and III and tissue inhibitor of metalloproteinase-1 transcripts; ↑ matrix metalloproteinase-13 | 97        |
| 12     | Scutellaria baicalensis | Lamiaceae     | Methanolic root extract                                     | bile duct ligation or carbon tetrachloride induced | In vivo       | ↑ MDA, hydroxyproline, α-SMA and serum enzymes (AST, ALT, ALP and total bilirubin) | 98        |
| 13     | Amomum xanthoides   | Zingiberaceae  | Methanolic fraction                                         | Thioacetamide induced | In vivo       | ↓ serum bilirubin, liver hydroxyproline and MDA, GSH, GPs, iNOS, TNF-α, TGF-β1, PDGF-β1, CTGF | 99        |
| 14     | Zingiber officinalis | Zingiberaceae | Rhizome extract (petroleum ether, ethyl, chloroform, ethanol) | CCl4 induced       | In vivo       | ↑ GSH, SOD, SDH, LDH, G-6-Pase, AP and 5’ NT; ↑ MDA, AST, ALT, ALP, GGT and total bilirubin | 100       |
| 15     | Turmeric            | Zingiberaceae  | Curcumin                                                    | CCl4 induced       | In vivo       | ↓ α-SMA; ↑ apoptotic index                                          | 101       |
| 16     | Panax ginseng       | Araliaceae     | Ginseng                                                     | CCl4 induced       | In vivo       | ↓ serum ALT, α-SMA and expression of m RNAs of TGF-β and PAI-1      | 102       |
| 17     | Panax notoginseng   | Araliaceae     | Root water extract                                          | Hepatic microvascular dysfunction | In vivo       | ↓ sera transaminases and bilirubin                                   | 103       |
| 18     | Cnidium monnieri    | Apiceae        | Osthole                                                     | Thioacetamide induced | In vivo       and in vitro | ↓ serum AST, ALT, hepatic collagen, α-SMA, TGF-β1 and NF-κB activities | 88        |
| 19     | Buflebusm kooi      | Apiceae        | Root extract                                               | NDMA induced       | In vivo       | ↓ serum ALT, AST, collagen of liver; ↑ total protein, albumin of liver and serum, IFN-γ and IL-10 of serum and hepatic GSH | 104       |
| 20     | Ginkgo biloba       | Ginkgoaceae    | Green leaves extract                                        | CCl4 induced       | In vivo       | ↓ serum AST, ALT and bilirubin; ↑ serum albumin; ↓ liver collagen, reticulin, TIMP-1 and α-SMA; ↓ MMP-1 | 105       |
| 21     | Camellia sinensis   | Theaceae       | Epigallocatechin-3-gallate                                   | CCl4 induced       | In vivo       and in vitro | ↓ MDA, hydroxyproline, α-SMA, collagen (α1) (TGF-β1), hepatic collagen deposition and serum AST, ALT | 74        |
| 22     | Solanum nigum      | Solanaceae     | Whole plant extract                                         | Thioacetamide induced | In vivo       and in vitro | ↓ hepatic hydroproline, α-SMA, collagen (α1), TGF-β1, hepatic collagen deposition and serum AST, ALT | 106       |
| 23     | Stephania tetrandra | Menispermaceae | Tetrandrine                                                 | NDMA induced       | In vivo       and in vitro | ↓ NFκB, IACAM-1, α-SMA, and TGF-β1, hepatic collagen deposition and serum AST, ALT | 107       |
| 24     | Cudrania cochinchinensis | Moraceae | Water extract                                               | CCl4 induced       | In vivo       | ↓ serum AST, ALT, procollagen-III, hyaluronic acid and liver hydroproline; ↓ serum total protein, albumin and SOD | 108       |
| 25     | Blue berry          | Ericaceae      | Fresh fruit juice                                           | CCl4 induced       | In vivo       | ↓ α-SMA, collagen-III and MDA; ↓ metallothionein and SOD            | 109       |
| 26     | Turnip             | Brassicaceae   | Water extract                                               | Thioacetamide induced | In vivo       | ↓ serum AST, ALT                                                   | 110       |
| 27     | Ganoderma lucidum   | Ganodermataceae | Crude extract                                              | CCl4 induced       | In vivo       | ↑ plasma albumin, A/G ratio; ↓ serum AST, ALT, TGF-β1, hepatic hydroproline, MDA and changes in expression of MAT1A and MAT2A | 111       |
| 28     | Phellinus linteus   | Hymenochaetaceae | Polysaccharide extract                                      | Thioacetamide induced | In vivo       |                                                                   | 112       |

(continued on next page)
| S. No. | Plant                  | Family             | Part/Extract/Active ingredient          | Experimental model | Type of study | Biomarkers/parameters affected                                                                 | Reference |
|-------|------------------------|--------------------|----------------------------------------|--------------------|---------------|-----------------------------------------------------------------------------------------------|-----------|
| 29    | Allium sativum         | Amaryllidaceae     | Peeled garlic extract                  | CCl4 induced       | In vivo       | ↓ serum ALT, α-SMA, IL-1, tissue transglutaminase mRNA and tissue transglutaminase protein     | 113       |
| 30    | Lygodium flexuorum     | Lygodiaceae        | Whole plant extract                    | CCl4 induced       | In vivo       | ↓ serum AST, ALT, LDH, liver hydroxyproline                                                   | 114       |
| 31    | Dioscorea panthaica    | Dioscoreaceae      | Aqueous extract                        | CCl4 induced       | In vivo       | ↓ hepatic hydroxyproline, LPO and α-SMA; ↑ glutathione                                        | 115       |
| 32    | Nelumbo nucifera       | Nelumbonaceae      | Armepavine                             | TNF-α or           | In vivo and in vitro | ↑ metallothionein genes; ↓ col 1 and 2, TGF-β1, ICAM-1, INF-γ, and IL-6 gene expression       | 45        |
| 33    | Rhus javanica          | Anacardiaceae      | Ethanol extract                        | CCl4 induced       | In vitro      | ↓ Col 1 and 2, TGF-β, α-SMA                                                                    | 116       |
| 34    | Litsea coreana         | Lauraceae          | Total flavonoids                       | CCl4 induced       | In vivo       | ↓ AST, ALT hyaluronic acid, laminin, procollagen IV-terminal peptide, procollagenase IV, hepatic hydroxyproline, α-SMA, TGF-β1, TGFβRI          | 117       |
| 35    | Apricot                | Rosaceae           | Kernel                                 | NDMA induced       | In vivo       | ↓ serum AST, ALT and MDA; ↓ SOD, CAT and GSH                                                   | 118       |
| 36    | Punica granatum        | Puniceae           | Peel                                   | Bilary obstructed  | In vivo       | ↓ serum AST, ALT, LDH and cytokines; ↑ plasma AOC and GSH; ↓ hepatic MDA and MPO level       | 119       |
| 37    | Plumbago zeylanica     | Plumbaginaceae     | Plumbagin                             | CCl4 induced       | In vivo and in vitro | ↓ serum AST, ALT, α-SMA, EGFR, STAT3 and HB-EGF                                                | 50        |
| 38    | Rheum officinale       | Polygonaceae       | Rhein                                  | CCl4 induced       | In vivo       | ↑ ALT, hyaluronic acid, procollagen, MDA, α-SMA and TGF-β1                                    | 56        |
| 39    | Operculina turpethum   | Convolvulaceae     | Root extract                           | NDMA induced       | In vivo       | ↑ microvascular count, liver function enzymes, serum                                             | 7         |
| 40    | Hibiscus sabdariffa    | Malvaceae          | Dried flower extract                   | CCl4 induced       | In vivo and in vitro | ↓ AST, ALT, LPO and activated hepatic stellate cells; ↑ glutathione                               | 120       |
| 41    | Paeonia lactiflora     | Paeoniaceae        | Root extract                           | CCl4 induced       | In vivo       | ↓ serum transaminases, hyaluronic acid, laminin and procollagen type III levels, and contents of hydroxyproline, LPO and TGF-β1, ↓ SOD and GSH-Px; ↓ thymidine and prolinc incorporation | 92        |
| 42    | Moringa oleifera       | Moringaceae        | Seed extract                           | CCl4 induced       | In vivo       | ↓ serum aminotransferase activities, globulin, hydroxyproline, myeloperoxidase, collagen I and III, α-SMA, protein carbonyl and MDA; ↓ SOD and antioxidant properties | 121       |
| 43    | Nigella sativa         | Ranunculaceae      | Oil extract                            | CCl4 induced       | In vivo       | ↓ α-SMA and lysozyme                                                                            | 122       |
| 44    | Urtica dioica          | Urticaceae         | Oil and decoction extract              | CCl4 induced       | In vivo       | ↓ α-SMA and lysozyme                                                                            | 122       |
| 45    | Grape                  | Vitaceae           | Resveratrol                            | NDMA induced       | In vivo       | ↓ α-SMA and lysozyme                                                                            | 5         |
| 46    | Zizyphus spina-christi | Rhamnaceae         | Water extract                          | CCl4 induced       | In vivo       | ↓ AST, AST, LPO, collagen type I and III; ↓ SOD, CAT and GSH                                    | 123       |
| 47    | Praxinus rhytmophysical | Oleaceae           | Ethanol extract                        | CCl4 induced       | In vivo       | ↓ AST and protein levels of uPA, MMP-2, MMP-9 and TIMP-1; ↓ catalase, SOD and GPX               | 124       |
| 48    | Dunaliella salina      | Dunaliellaceae     | β-Carotene                             | CCl4 induced       | In vivo       | ↓ AST, ALP, LPO; ↓ SOD, catalase, GSH-Px, glutathione                                         | 125       |
| 49    | Cordyceps sinensis     | Cordycipitaceae    | Whole extract                          | ACTIVValue®/N-931 complex | In vivo       | ↓ hydroxyproline,TIMP-2, collagen type I and IV                                                | 126       |
| 50    | Aloe vera and Silybum marianum | Xanthorrhoeaceae and Asteraceae | Flavonoids and | CCl4 induced       | In vivo       | ↓ serum AST, ALT, hepatic MDA hydroxyproline, TGF-β1, TIMP-1 and expression of TNF-α, TNF-β, INOS, COX-2 mRNA; ↑ hepatic glutathione | 127       |

**List of abbreviations given in the Table:**
- ↑ Increase; ↓ Decrease; ALP = Alkaline phosphatase; ALT = Alanine transaminase; AST = Aspartate transaminase; CCl4 = Carbon tetrachloride; COX-2 = Cyclooxygenase 2; CTGF = Connective tissue growth factor; FN = Fibronectin; GPx = Glutathione peroxidase; GSH = Glutathione; ICAM-1 = Intercellular adhesion molecule 1; IL-1 = Interleukin 1; INOS = Inducible nitric oxide synthase; MAT 1A = Methionine adenosyltransferase 1 alpha; MDA = Malondialdehyde; MMP-1 = Matrix metalloproteinase 1; NFkB = nuclear factor kappa-light-chain-enhancer of activated B cells; PAI-1 = Plasminogen activator inhibitor 1; PDGF-β = Platelet derived growth factor beta; PINP = Type 1 procollagen peptide; SOD = Superoxide dismutase; TGF-β = Transforming growth factor beta; TIMP-1 = Tissue inhibitor of metalloproteinase 1; TNF-α = Tumor necrosis factor alpha; α-SMA = Alpha smooth muscle actin; uPA = Urokinase.
pathways, artemepavine exerts both in-vitro and in-vivo anti-fibrotic effects in rats.45

4.3. Plumbagin

Plumbagin is an active napthoquinone extracted from the roots of traditional medicinal plant *Plumbago zeylanica* L. It possesses several pharmacological properties, such as the induction of apoptosis, anti-inflammation, anti-angiogenesis, antioxidant activity and anti-cancer.46–48 Plumbagin increases the matrix metalloproteinase-1 (MMP-1) expression which is beneficial for ECM degradation.49 It decreases the content of type-I collagen and HSC activation and thus, restoring the normal functions of HSCs.49 It reduces the activation of HSCs by targeting EGFR signalling pathway which may prove a potential therapeutic strategy to treat hepatic fibrosis.50 There is a prominent inflammation associated correlation between TNF-α and α-SMA and, plumbagin reportedly decreases the expression of these two in CCl4 lesioned rats thus, contributing to degradation of ECM for mitigating liver fibrosis.51

4.4. Rhein

Rhein, an anthraquinone, is one of the most important active components of rhubarb (*Rheum officinale*), a traditional Chinese herb to treat chronic liver disease. It possesses several biological properties such as anti-microbial, anti-angiogenic and anti-cancer activities.52–55 In CCl4 induced rats, Rhein inhibits TGF-β1 which plays a central role in liver inflammation.56 It also inhibits α-SMA, preventing the activation of hepatic stellate cells and thus reducing hepatic fibrosis.56

4.5. Glycyrrhetic acid

Glycyrrhetic acid (GA) is one of the derivative products of Glycyrrhizin acid. It is the most effective medicine available in clinics and is extracted from *Glycyrrhiza glabra*. It has several pharmacological properties like, antiviral, anti-mutagenic, anti-inflammatory, anti-injury and antioxidant properties as well as liver protection.57–62 It protects liver from reactive hydroxyl radicals derived from H2O2 by upregulating Nrf-2, raising its target gene catalase expression in CCl4 induced liver fibrosis in rats.63 Expression of type I and type III collagen are also down-regulated by GA,64 thereby preventing hepatic fibrosis.

4.6. Ginseng

Ginseng, referred to as the roots of *Panax ginseng*, possesses biological properties that include anti-cancer, anti-inflammatory and anti-diabetic, as well as cardiovascular- and neuro-protection.65–67 COX-2 expression is stimulated by TNF-α and IL-1β during CCl4 induced liver fibrosis in rats while ginseng suppresses TNF-α and IL-1β mRNA expression,68 thus, preventing inflammation. It mitigates fibrosis by reducing α-SMA expression69 and inhibition of the HSCs activation and thus helps to stop fibrogenesis.

4.7. Epigallocatechin-3-gallate

Epigallocatechin-3-gallate (EGCG) is the most abundant and active polyphenol in green tea (*Camellia sinensis*). It is a powerful antioxidant that has attracted considerable attention because of its role in preventing oxidative stress-related diseases including cancers, cardiovascular diseases and fibrosis.70–72 MMP-2 increased expression and activity is one of the major causes of hepatic fibrosis. Increase in the MMP-2 activity is related with an enhanced destruction of normal liver architecture, stimulating its replacement by interstitial collagen.73 EGCG suppresses the expression of endogenous MMP-2 mRNA and subsequent protein expression.74 It has been reported that in CCl4 induced liver fibrosis, EGCG suppresses MMP-2 activity via down-regulating NF-κB expression.75 It also decreases COX-2 and iNOS expression through regulation of the activities of NF-κB and C/EBP-α respectively.76

4.8. Curcumin

Curcumin is a polyphenol and the main active compound found in the plant *Curcuma longa* (commonly known as turmeric). It has various biological activities such as anticancer, antiviral, antioxidant and anti-inflammatory activities.76–79 It affects cell proliferation by inhibiting the expression of NF-κB in CCl4 induced liver fibrosis and also triggers apoptosis by activating caspase-3 and caspase-9, and by changing nuclear morphology and phosphodiesterase expression.80,81 TGF-β1 signals transmembrane receptors stimulating cytoplasmic proteins i.e., Smad proteins which, in turn,
modulate the transcription of target genes including those of ECM components, procollagen-I and -III. Curcumin inhibits hepatic TGF-β1 expression in liver tissues and thus it prevents the deposition of ECM in fibrosis.

4.9. **Salvianolic acid**

Salvianolic acid (SA) is a phenolic compound extracted from *Salvia miltiorrhiza*. It has been reported to exert free radical scavenging and anti-peroxidative effects in liver microsomes, hepatocytes and erythrocytes. SA suppresses the expression of TGF-β1 and α-SMA in CCl4 induced liver fibrosis in rats and inhibits inflammation and fibrogenesis. TNF-α and IL-1β are recognized as pro-inflammatory cytokines in various liver diseases, and SA reduces their expression, thus prevents inflammation and declines liver fibrosis.

4.10. **Osthole**

Osthole is a coumarin compound present in many medicinal plants especially in the fruit of *Cnidium monnieri*. It possesses various pharmacological properties, such as anti-oxidation and anti-inflammation. It is reported to reduce α-SMA in thioacetamide-induced liver fibrosis in rats, which suppresses HSC activation. It also inhibited both TNF-α induced NF-κB and TGF-β1 induced α-SMA activity in HSCs, consequently leading to inhibition of fibrogenesis.

5. **Current phyto-products in treating liver fibrosis**

Table 1 displays the names of the herbs/botanicals together with the extract used or the compound isolated from a particular herb. The table also demonstrates the suggested molecular mechanisms of amelioration of a particular herb/drug on hepatic fibrosis in test animals.

6. **Conclusions**

In conclusion, this review amply demonstrates that the herbal products can protect the liver from oxidative stress, inflammation and ceases fibrogenesis. It is expected that integrated tabulation of herbs with corresponding medicinal properties will facilitate identification of different ingredients with similar bioactivities or similar ingredients with different bioactivities. As the drug discovery is becoming increasingly extortontane, unsafe and ineffective, plant products offer better alternatives, since they have traditionally served as modest means of disease containment. 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 fibrosis is inadequate and only few of them are well standardized and also free of serious side effects. Therefore, successful development of novel and promising therapies for liver fibrosis requires careful designs using various experimental approaches. The standardization and characterization of natural products should be complimentary to success with animal models. The key cytokines regulating the process of fibrosis, the markers of ongoing fibrosis and advances in the molecular research techniques also have highlighted a number of potential therapeutic approaches that are suitable for future development for treating this disease. Because of logistic and legal problems such as restrictions to liver biopsies, the efficacy of antifibrotic treatments to attenuate experimental liver fibrosis has not been documented in humans, so far. Consequently, the ideal antifibrotic agent which is specific, safe when used for prolonged periods of time and inexpensive has yet to be discovered. Certain herbal formulations are in clinical trials, but their effectiveness as antifibrotic medicine is not proven. Silybin-phospholipids and vitamin E complex (SPV complex) treatment significantly reduces liver fibrosis and down-regulated fibrosis markers in fatty liver associated HCV patients. Chinese medicine Fuzhenghuayu (FZHY), having active ingredients salvianolic acid B and adenosine, also helps to prevent hepatic fibrosis and improves liver functions in humans. It should be expected that the laboratory success of clinical trials with botanical pharmaceuticals would pave the way to successfully treat human fibrosis.

**Declaration of interest**

The authors declare no potential conflict of interest and are responsible for the writing and content of the paper.

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