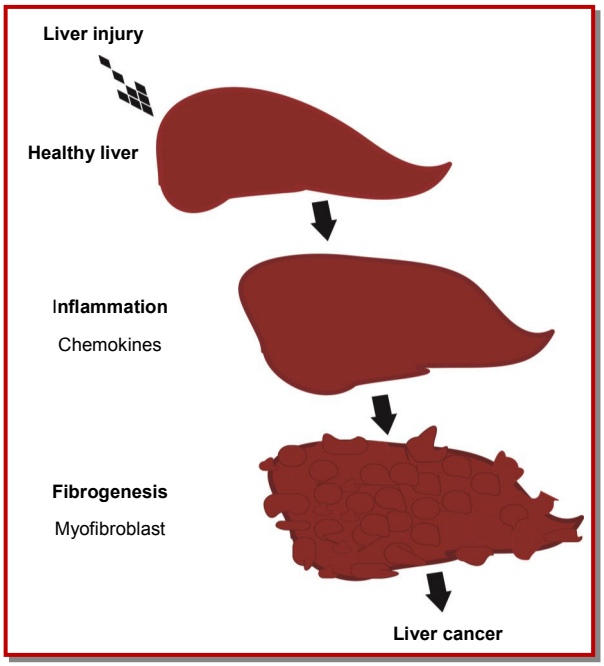

BJP

Bangladesh Journal of Pharmacology

Mini Review

Anti-fibrotic activity of medicinal plants

A Journal of the Bangladesh Pharmacological Society (BDPS)
Journal homepage: www.banglajol.info
Abstracted/indexed in Academic Search Complete, Asia Journals Online, Bangladesh Journals Online, Biological Abstracts, BIOSIS Previews, CAB Abstracts, Current Abstracts, Directory of Open Access Journals, EMBASE/Excerpta Medica, Global Health, Google Scholar, HINARI (WHO), International Pharmaceutical Abstracts, Open J-gate, Science Citation Index Expanded, SCOPUS and Social Sciences Citation Index;

Bangladesh J Pharmacol 2017; 12: 417-426

ISSN: 1991-0088

Mini-review

Anti-fibrotic activity of medicinal plants

Usman Akhtar and Mobasher Ahmad

Department of Pharmacology, University College of Pharmacy, University of the Punjab, Lahore, Pakistan.

Article Info

Received: 13 June 2017
Accepted: 13 October 2017
Available Online: 20 November 2017

DOI: 10.3329/bjp.v12i4.32947

Cite this article:
Akhtar U, Ahmad M. Anti-fibrotic activity of medicinal plants. Bangladesh J Pharmacol. 2017; 12: 417-26.

Abstract

The aim of this review is to report the medicinal plants which have anti-fibrotic effect characterized in different studies. They are summarized which include name of the plants, part used, liver fibrosis model, fraction of plant used and observations. The medicinal plants play an important role in treatment and prevention of liver fibrosis through different physiological mechanism. The effects of medicinal plant may delay the development of liver fibrosis and have potential to reverse or degrade the accumulation of extra cellular matrix. Four different databases are used and 18 plants are included which have the potential for reversal of liver fibrosis. There are also few more plants but they are not characterized well in literature.

Introduction

Worldwide 80% of people rely on the use of traditional medicine and these have a characteristic role in human health care system (WHO, 1993). These include a broad range of prehistoric natural health care system like folk practices, Ayurveda, Siddha, Amchi. These were originated from time immemorial and gradually developed based on experiences without any scientific protocols. These traditional medicines were transferred from one generation to another generation by oral or guarded literature.

Liver Fibrosis

Liver fibrosis is the pathophysiologic process due to chronic liver injury, recognized by the accumulation of extra cellular matrix (Paik et al., 2014). For *in vivo* studies, carbon tetrachloride (CCl_4) has been widely used to study liver fibrosis in experimental rodents (Uehara et al., 2014). Fibrosis is a protective response to any type of tissue injury. Fibrosis may be self limiting and homeostatic, or it may be uncontrolled and excessive determined by the different pathways, molecules and systems. Immune cells play a leading role in this fibrotic cascade, with the ability to exert either repair promoting or injury inducing effects (Pellicoro et al., 2014). The important role of normal liver is in maintaining the homeostasis of the body. Liver has regeneration capacity which enables it to withstand against functional parenchymal loss or liver injury. When liver is subjected to a continuous liver injury it loses its regeneration ability. Irrespective of the cause, liver injuries generally result in accumulation of extracellular matrix proteins and causes fibrosis. After continuous injury oxidative stress is produced by several sources can influence liver fibrosis. The cytochrome P4502E1 enzyme mainly found in liver and is one of the potential sources of oxidative stress. This enzyme is induced by ethanol and in alcohol-induced liver diseases. Similarly, the phagocytic NADPH oxidase in the Kupffer cells is another potential source of oxidative stress. Several evidences indicate the pivotal role of oxidative stress in liver fibrosis. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, is an enzyme complex that exerts oxidative stress through production of reactive oxygen species (ROS) (Paik et al., 2014). In liver, phagocytic and non-phagocytic forms of NADPH oxidase are functionally expressed. Both are structurally and functionally similar that generate superoxide by reduction of molecular oxygen. Non-

phagocytic form of NADPH oxidase contains six types of homologous NOX proteins. It is now believed that both forms of NADPH oxidase in hepatic stellate cells mediate liver fibrosis (Paik and Brenner, 2011).

Animal Model of Liver Fibrosis

Different animals are used in the study of liver fibrosis and cirrhosis. The suitable animal should be considered regarding the purpose of study in accordance with pathogenesis of liver fibrosis. The animals used in the study of liver fibrosis are (in order of frequency) rat, mouse, rabbit, dog, guinea pig, micropig, monkey and baboon. Rodents (rat and mouse) are extensively used to study liver fibrosis because they can easily provide study cell and molecular mediators of liver fibrosis during the progression (Figure 1) and reversal of fibrosis (Constandinou et al., 2005).

The commonly used chemical substances to induce liver fibrosis in animal model are CCl_4, thioacetamide (TAA), dimethylnitrosamine (DMN), and diethylnitrosamine (DEN) (Delire et al., 2015). CCl_4 is widely used because CCl_4 induced model is best with respect to all changes (e.g., histological, biochemical, molecular and cell changes) which leads to the development of liver fibrosis. CCl_4 administration can induce the zone III necrosis and apoptosis of hepatocytes which leads to hepatic stellate cell activation and fibrosis. With chronic administration, CCl_4 can induce bridging liver fibrosis (4 weeks with twice week dosing) or cirrhosis (8 weeks with twice week dosing).

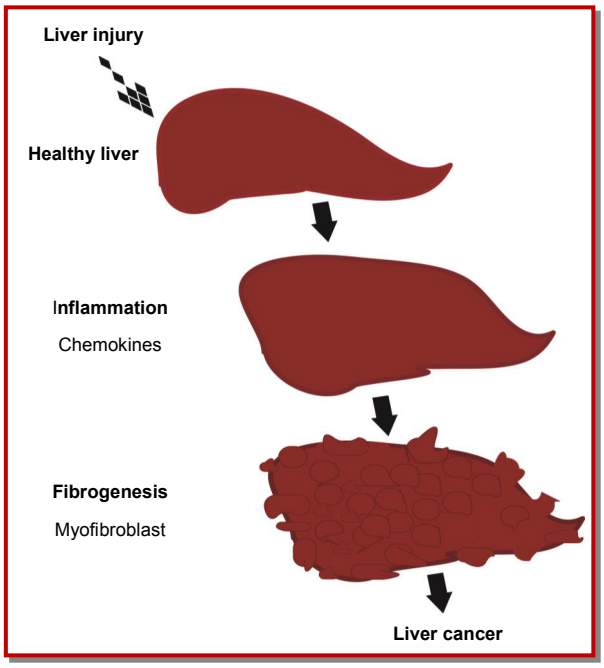

Figure 1: Progression of liver fibrosis which leads to cancer

The other most commonly used method to develop liver fibrosis is bile duct ligation. Bile duct ligation is most commonly used in rat model because there is no gall bladder. In the mouse model, it is considered as a drawback due to leakage or rupture of biliary cyst (Liu et al., 2013). In short, this whole procedure for bile duct ligation requires a midventral laparotomy and separation of the bile duct above the duodenum, usually, this procedure was then followed by double ligation and dissection of the bile duct between the ligatures (Starkel and Leclercq, 2011).

Reversal of Liver Fibrosis

Liver fibrosis is a constant process in which two pathways co-exist and interact i.e., fibrogenic pathway and fibrolytic pathway. During the liver damage, hepatic stellate cells become activate and proliferate due to activating mediators and antiapoptotic factors respectively. Therefore, activated hepatic stellate cells produce an excessive accumulation of extracellular matrix and its degradation is prevented by increased activity of tissue inhibitors of metalloproteinases (TIMPS) that leads to fibrogenic condition. After removal of the causative agents of liver injury, apoptosis of hepatic stellate cells takes place with the decreased in the activity of TIMPs followed by increased activity of tissue matrix metalloproteinases which exert their fibrolytic activity, initiate the process known as remodeling (Bataller and Brenner, 2005; Benyon and Iredale, 2000).

In animal models of liver fibrosis, the reversal of liver fibrosis has been characterized by the removal of the causative agent (CCl_4 infusion and bile duct ligation) (Abdel-Aziz et al., 1990). Similarly, in humans reversal of liver fibrosis has also been characterized by the removal and treatment of the causative agent, such as alcoholic liver disease, copper and iron overload, viral hepatitis and auto-immune hepatitis (Bataller and Brenner, 2005; Hammel et al., 2001). The most studied condition is of hepatitis C. As hepatitis C is successfully treated with interferon α plus ribavirin, almost half of the patients showed a significant improvement in liver fibrosis (Arthur, 2002; Benyon and Iredale, 2000). However, several fundamental questions are still to be answered about the resolution of liver fibrosis. Several clinical evidences have characterized that fibrosis/cirrhosis not only resolved (histological reversion), but there are evidence that also showed improved clinical condition (Friedman and Bansal, 2006; Mallet et al., 2008). As previously described, reversibility of liver fibrosis is mainly due to decreased TIMPs expression and the activity of increased interstitial collagenases that is helpful in the clearance of activated hepatic stellate cells which is due to apoptosis, senescence or reversion to quiescence (Gonzalez et al., 2009).

The senescent hepatic myofibroblast may be helpful in the resolution of liver fibrosis. It may decrease or stop proliferation. It also increases the expression of matrix degrading enzymes and decreases the expression of extracellular matrix proteins. It can be easily cleared by the natural killer cells *in vitro* and *in vivo,* therefore, contribute to the resolution of liver fibrosis (Krizhanovsky et al., 2008).

Fibrous scar is produced by the myofibroblast which is the activated form of quiescent hepatic stellate cells in the liver fibrosis induced by CCl_4 in the rodent model and after the removal of the causative agent (CCl_4), there is significant regression in clinical and experimental fibrosis with complete clearance of these myofibroblasts. However, some are cleared by apoptosis. It is unknown whether other cells may revert during regression of liver fibrosis to an inactive phenotype and retain a state with more ability to react more rapidly to fibrotic stimuli and strongly participate in liver fibrosis (Kisseleva et al., 2012).

In the present work, the articles of natural plants activity in CCl_4-induced liver fibrosis have been reviewed (Table I).

Medicinal Plants having Antifibrotic Activity

Rhodiola sachalinensis

The root of the *Rhodiola sachalinensis* is used in the traditional treatment in Siberia and Asia. The therapeutic compounds isolated from this plant have anti-diabetic (Cheng et al., 1993), sedative, hypnotic, anti inflammatory, anti-oxidant potential (Choe et al., 2012; Lee et al., 2000) and hepatoprotective effects (Nan et al., 2003b). The root extract has protective effect in the liver injury of rat model induced by continuous administration of CCl_4. The extract was administered for 28 days through oral route at doses of 50, 100, 200 mg/kg continuously with CCl_4. Comparison of malondialdehyde (MDA) and hydroxyproline in the liver and enzyme activities in the serum of CCl_4-treated rat showed a significant increase when compared to rat treated with plant extract. The plant extract significantly inhibits the hepatic stellate cell activation, as observed in the immunohistological findings.

Salvia miltiorrhiza

Salvia miltiorrhiza is widely used medicinal plant as oral herbs in different countries for the treatment of different diseases (Kim et al., 2010). The root is pharmacologically important to prevent acute liver damage and also reduces the liver fibrosis induced by CCl_4 in animal model (Lee et al., 2003; Nan et al., 2001; Qi, 1991). The hot extract of the herb inhibits the liver fibrosis induced by biliary obstruction. After bile duct ligation surgery, the root extract was administered orally for 28 days through oral route at a dose of 100 mg/kg. The concentration of different enzymes was observed including serum aminotransferases, alkaline phosphatase, total bilirubin, malondialdehyde, hydroxyproline and total cholesterol in serum. Rat receiving plant extract after surgery had a significant low level of the above enzymes when compared to the rat which received only vehicle control. The tissue section studies also showed improved morphological characteristics in rat receiving plant extract. α–Smooth muscle protein expression also showed reduced expression which indicates hepatic stellate cell activation was inhibited during the fibrotic liver progression (Nan et al., 2001).

Aloe vera and Silybum marianum

Aloe vera is usually found in the deserts. Its leaves are pharmacologically important for the treatment of liver and spleen enlargement and also in eyes disorders (Chandan et al., 2007). Basically, they are important for its anti-inflammatory and anti-oxidative properties (Can et al., 2004; Lim et al., 2003). Likewise, *S. marianum* is also used to treat biliary and liver diseases because of its strong anti-oxidant potential (Post-White et al., 2007; Vaknin et al., 2008). The mixture of both plants against the acute liver injury and chronic liver fibrosis model in mice after administration of CCl_4 was studied. In acute liver injury, CCl_4 was intraperitoneal injected (50 µL/kg) alone and with 85, 170 and 340 mg/kg dose of mixture of plant was administered orally after 2 and 6 hours after injection. Liver toxicity was observed after 24 hours of injection. Chronic liver injury mice model was first prepared by intraperitoneal injection of CCl_4 for 8 weeks (0.5 mL/kg, twice per week) and mice were treated with mixture at dose of 85, 170, 340 mg/kg once a day orally. In both studies acute and chronic, aminotransferase concentration and lipid peroxidation were significantly increased and the liver glutathione content was decreased. Administration of plant in acute and chronic injury decrease aminotransferase concentration and lipid peroxidation and normalize liver glutathione level. In acute phase of injury, the plant mixture significantly reduces the expression of tumor necrosis factor-α and also effects nitric oxide synthase and cyclooxygenase-2. In chronic phase injury, tissue inhibitor of metalloprotease-1 mRNA was down-regulated by treatment (Kim et al., 2009b).

Artemisia iwayomogi

Artemisia iwayomogi is a perennial herb from Korea having traditional medicinal importance in the treatment of different disorders. Hot water extract and methanol extract of *A. iwaymogi* significantly improve the microenvironment of liver and also reduces the progression of liver fibrosis induced by CCl_4. CCl_4 was orally administered twice a week at a dose of 1 mL/kg for 4 weeks and they also received the plant extract orally at a dose of 2 g/kg for 4 weeks. After 4 weeks, the liver hydroxyproline concentration was signifi-

Table I

Plants used in treatment of liver fibrosis

Name of the plant	Plant parts	Liver fibrosis inducing agents	Animal model	Extracts studied	Biochemical and histopathological parameters studied
Rhodiola sachalinensis (Nan et al., 2003a)	Root	Carbon tetrachloride	Rat	Aqueous	Hydroxyproline, malondialdehyde, serum enzyme activities, masson's trichome method, smooth muscle cell α-actin
Salvia miltiorrhiza (Nan et al., 2001)	Whole herb	Bile duct ligation	Rat	Hot-water extract	Aminotransferases, alkaline phosphatase, total bilirubin, total cholesterol in serum, hydroxyproline, malondialdehyde, protein expression of α-smooth muscle cell-like actin
Aloe vera and *Silybum marianum* (Kim et al., 2009a)	Leaf	Carbon tetrachloride	Mouse		Tumor necrosis factor-α, inducible nitric oxide synthase, cyclooxygenase-2, mRNA expressions, tissue inhibitor of metalloprotease-1
Artemisia iwayomogi (Park et al., 2000)	Aerial part	Carbon tetrachloride	Rat	Hot-water extract	Hydroxyproline content, protein expression of alpha smooth muscle cell actin, liver malondialdehyde, serum cholesterol
Stephania tetrandra (Park et al., 2000b)	Chinese medicinal herb	Bile duct ligation and scission	Rat	Isolated alkaloid	Serum aminotransferases, alkaline phosphatase, cultured rat hepatic stellate cells
Gynostemma pentaphyllum(Chen et al., 2000)	Whole plant	Carbon tetrachloride	Rat	Saponin extract	Serum aminotransferases, pathologic observation
Hibiscus sabdariffa (Liu et al., 2006a)	Dried flower	Carbon tetrachloride	Rat		Serum aminotransferases, glutathione, hepatic lipid peroxidation, immunofloresence staining
Scutellaria baicalensis Georgi (Nan et al., 2002)	Chinese medicinal herb, the root	Bile duct ligation and scission (BDL) or carbon tetrachloride	Rat	Methanol extract	Histological observations, liver hydroxyproline, lipid peroxidation based on malondialdehyde production, serum enzyme activities, Masson's trichrome staining, immunostaining against smooth muscle cell α-actin
Piper betel (Young et al., 2007)	Leaf	Carbon tetrachloride	Rat	ddH2O	Pathological histology, glutathione S-transferase activity assay, superoxide dismutase, catalase activity, Lucigenin-enhanced chemiluminescence, immunohistochemistry, matrix metalloproteinase-2 activity assay, Western blot analysis
Foeniculum vulgare (Özbek et al., 2004)	Seed	Carbon tetrachloride	Rat	Essential oil	Serum aminotransferases, alkaline phosphatase, bilirubin, histopathological findings, body weight
Bidens pilosa L (Yuan et al., 2008a)	Dried leaf	Carbon tetrachloride	Mouse	80% Ethanol	Serum aminotransferases, hepatic malondialdehyde, superoxide dismutase, glutathione peroxidase (GSH-Px)
Han-Dan-Gan-Le (HDGL) (Li et al., 2003)	Herb	Carbon tetrachloride	Rat	Chinese herb preparation	Hyroxyplonine analysis, histopatholog1cal examination, imminohistochemistry
Lygodium flexuosum (Wills and Asha, 2007)	Dried powder of the whole plant	Carbon tetrachloride	Rat	n-Hexane	Western blot analysis of collagen-III, immunohistochemical analysis, hepatic markers

Table I

Plants used in treatment of liver fibrosis (Continued)

Name of the plant	Plant parts	Liver fibrosis inducing agents	Animal model	Extracts studied	Biochemical and histopathological parameters studied
Paeonia lactiflora and *Radix Astragali* (Sun et al., 2007)	Dried root	Carbon tetrachloride	Rat	70% Aqueous ethanol,	ALT and AST, hydroxyproline content in liver, Measurement of serum fibrotic markers and serum TGF-β1, hematoxylin and eosin (HE), MDA
Zizyphusspina-christi (Amin and Mahmoud-Ghoneim, 2009a)	Whole plant	Carbon tetrachloride	Rat	50% Ethanol and 50% water	Type I collage immuno-stained liver slides , malondialdehyde (MDA) , catalase (CAT) activity, superoxide dismutase (SOD) enzyme activity, Protein carbonyl (P. carbonyl) contents, total protein contents, Myeloperoxidase (MPO) activity
Green tea (Safer et al., 2015)		Carbon tetrachloride, ethanol	Rat	Green tea extract	Histopathological study, alanine aminotransferase; aspartate aminotransferase
Ocimum gratissimum (Chen et al., 2015)	Herb	Carbon tetrachloride	Rat	Polyphenol extract	Serum alanine aminotransferase and aspartate aminotransferase malondialdehyde, catalase and α-smooth muscle actin
Mallotus apelta (Zhao et al., 2002)	Root	Carbon tetrachloride	Rat	Methanolic	ALT, AST, MDA, NO and hydroxyproline in the blood or liver tissues

cantly reduced as compared to the control. Protein expression of α-smooth muscle was also down-regulated, which is a clear indication of the inhibition of hepatic stellate cell activation. Liver malodialdehyde concentration and serum cholesterol level in rat treated with the plant extract were highly reduced when compared with the control group (Park et al., 2000).

Stephania tetrandra

The pharmacological active compound derived from the *Stephania tetrandra* is tetrandrine. Tetrandrine acts as an antagonist of the calcium channel which is important for the hepatic stellate cell function and regulation (Hsu et al., 2007). It also plays an important role in the cancer therapy (Chen, 2002; Wang et al., 2004), anti-inflammatory effect (Choi et al., 2000). Various studies on isolated compound tetrandrine from the plant show that it has the potential for anti-fibrotic effect in different types of cell lines. Hepatic fibrosis model was prepared by using scission and bile duct ligation in the rat. After surgery, rat was treated with tetrandrine 10 mg/kg daily. It significantly reduces the serum aminotransferases, alkaline phosphatase and liver hydroxyproline concentration in the treated groups when compared with the control group. On cultured rat hepatic stellate cells, tetrandrine has a significant effect on the expression of α-smooth muscles. α-Smooth muscle actin expression was unregulated in the hepatic stellate cell activation. Tetrandrine has the potential to decrease the expression of α-smooth muscle actin (Park et al., 2000a).

Gynostemma pentaphyllum

The active pharmacological compound extracted from *Gynostemma pentaphyllum* is gypenoside. It has hepatoprotective properties (Lin et al., 1993) and also has therapeutic potiential in the liver fibrosis. The saponin extract gypenoside of the plant has potential to prevent the acute and chronic liver injury induced by CCl_4 for 8 weeks in the rat model. Gypenoside treated rat significantly reduces the concentration of serum aminotransferases when compared to the control and collagen production is also reduced to 33% (Chen et al., 2000).

Hibiscus sabdariffa

Hibiscus sabdariffa is one of the famous Chinese rose tea and is also used as folk medicines for the relief of different pathopysiological disorders e.g., liver damage (Tseng et al., 1997), hypertension (Herrera-Arellano et al., 2004; Onyenekwe et al., 1999). It has a strong antioxidant effect (Tsai et al., 2002). Dried flower extract of the plant has the potential for the prevention of liver fibrosis in rat model. Rats were administered CCl_4 through intraperitoneal injection for 7 weeks. The flower extract highly reduced the liver injury and fibrosis in a dose-dependent manner. It also significantly reduces the serum aminotransferases and also normalizes the glutathione concentration (Liu et al., 2006b).

Scutellaria baicalensis

Scutellaria baicalensis is a traditional herb widely used in different countries like Korea, China and Japan. It is

commonly used in the liver diseases and inflammatory conditions (Huang et al., 2006; Pan et al., 2012). It has a strong anti-oxidant activity and is rich in flavonoids content (Gao et al., 1999; Huang et al., 2006). The methanolic extract of the plant has the therapeutic effect against the liver fibrosis induced by the bile duct ligation and scission or CCl_4-induced in the rat model. The fibrotic rat model was assessed by measuring liver enzyme concentration and histopathological observations. The methanol extract of the plant was administered orally 150 mg/kg for 28 days daily. The level of liver hydroxyproline and malondialdehyde was significantly reduced in treated groups when compared to the control. Masson's trichrome staining and immunostaining for α-smooth muscle actin showed improved liver tissue histology in the treated groups (Nan et al., 2002).

Piper betel

Piper betel has a significant role in the treatment of different diseases because of an significant amount of anti-oxidants present such as β-carotene, eugenol, ascorbic acid and hydroxychavicol (Capdevielle-Pardies et al., 1985; Norton, 1998). It has a significant effect in the reversal and protection of liver fibrosis. The leaves of the plant have therapeutic value for detoxication, anti -oxidation and antimutation effects. The rat model of the liver injury was prepared by CCl_4 administration thrice a week at a dose of 1 mL/kg. Liver damage and fibrosis were assessed by the liver enzymes and histological findings. The extract from the leaves played a significant role in the inhibition of increased concentration of serum aminotransferases and total glutathione S-transferase activity (GST). The histological findings showed the protective effect of the liver injury through a decrease in α-smooth muscle actin and inducting the matrix metalloproteinase-2 expression (Young et al., 2007).

Foeniculum vulgare

The plant parts including leaf, seed and stalk are edible. The plant has anti-microbial, anti-oxidant, anti-inflammatory and also hepatoprotective activities (Choi and Hwang, 2004; Oktay et al., 2003; Özbek et al., 2003). Hepatoprotective effect of the plant was studied using the liver fibrosis model. Liver fibrosis was induced in rat. Essential oil of the plant significantly attenuates the concentration of serum aminotransferases, alkaline phosphatase and bilirubin. It also plays a significant role in the prevention of liver fibrosis when co-administered with CCl_4 as revealed through the histopathological findings. So, it has the potential for reversal of liver fibrosis and improves the micro-environment of the liver (Özbek et al., 2004).

Bidens pilosa

Bidens pilosa is an important and active ingredient of the tea in China. The percentage of usage of this plant in different herbal treatment is comparatively higher than other herbal plants. It is widely used as antimalarial, stomach disorders, hypertension and anti-inflammatory (Alvarez et al., 1999; Andrade-Neto et al., 2004; Dimo et al., 2002; Pereira et al., 1999). The therapeutic potential for the liver fibrosis of the plant was assessed through rat and mouse model of the liver injury. Liver injury was induced by CCl_4. Plant extract was administered orally for 10 days at three different doses (25, 50, 100 mg/kg) to CCl_4-treated mouse and administration of three different doses of the plant (30, 60, 90 mg/kg) for 6 weeks to treated rat. Liver enzymes (aminotransferases, malondialdehyde, SOD, GSH-Px) were increased during liver injury and histopathological examination and nuclear factor-κB were also assessed for the liver injury and fibrosis. The plant extract significantly reduced all the parameters which were assessed for the liver injury and fibrosis model in mouse and rat. The histopathological findings showed that it attenuates the severity of liver fibrosis which might be linked to its anti-oxidant property (Yuan et al., 2008b).

Han-Dan-Gan-Le

Han-Dan-Gan-Le is composed of five different medicinal herbs (*Ginkgo biloba, Radix paoniae, Salvia miltorrhiza, Stephaniat tetrandra* and *Astragalus membranaceus*) from the China. It is claimed to be helpful in the treatment of liver fibrosis. This property was examined through chemical induction of liver fibrosis in rat model. CCl_4 was administered two times per week 1.2 mL/kg, after the first dose of 5 mL/kg, subcutaneously. After the last dose of CCl_4, the mixture was administered 0.5-1/kg through intragastric route for 6 weeks daily. The treatment for 6 weeks had great influence on the reversal of liver fibrosis. Immunohistochemical analysis revealed that the hepatic collagen accumulation was reduced by treatment. Urinary analysis showed that Han-Dan-Gan-Le stimulated the collagenolytic signaling in the liver as 30-50% excretion of hydroxyproline was present in urine sample when compared to the control (Li et al., 2003).

Lygodium flexuosum

Lygodium flexuosum is most commonly found in India. It has potential in the treatment of liver diseases. The protective and treatment effect of the plant was assessed through liver injury and fibrosis in rat model. Chronic liver fibrosis model was induced by CCl_4 150 µL/100 g twice a week for 10 weeks. After 10 weeks, the plant extract was given orally for 2 weeks at a dose of 200 mg/kg. In the preventive group, the daily dose was administered with CCl_4 for 10 weeks. Both groups showed reduced mRNA levels of proinflammatory cytokines, signaling molecules, growth factors which have a potential role in the liver fibrosis. Treatment with the plant extract has the potential for down-regulation of tumor necrosis factor-α, transforming growth factor, interleukin-1β, procollagen-I, pro-

collagen-III and tissue inhibitor of metalloproteinase-1 when compared with the control group. The up-regulation of matrix metalloproteinase-13 in the treated and protective groups were the indication of improvement of liver fibrosis (Wills and Asha, 2007).

Paeonia lactiflora and Radix astragali

Both plants have hepatoprotective effect. The mixtures of these plants are used in the treatment of liver disorders because they have synergistic effect to treat liver fibrosis. To explore the possible mechanism, liver fibrosis rat model was induced by the injection of 50% CCl_4 twice a week for 8 weeks. Preventive groups were also receiving the mixture at three different doses 40, 80, 160 mg/kg through intragastric route. Liver damage was assessed by liver enzymes concentration, hyaluronic acid, laminin, procollagen type III concentration and contents of hydroxyproline. Treated groups have significantly reduced level of the above said parameters when compared to the control. The mixture also restored the normal level of SOD and GSH-Px and also attenuated the formation of malondialdehyde. In primary cell studies, hepatic stellate cells were cultured which showed that the mixture significantly reduced the thymidine incorporation in hepatic stellate cells stimulated with the platelet derived homodimer subunit of growth factoe-β and also reduced incorporation of proline. The possible mechanism of reversal of liver fibrosis might be linked with the scavenge of free radicals, proliferation in hepatic stellate cells and inhibition of collagen synthesis (Sun et al., 2007).

Zizyphusspina-christi

Zizyphusspina-christi is mainly used for the hepatoprotective, anti-inflammatory, antiseptic, antimicrobial and also urinary tract disorders (Amin and Mahmoud-Ghoneim, 2009b; Tanira et al., 1988). It is enriched with sterols, tannins, butulinic acid and flavonoids (Amin and Mahmoud-Ghoneim, 2009b; Pawlowska et al., 2009). The potential of the plant in liver fibrosis treatment was assessed by CCl_4-induced liver rat model. The extract was administered daily in the treated group at 3 different doses 0.125, 0.250 and 0.350 g/kg for 8 weeks. Treated group showed significantly reduced concentration of the serum aminotransferases and also resorted the normal concentration of malondialdehyde and also maintain the normal endogenous concentration of anti-oxidants. Histopathological examination revealed that it also down-regulates the expression of α-smooth muscle actin and the deposition of collagen in the treated group (Amin and Mahmoud-Ghoneim, 2009b).

Green tea

Green tea extract has a beneficial effect on the vital organ of the body such as liver and kidney which are apparent within the 30 days. It also improves the function of the liver in disease condition and resolution of liver fibrosis. It was investigated in the liver fibrosis model induced by CCl_4 only, ethanol only and combination of these two in the rat. Scanning electron microscopy was used to investigate the prevention of liver fibrosis. This technique was used to study type, thickness and distribution of fibers in all the groups. The treatment with green tea extract improves the architecture of the liver and also improves the body weight. The liver autopsy showed that the treated rat has normal shape and color liver when compared to the liver fibrosis model group and normal rat group. The green tea extract improves the liver function through collagen fibers resolution, reduction in the lipid peroxidation product (Safer et al., 2015).

Ocimum gratissimum

Ocimum gratissimum is widely used as herbal medicine. It is found in the tropical and warm temperature areas. This plant is enriched with anti-oxidant compounds (Prakash et al., 2011). It has important pharmacological effects including the antibacterial (Nakamura et al., 1999), hypoglycemic activity (Aguiyi et al., 2000) and also improves the liver function. The polyphenol extract of the plant was used to investigate the anti-fibrotic activity of the plant. Liver fibrosis was induced in male Wistar rats through the administration of CCl_4. the extract of the plant was administered at different doses according to body weight for 8 weeks. It significantly reduced the toxic effects of CCl_4 such as liver weight, serum aminotransferases, malondialdehyde, catalase when compared with the control group. These effects might be due to the anti-oxidant property of the plant and also high polyphenol concentrations were important for high anti-fibrotic activity (Chen et al., 2015).

Mallotus apelt

Mallotus apelt is found in south of China. It is commonly used in the treatment of chronic hepatitis (Cheng et al., 1998) and contains special type of alkaloids (Cheng et al., 1998) and show significant role in the liver diseases (Xu et al., 2008). The root of the plant was studied for its anti-fibrotic and anti-oxidant effect in the liver fibrotic model. Liver fibrosis was induced in rats with the administration of 40% CCl_4 in peanut oil. Blood concentration for the liver enzymes (serum aminotransferases, malondialdehyde, hydroxyproline) were analyzed. These were significantly reduced in the treated group when compared to the control group. It also improved the overall performance of liver which might be due to anti-oxidant components present in the plant (Zhao et al., 2002).

Conclusion

The goal of the liver fibrosis studies on natural plants should not be restricted to all types of severe liver

diseases. Effective formulations have to be developed using native medicinal plants, with proper pharmacological experiments and clinical trials. The manufacturing of plant products should be governed by the standards of safety and efficacy. The plants described in this review have the potential for reversal of liver fibrosis.

Conflict of Interest

All authors have completed the ICMJE uniform disclosure form and declare no support from any organization for the submitted work.

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Author Info
Usman Akhtar (Principal contact)
e-mail: usmanakhtarpk@gmail.com