Annals of Gynecology and Obstetrics Research

Review Article
Published: 09 Jun, 2021

Scientific Evaluation of Medicinal Plants in Amelioration of Liver Cirrhosis; a Prevalent Liver Disease

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Abstract

The abnormal regeneration of the lobular structure, the appearance of prevalent fibrosis, and hepatic parenchymal nodular lesions are the focal characteristics of liver cirrhosis. Liver cirrhosis is characterized by fibrotic regeneration of inflamed hepatocytes due to stellate cell activation. Research on antifibrotic therapies has become urgent need due to pervasive obesity trend associated with viral hepatitis and alcohol intake. Therefore, it is a need to find versatile, accessible, effaceable and economical antifibrotic therapies. Efficacy and mode of action of medicinal plants have been confirmed by clinical researches in liver diseases. Medicinal plants have proven to be effective antifibrotic agents. Focus of this study is to describe pathogenesis of cirrhotic liver disease and management by medicinal plants in order to reduce liver fibrosis.

Keywords: Hepatocytes; Chronic liver disorder; Fibrosis; Liver cirrhosis; Hepatoprotective; Medicinal plants; Pathogenesis; Cirrhotic liver disease; Herbal plants

Introduction

In liver cirrhosis, fibrosis is described as collagenous scar in order to replacing or encapsulating the injured tissue in normal wound healing process, regeneration undergoes abnormal continuation of connective tissue deposition. In case of almost all chronic liver injuries, fibrosis occurs and if it becomes uncontrolled, it can progressively develop into cirrhosis. Progression rate of fibrosis is associated with etiology of liver disease, environmental and host factors. Cirrhosis is a complicated stage of liver fibrosis that is accompanied by portal hypertension that compromises the exchange between liver parenchyma and hepatic sinusoids. Fenestrated endothelia present in space of Disse, lines the hepatic sinusoids. In addition to fenestrated endothelia, stellate cells are found in space of Disse. In cirrhosis, sinusoidal capillarization occurs that refers to loss of fenestrated endothelia and filling of space of Disse with scar [1].

Pathophysiology of liver cirrhosis is complex as it varies with types of hepatic injuries. Usually when liver undergo acute injury, parenchymal cells are replaced with the apoptotic and necrotic cells when regenerating process starts. Extracellular matrix deposition and inflammatory response are also associated with this regeneration process. If the injury persists, it results into failure of regeneration process and eventually the abundant extracellular matrix substitutes in hepatocytes, which is mainly composed by collagen type I-III-IV, laminin fibronectin, proteoglycans, and elastin. Hence, the main source of extracellular matrix is activated stellate cells [2].

Fibrosis of liver initiates with activation of Hepatic Stellate Cells (HSC); several mediators' effects contribute in activation of HSC such as reactive oxygen species, products of lipid peroxidation, transforming growth factor beta (TGF-β1), and Platelet Derived Growth Factor (PDGF). Following hepatic injury, these substances are released from damaged hepatocytes and/or activated Kupffer cells, macrophages, and platelets following hepatic injury. Activated HSC acquire different phenotypes such as enhanced Extracellular Matrix (ECM) production, proliferation, secretion of cytokines (pro-inflammatory), expression of contractile Smooth Muscle α-Actin (α-SMA), and release of matrix-degrading enzymes and their inhibitors [3].

On histological basis, vascularized fibrotic septa are the characteristic of cirrhosis that interlink portal veins with central veins. These linkages result in Hepatocyte Island that is surrounded by fibrotic septa. Cirrhotic liver has compromised functions, portal hypertension (raised intrahepatic resistance) and ultimately can develop into hepatocellular carcinoma. Portal hypertension and Hepatic vascular alterations are resulted due to general circulatory abnormalities. Cirrhotic liver and associated vascular distortion is considered irreversible but according to recent researches

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Received Date: *05 May 2021*
Accepted Date: *04 Jun 2021*
Published Date: *09 Jun 2021*

Citation:
Abbaass W, Zainab R, Akram M. Scientific Evaluation of Medicinal Plants in Amelioration of Liver Cirrhosis; a Prevalent Liver Disease. Ann Gynecol Obstetr Res. 2021; 4(1): 1019.

regression and even reversal of cirrhosis is possible [1,4].

Until, specific treatment for liver cirrhosis is not present. Patients are being treated to reduce the complications due to the damaged liver. In developing countries, there is high population rate of liver cirrhosis and the available treatments are often expensive. Due to these factors, phytomedicine approach of treatment emerging as an alternative economical approach. Use of natural ingredients in various combinations with herbs has been suggested to achieve synergistic effects. The focus of this study is to evaluate potential curative effects of medicinal plants that would be useful in ameliorating liver cirrhosis as well as support liver functions.

Management of Liver Cirrhosis

Liver fibrosis can be reversed or prevented by promoting HSC apoptosis or through protection of hepatocytes from apoptosis as these two factors are major contributors in the development of liver cirrhosis.

Stellate Cells Apoptosis

Activated HSC are the major and minor contributors of the fibrotic liver matrix proteins including collagen types I, III, and IV, fibronectin, laminin, and proteoglycans. Many other cells such as bone marrow circulating cells, portal fibroblasts, hepatocytes, and mesenchymal transition billiariary epithelial cells also contribute in ECM production. Survival of activated HSC and liver fibrosis progression is promoted by hepatic macrophages in a nuclear factor-kappaB- (NF-κB-) dependent manner [5]. However, hepatic fibrosis can be reversed by inhibition of NF-κB pathway, which ultimately leads to apoptosis of activated HSC.

Protection of Hepatocytes from Apoptosis

Under chronic liver injury, hepatocyte-derived apoptotic bodies are liberated by hepatocytes undergoing apoptosis. This initial event is considered as a potent inductor of liver fibrosis. Phagocytic capacity of HSC enables the profibrogenic response following the apoptosis of hepatocytes. Phagocytosis of the hepatocyte-derived apoptotic bodies undergo phagocytosis and directly activate HSC and matrix deposition by up-regulation and induction of TGF-β1 and collagen α1 through PI3K and p38 MAPK pathways. DNA from apoptotic hepatocytes induces HSC differentiation, hence mobile HSC stop, via toll-like receptor 9, when they reach an area of apoptosing hepatocytes. Adenosine, product of apoptosing hepatocytes, has been reported as a contributor of fibrogenic cascade [5]. Therefore, therapeutic strategies that can protect hepatocytes from apoptosis would be useful to reverse the fibrotic liver condition.

Anti-Fibrotic Medicinal Plants

Fibrosis progresses with the key process of inflammation, hence the relevant way to treat liver fibrosis is to reduce inflammation and immune response [3]. In this review, plants were reported to produce compounds that restrict inflammation and induce HSC apoptosis thus an important antifibrotic mechanism of medicinal plants was highlighted.

Glycerrhizaglabra

Glycyrrhizin is the main bioactive constituent of *G. glabra*. *In vitro* and *in vivo* studies, Glycyrrhizin is reported to have protective role against hepatocytes apoptosis [6]. *In vitro*, the reported mode of action highlighted the antioxidant properties of this plant as it depletes glutathione depletion, and Lipid per-oxidation, and increases the activity of superoxide dismutase. Inhibition action of this plant was also reported for, cytochrome c release, p38 activation, MMP, and caspases-3 and -9 activities [5]. Moreover, this plant was reported to decreases expression of Nitric Oxide (NO) and intercellular adhesion molecule. *In vivo*, inhibitory action of this plant for caspases pathway was also investigated.

Ginkgo biloba

G. biloba extract is composed of 6% and 24% of terpenes and flavonols hetero sides respectively. In rats, extract of the plant was reported to have inhibitory action for CCL4-, technetium ^{99m}Tc- and ethanol-induced apoptosis mainly by reduction in oxidative stress via inhibition of lipid per-oxidation and up-regulation of Home Oxygenase-1 (HO-1) activity [5]. Moreover, reduction in p53/Bcl-2 ratio, glutathione, and glutathione peroxidase and catalase activities was also investigated for this plant extract.

Moringa oleifera

In a recent study, *M. oleifora* seed extract was reported to subside fibrosis. This study involved CCL4 induced liver fibrosis and concurrent administration of MO seed extract. MO seed extract was reported to control the CCL4-induced elevated serum levels of globulin and aminotransferases [7]. In addition, immunohistochemical studies had suggested reduction in liver fibrosis.

Orthosiphon stamineus

In a recent study, histological studies suggested reduction in TAA-induced liver injury in the rats with cirrhotic liver disease treated with *O. stamineus* plant extract. Certainly, the plant extract was reported to exhibit remarkable reduction in fibrosis and stellate infiltration compared to control group (TAA). Furthermore, hepatoprotective properties of plant extract was suggested through histological investigations as rat liver sections (TAA treated) showed cell necrosis and hepatocyte fatty degeneration. The extract treatment (200 mg/kg) was reported to normalized these effects in the liver histo-architecture [8,9]. Hence, this plant was reported to have extensive hepatoprotective properties.

Hydrocotyle sibthorpioides

Genistein (isoflavone), a bioactive component from *Hydrocotyle sibthorpioides* was reported to decrease the levels of inflammatory mediators, including, TNFα, myeloperoxidase and IL-6 through down-regulation of NF-κBin CCL_4, and alcohol-induced liver fibrosis in rats [10,11]. With estrogenic activities, this plant is considered a potent chemopreventive agent with estrogenic activities against breast cancer.

Curcuma longa

Curcumin, the key active constituent of turmeric, has extensive antioxidant property as it was reported to have protective role for the CCL_4-induced liver. Curcumin was reported to suppress multiple proangiogenic factors such as modification of cannabinoid receptors, increase in glutathione level as well as inhibition of extracellular matrix expression that ultimately decreases the collagen deposition. In a study, treatment with curcumin was reported to increase serum MMP-13 and glutathione levels thus reversed the fibrosis in CCL_4-induced liver fibrosis in rats [10,12]. With curcumin treatment, *in vitro* and *in vivo*, activation of PPAR-gamma was reported to occur which diminish cell proliferation, stimulate apoptosis and repress

extracellular matrix gene expression [13]. Hence, curcumin was reported to have remarkable hepatoprotective therapeutic properties.

Silybum marianum

Silymarin, the extract of *Silybum marianum*, consists of four flavonolignan isomers: Silydianin, silybin, silychristin, and isosilybin. Silymarin was reported as a single herb remedy for liver diseases due to its anti-inflammatory and antioxidant medicinal properties. Silybin, also called silybinin, was reported to inhibit collagen secretion (TGF- β1-induced) and oxidative stress both *in vitro* and *in vivo* in Thiocetamide-induced fibrosis in rats [2,14]. Hence, this plant extract was investigated for its miraculous therapeutic properties in several research studies.

Salvia miltiorrhiza

Plant extract was investigated for hepatoprotective role in Dimethyl Nitrosamine (DMN) and CCL4-induced hepatic fibrosis rat models. In dose dependent manner, *Salvia miltiorrhiza* was reported to improve serum Superoxide Dismutase (SOD) and glutathione activity. Moreover, decrease in Malondialdehyde (MDA), hepatic glutathione levels, and peroxidation products were reported with plant extract treated group [13]. Hence, remarkable hepatoprotective activity of this plant extract was reported.

Ganoderma lucidum

The plant extract was reported to reduce aminotransferases and collagen substance in rats with biliary obstruction-induced liver fibrosis. Moreover, the plant extract was reported to inhibit proliferating hepatic stellate cell through inhibition of phosphorylation of PDGFβR [13]. Hence, *G. lucidum* reported to have remarkable therapeutic properties.

Berberis vulgaris

Berberine, derived from *Berberis*, showed hepatoprotective activity in CCL_4- or paracetamol-induced liver damage. In addition, antioxidant property of the plant was investigated for oxidative damage induced by tert-butyl hydroperoxide in rats. In dose dependent manner, Berberine was reported to diminish cetaldehyde-induced activity and production of NF-κB and cytokine, suggesting the possible role of Berberine for Alcoholic Liver Disease (ALD). In addition, marked reduction in the level of aminotransferases, Malondialdehyde (MDA) and elevation in serum Superoxide Dismutase (SOD) was reported in hepatotoxic-induced liver fibrosis. In berberine-treated group, down-regulation of α-SMA and TGF-β1 was reported which ultimately reduce histopathological changes [13,15]. Hence, this plant was reported to have remarkable anti-fibrotic medicinal properties.

Casuarina equisetifolia

Methanolic extract of Leaf and bark of *Casuarina equisetifolia* was reported to have hepatopretective properties in CCL4-induced hepatotoxic rats. Thrice dose of 500 mg/kg b.wt and 250 mg/kg b.wt of methanol extract of *C. equisetifolia* was administered to test Group-I and Group-II of hepatotoxic rats. On biochemical screening, increase in serum levels of SGPT 28.16 ± 0.94 U/L (20.67% Δ), SGOT 51.68 ± 0.59 U/L (26.59% Δ) and decrease in serum bilirubin 0.77 ± 0.04 mg/dl (25.96% ▼), and cholesterol 174.75 ± 1.17 mg/dl (23.91% ▼) was reported in Group-I.

While, in Group-II, decrease in serum levels of SGPT 24.33 ± 0.76 U/L (31.46% ▼), SGOT 57.29 ± 1.31 U/L (18.62% ▼), bilirubin 0.85 ± 0.02 mg/dl (18.26% ▼), cholesterol 167.29 ± 0.73 mg/dl (27.16% ▼) and glucose 89.08 ± 1.20 mg/dl (1.74% ▼) was reported [16]. Medicinal properties of this plant was investigated in number of scientific trials against chronic liver diseases.

Moringa is being used as a regular part of conventional eatables for nearly 5000 years. It has been reported by Bureau of plant industry as they found *Moringa* as outstanding source nutritional components. Calcium deposits of this plant are four times that of milk. Moreover, vitamin C are seven times and potassium deposits are three time than that of oranges and bananas respectively. This plant has remarkable medicinal properties that can serve the humanity in several health care needs. Fortunately, *Moringa* can be cultivated in unfavorable environmental exposure. Wide availability of this plant has an attraction for developing countries due to economic and health related potential. Besides its remarkable results for liver fibrosis, this plant has multiple medicinal properties such as Antimicrobial, anti-inflammatory, bronchodilator, anti-diabetic, anti-oxidant, anti-pyratic, anti-hypertensive, anti-tumor and cardiac & circulatory stimulant. Being effaceable, safe and economical, this plant can be used for multiple health conditions.

Conclusion

Cirrhosis is a chronic disease of liver as multiple factors are involved in its pathophysiology that still have made complicated to treat this condition satisfactorily. Medicinal plants are gaining recognition due to their easy availability, high efficacy and least side effects. Number of plants has been investigated for their mode of action. Hence, research studies on other plants should be performed to investigate their active constituents and mechanism of action responsible for their use in liver cirrhosis.

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