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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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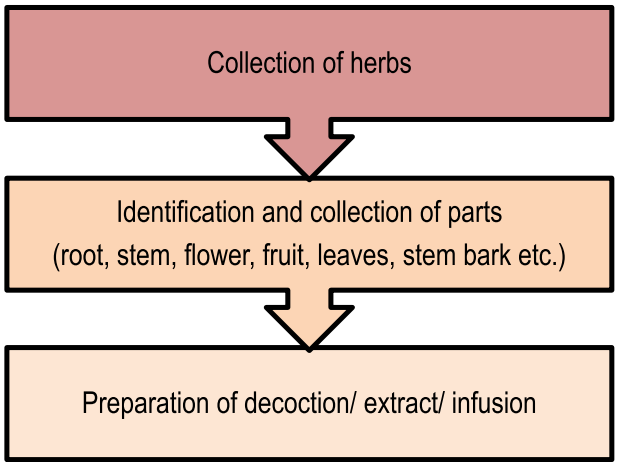

Fig. 1. Flow chart representing the general process of preparation of plant extract.

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.

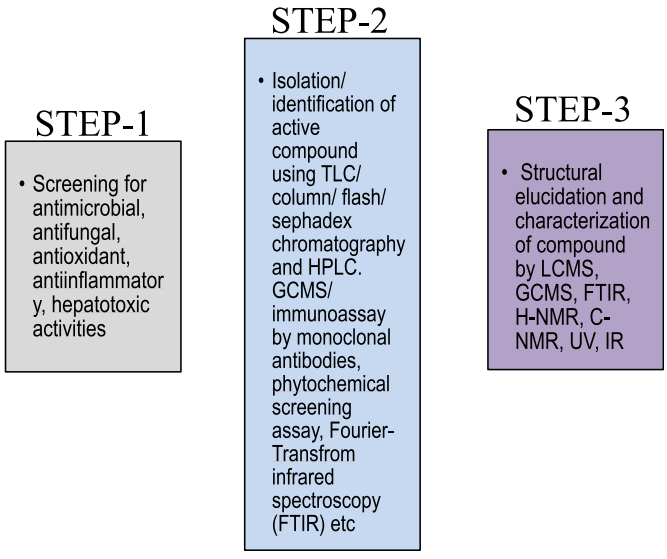

Fig. 2. Representation of the systematic process followed to search a bioactive compound from herb.

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

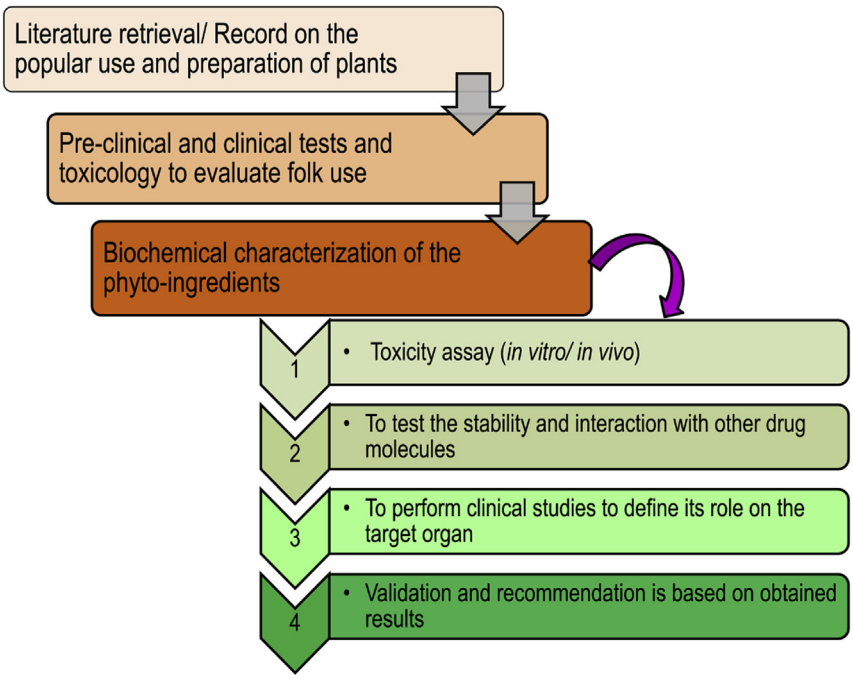

Fig. 3. Schematic representation of the biochemical characterization of active phyto-ingredients.

development.[25] In contrast, adiponectin markedly inhibits hepatic fibrosis both *in vitro* and *in vivo*.[24] Ghrelin also attenuates liver fibrosis in experimental animals.[26] Peroxisome proliferator activated receptors (PPARs) regulate lipid and glucose metabolism and their expression decreases with the activation of HSCs.[27,28] In contrast, PPAR-γ impedes the fibrogenic actions in HSCs and attenuates hepatic fibrosis.[29,30] 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.[31] 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.[5,7] 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.[32] It has a major role in inflammation and carcinogenesis and is related with various liver diseases.[33] 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.[34]

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, varieties of 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 silychrisin 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.[35] It assists in combating hepatic fibrosis by restoring the level of α-SMA in CCl_4 treated rats.[36] α-SMA is a well known marker of hepatic stellate cells activation leading to fibrous tissue deposition[37] and also a reliable marker of myofibroblast like cell recognition in both rat and man.[38] It is reported that decrease in α-SMA level is accompanied by reduction in the number of activated HSCs.[39] 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.[40]

4.2. Armepavine

Armepavine 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.[41,42] It can attenuate liver fibrosis by down-regulating the expression of TNF-α stimulated α-SMA expression in thioacetamide induced rats.[43] 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-κβ and other redox-regulated transcription factors,[44] thus, reducing fibrosis. Possibly, through anti-NF-κβ 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	CCl_4 induced	*In vivo*	↓liver types I and IV collagen	89
2	*Pureria lobata*	Fabaceae	Purerin	Alchol + CCl_4 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 PINP and PIIINP and TIMP-1	91
4	*Astragalus membranaceous*	Fabaceae	Root extract	CCl_4 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	Glycyrrhetinic Acid	CCl_4 induced	*In vivo*	↓ALT, AST, MAO, LPO; ↑Nrf2, SOD 3, GPX2 and CAT	63
6	*Cichorium glandulosum*	Compositae/ Asteraceae	Root extract (petroleum ether, ethyl acetate, and n-butyl alcohol)	CCl_4 induced	*In vivo*	↓serum AST, ALT, FN, Smard3 and TGF-β1; ↑apoptotic index	93
7	*Silybum marianum*	Asteraceae	Silymarin	CCl_4 induced	*In vivo*	↓serum AST, ALT, ALP hepatic α-SMA	36
8	*Artemisia iwayomogi*	Asteraceae	Plant extract (ethanol, methanol and hot water)	CCl_4 induced	*In vivo*	↓ liver hydroxyproline, α-SMA, MDA and serum cholesterol	94
9	*Bidens pilosa*	Asteraceae	Total flavonoids	CCl_4 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 cholestrol	96
11	*Salvia miltiorrhiza*	Lamiaceae	Salvionolic acid	CCl_4 induced	*In vivo*	↓TGF-β1, procollagens I 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, GPx, iNOS, TNF-α, TGF-β, PDGF-β, CTGF	99
14	*Zingiber officinale*	Zingiberaceae	Rhizome extract (petroleum, ether, chloroform, ethanol)	CCl_4 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	CCl_4 induced	*In vivo*	↓α-SMA; ↑apoptotic index	101
16	*Panax ginseng*	Araliaceae	Ginseng	CCl_4 induced	*In vivo*	↓serum ALT, AST, α-SMA and expression of m RNAs of TGF-β and PAI-1	102
17	*Panax notoginseng*	Arialiaceae	Root water extract	Hepatic microvascular dysfunction	*In vivo*	↓sera transaminases and bilirubin	103
18	*Cnidium monnieri*	Apiaceae	Osthole	Thioacetamide induced	*In vivo* and *in vitro*	↓serum AST, ALT, hepatic collagen, α-SMA, TGF-β1 and NF-κB activities	88
19	*Bupleurum kaoi*	Apiaceae	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	CCl_4 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	CCl_4 induced	*In vivo* and *in vitro*	↓serum ALT, AST, histological and hepatic hydroxyproline, α-SMA and MMP-2	74
22	*Solanum nigrum*	Solanaceae	Whole plant extract	Thioacetamide induced	*In vivo*	↓hepatic hydroxyproline, α-SMA, collagen (α1) (I), TGF-β1	106
23	*Stephania tetrandra*	Menispermaceae	Tetrandrine	NDMA induced	*In vivo* and *in vitro*	↓ NFκB, ICAM-1, α-SMA, and TGF-β1, hepatic collagen deposition and serum AST, ALT	107
24	*Cudrania cochinchinensis*	Moraceae	Water extract	CCl_4 induced	*In vivo*	↓serum AST, ALT, procollagen-III, hyluronic acid and liver hydroxyproline; ↑serum total protein, albumin and SOD	108
25	Blue berry	Ericaceae	Fresh fruit juice	CCl_4 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	CCl_4 induced	*In vivo*	↑plasma albumin, A/G ratio; ↓serum AST, ALT, TGF-β1, hepatic hydroxyproline, MDA and changes in expression of MAT 1A and MAT 2A.	111
28	*Phellinus linteus*	Hymenochaetaceae	Polysaccharide extract	Thioacetamide induced	*In vivo*		112

(*continued on next page*)

Table 1 (*continued*)

S. No.	Plant	Family	Part/Extract/Active ingredient	Experimental model	Type of study	Biomarkers/parameters affected	Reference
						13 proteins showing differential expression are actin, tubulin alpha-1C chain, preprohaptoglobin, hemopexin, galectin-5, glutathione S-transferase alpha-4 (GSTA4), branched chain keto acid dehydrogenase heterotetrameric E1 subunit alpha (BCKDHA), glutathione S-transferase mu (GSTmu), glyceraldehyde-3-phosphate dehydrogenase (GAPDH), thiosulfate sulfurtransferase (TFT), betaine-homocysteine S-methyltransferase 1 (BHMT1), quinoid dihydropteridine reductase (QDPR), ribonuclease UK114	
29	*Allium sativum*	Amaryllidaceae	Peeled garlic extract	CCl_4 induced	*In vivo*	↓serum AST, ALT, α-SMA, IL-1, tissue transglutaminase mRNA and tissue transglutaminase protein	113
30	*Lygodium flexuosum*	Lygodiaceae	Whole plant extract	CCl_4 induced	*In vivo*	↓serum AST, ALT, LDH, liver hydroxyproline	114
31	*Dioscorea panthaica*	Dioscoreaceae	Aqueous extract	CCl_4 induced	*In vivo*	↓hepatic hydroxyproline, LPO and α-SMA; ↑glutathione	115
32	*Nelumbo nucifera*	Nelumbonacea	Armepavine	TNF-α or lipopolysaccharide and bile duct ligation	*In vivo* and *in vitro*	↓serum AST, ALT, hepatic α-SMA and collagen, AP-1; ↑metallothionein genes; ↓col 1α2, TGF-β1, TIMP-1, ICAM-1, iNOS, and IL-6 gene expression	45
33	*Rhus javanica*	Anacardeacea	Ethanol extract	Activated HSCs	*In vitro*	↓ Col 1 α2, TGF-β, α-SMA	116
34	*Litsea coreana*	Lauraceae	Total flavonoids	CCl_4 induced	*In vivo*	↓AST, ALT hyaluronic acid, laminin, procollagen III N-terminal peptide, procollagenase IV, hydroxyproline, α-SMA, TGF-β1, TGFβR1,	117
35	Apricot	Rosaceae	Kernel	NDMA induced	*In vivo*	↓serum AST, ALT and MDA; ↓SOD, CAT and GSH	118
36	*Punica granatum*	Punicaceae	Peel	Biliary obstructed	*In vivo*	↓serum AST, ALT, LDH and cytokines; ↑plasma AOC and GSH; ↓ hepatic MDA and MPO level	119
37	*Plumbago zeylanica*	Plumbaginaceae	Plumbagin	CCl_4 induced	*In vivo* and *in vitro*	↓serum AST, ALT, α-SMA, EGFR, STAT3 and HB-EGF	50
38	*Rheum officinale*	Polygonaceae	Rhein	CCl_4 induced	*In vivo*	↓ALT, hyaluronic acid, procollagen, MDA, α-SMA and TGF-β1	56
39	*Operculina turpethum*	Convolvulaceae	Root extract	NDMA induced	*In vivo*	↓micronuclei count, liver function enzymes, serum hydroxyproline, LDH isoenzymes 4 and 5 and α-SMA	7
40	*Hibiscus sabdariffa*	Malvaceae	Dried flower extract	CCl_4 induced	*In vivo* and *in vitro*	↓AST, ALT, LPO and activated hepatic stellate cells; ↑glutathione	120
41	*Paeonia lactiflora*	Paeoniaceae	Root extract	CCl_4 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
42	*Moringa oleifera*	Moringaceae	Seed extact	CCl_4 induced	*In vivo*	↓serum aminotransferase activities, globulin, hydroxyproline, myeloperoxidase, collagens I and III, α-SMA, protein carbonyl and MDA; ↑SOD and antioxidant properties	121
43	*Nigella sativa*	Ranunculaceae	Oil extract	CCl_4 induced	*In vivo*	↓α-SMA and lysozyme	122
44	*Urtica dioica*	Urticaceae	Oil and decoction extract	CCl_4 induced	*In vivo*	↓α-SMA and lysozyme	122
45	Grape	Vitaceae	Resveratrol	NDMA induced	*In vivo*	↓sera transaminases, ALP, bilirubin, LPO, protein carbonyl, hydroxyproline and α-SMA; ↑liver glycogen, SOD, ATPases (Ca^{2+}, Mg^{2+}, Na^{+}/K^{+})	5
46	*Zizyphus spina-christi*	Rhamnaceae	Water extract	CCl_4 induced	*In vivo*	↓ALT, AST, LPO, collagen type I and III; ↑SOD, CAT and GSH	123
47	*Fraxinus rhynchophylla*	Oleaceae	Ethanol extract	CCl_4 induced	*In vivo*	↓ALT, AST and protein levels of uPA, MMP-2, MMP-9 and TIMP-1; ↑catalase, SOD and GPx	124
48	*Dunalliela salina*	Dunaliellaceae	β-Carotene	CCl_4 induced	*In vivo*	↓ALT, AST,ALP, LPO; ↑SOD, catalase, GSH-Px, glutathione reductase, and GSH	125
49	*Cordyceps sinensis*	Cordycipitaceae	Whole extract	NDMA induced	*In vivo*	↓hydroxyproline,TIMP-2, collagen type I and IV	126
50	Aloe vera *and Silybum marianum*	Xanthorrhoeaceae and Asteraceae	ACTIValoe®N-931 complex	CCl_4 induced	*In vivo*	↓serum ALT, AST, hepatic MDA hydroxyproline, TGF-β1, TIMP-1 and expression of TNF-α, 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; CCl_4 = Carbon tetrachloride; COX-2 = Cycloxygenase 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; NFκB = 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.

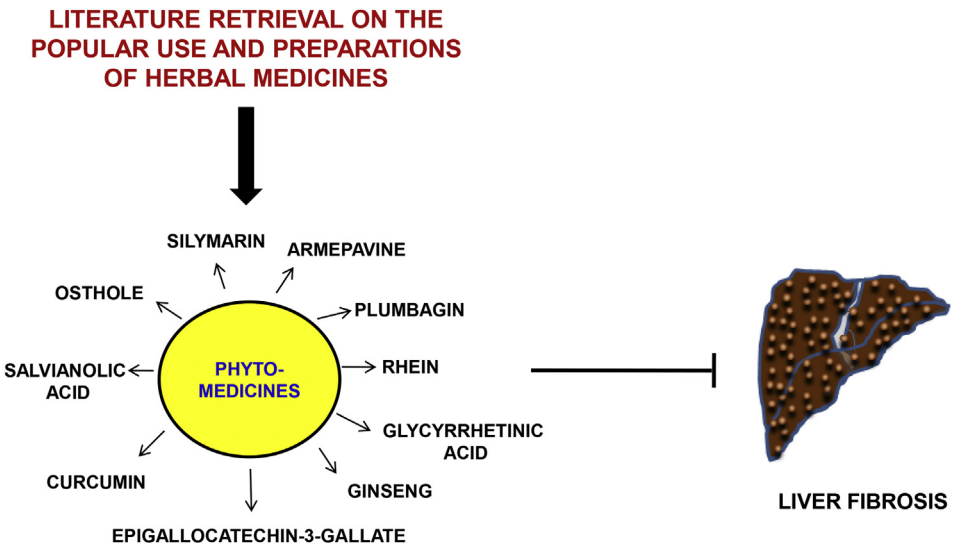

Fig. 4. Schematic representation of active ingredients of phyto-medicine used in the treatment of liver fibrosis.

pathways, armepavine 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 CCl_4 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 CCl_4 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. Glycyrrhetinic acid

Glycyrrhetinic acid (GA) is one of the derivative products of Glycyrrhizic acid. It is the most effective medicine available in clinics and is extracted from *Glycirrhiza 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 H_2O_2 by upregulating Nrf-2, raising its target gene catalase expression in CCl_4 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 CCl_4 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 expression[69] 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 CCl_4 induced liver fibrosis, EGCG suppresses MMP-2 activity *via* down-regulating NF-κβ expression.[74] It also decreases COX-2 and iNOS expression through regulation of the activities of NF-κβ and C/EBP-α respectively.[75]

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-κβ in CCl_4 induced liver fibrosis and also triggers apoptosis by activating caspase-3 and caspase-9, and by changing nuclear morphology and phosphotidylserine 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.[82] Curcumin inhibits hepatic TGF-β1 expression in liver tissues[83] 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.[84] SA suppresses the expression of TGF-β1 and α-SMA in CCl_4 induced liver fibrosis in rats[85] 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,[86] 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* L. Cusson. It possesses various pharmacological properties, such as anti-oxidation and anti-inflammation.[87] It is reported to reduce α-SMA in thioacetamide-induced liver fibrosis in rats[88]; which suppresses HSC activation. It also inhibited both TNF-α induced NF-κβ and TGF-β induced α-SMA activity in HSCs,[88] 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 (Fig. 4). 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 extortionate, 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 liver 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.[128] Chinese medicine Fuzhenghuayu (FZHY), having active ingredients salvianoic acid B and adenosine, also helps to prevent hepatic fibrosis and improves liver functions in humans.[129,130] 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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