Potent Natural Product Used In The Management of Liver Fibrosis

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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. The pathological determining factor of liver fibrosis involves secretion of extracellular matrix proteins and formation of scar tissue. The major regulators involved in hepatic fibrogenesis are the transforming growth factor (TGF)-β1/SMAD and toll-like receptor 4 (TLR4)- initiated myeloid differentiation primary response 88 gene (MyD88)/NF-κB cell signalling pathways In the progression of chronic liver entry to fibrosis, all hepatic cells undergo specific changes. The hepatocytes are injured and they undergo apoptosis. The sinusoidal endothelial cells undergo a loss of fenestrae that is termed acapillarization of the sinusoids. The resident macrophage in the liver, the Kupffer cell, activates and produces a variety of chemokine's and cytokines. Lymphocytes infiltrate the injured liver and contribute to the inflammation.. This article reviews potent natural products and herbal medicines that have demonstrated activity against liver fibrosis through different mechanisms of action.

Keywords: Extracellular matrix proteins; Fibrosis; Hepatocytes; Herbal medicine; Liver; Natural products; Regulators

INTRODUCTION

Fibrosis, or scarring of the liver, is a wound-healing response that engages a range of cell types and mediators to encapsulate injury. Although even acute injury will activate mechanisms of fibrogenesis, the sustained signals associated with chronic

liver disease caused by infection, drugs, metabolic disorders, or immune attack are required for significant fibrosis to accumulate(Scott,L.F.,2008). Excessive alcohol consumption, virus infection, obesity, diabetes and drug-induced liver damage are the leading causes of this liver disease (Lazerow,S.k et al., 2006).So therefore the range of biological activities offered by natural product has had a drastic

improvement in their potency for the treatment and most importantly the management of liver fibrosis.

MECHANISM OF LIVER FIBROSIS

A key discovery in understanding fibrosis has been that the hepatic stellate cell (HSC) is the primary effector cell, orchestrating the deposition of ECM in normal and fibrotic liver. HSCs are resident perisinoma cells which are found in the sub endothelial space between hepatocytes and sinusoidal endothelial cells. They are strategically positioned to intimately interact with hepatocytes, endothelial cells, and nerve endings. (Wake,K.,1995). Additionally, the HSC plays a pivotal role in starting the immune response through the release of chemical medators like cytokines and chemokine and interacting with immune cells. HSC also contributes to angiogenesis and the regulation of oxidant stress (Bonacchi,A et al.,2003)

Activation of the HSC into a myofibroblast like phenotype can be rovoked by a range of chronic injuries to the liver, amongst which are viral hepatitis, toxins, [non-] alcoholic steatohepatitis and autoimmune disorders (Bataller, R et al., 2005).Activation consists of two major phases, initiation [also called a "preinflammatory stage"] and perpetuation, followed by a resolution phase if the injury subsides (Friedman, S.L., 2004).Hepatic fibrosis activation comprises of two primary major steps and they are 1) Initiation step and 2) Perpetuation.Initiation is primarily linked with paracrine mediated changes in gene expression as the cells are now receptive to mediators like cytokines while perpetuation is a factor that arises as a result of the maintenance of these signals which furthermore lease to an increase in cytokine secreation and progression of extracellular matrix remodelling.Several cytokines and growth factors are very important in the initiation of hepatic fibrogenesis.The major factors are the Transforming growth factor β (TGF-β) which is the main fibrogenic cytokine released by kupffer cells, endothelial cells and hepatocytes in the liver and is a key mediator in human fibrogenesis.(Inagaki Y., et al 2007). It has three major isoforms: TGF-β1, TGF-β2 and TGF-β3. TGF-β1 which is stored as an inactivated protein and when activated, signals through its receptors to Smad proteins, which improves the transcription of target genes such as procollagen I and III.(Yoshida,k.et al.,2012). Once the cell is primed for activation, perpetuation results from the effects of these stimuli on maintaining an activated phenotype and generating fibrosis. Sustained activation involves at least seven discrete changes in cell behaviour: proliferation, chemotaxis, fibrogenesis, contractility, matrix degradation, retinoid loss, and WBC chemo attractant/cytokine release. The overall effect of these changes is to increase accumulation of extracellular matrix. During this stage there is a release of proinflammatory, profibrogenic and promitogenic stimuli that act in an autocrine and paracrine manner. Resolution of fibrosis refers to pathways that cause either HSC apoptosis, senescence, or quiescence (Knittel, T et al., 1999).The HSC is the central effector in hepatic fibrosis and undergoes activation through a two-phase process. Initial liver injury results in hepatocyte cell apoptosis with generation of apoptotic bodies, reactive oxygen species, and paracrine

stimulation of HSCs. Additionally, LPS from the gut can simulate HSCs. These initial stimuli allow the cell to become sensitized to additional activation by up regulating various receptors and is termed the initiation phase. Subsequently, it is able to secrete autocrine and paracrine growth factors, chemokines, and ECM. Maintenance of HSC activation is termed the perpetuation phase, and involves changes in HSC behaviour, including proliferation, chemotaxis, fibrogenesis, and contractility. (A) Among other cell types that may contribute to ECM production, fibrocytes derived from the bone marrow are believed to trans differentiate into myofibroblasts. (B) Mechanical stiffness of the ECM can be sensed by and activate HSCs. (C) The contribution of dendritic cells to fibrosis is complex and not yet well understood, however, they can activate NK cells. HSCs become sensitized to NK cell mediate apoptosis after cellular activation causes down regulation of their inhibitory MHC class I molecules. (D) New evidence suggests fibrosis can regress through reversion, senescence or apoptosis of HSCs. Fibrosis progression and regression require specific signalling pathways; thus, understanding how they interact and evolve with injury can contribute to efforts to reverse fibrosis. Progressive fibrosis, while permitting their regulated clearance during resolution of fibrosis.

PHARMACOLOGICAL EFFECTS OF NATURAL PRODUCTS

Helioxanthin

Helioxanthin (was originally isolated from the shrub Taiwania cryptomerioides (Taiwan Shan). Helioxanthin exhibited potent inhibitory activity against HBV replication in HepG 2.2.15 cells and Lamivudine-resistant HBV L536M/M550V double mutant HBV strain [Li, Y et al., 2005]. Treatment with helioxanthin suppressed IL-1-induced c-jun transcription and c-jun-mediated DNA- binding activity of AP-1 (Tseng, P.C et al., 2008).

Wogonin

The herbal medicine Scutellaria baicalensis (Huangqin) has been used to reduce inflammation . Studies have shown its effects and it was found out that wogonin significantly attenuated inflammatory response in EtOH-fed mice, and reduced the expression of inflammatory.(Li, H.D et al., 2017)

Matrine And Oxymatrine

The synergistic effect of these two drugs are the influence of there metabolic course.When administered produced its therapeutic action and it was done by inhibiting secretion of hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg), and replication of HBV DNA (Zhi-Jie, Ma et al., 2013)

Rhodiola Kirilowii (Maxim)

Polyphenols (−)-epigallocatechin-3-O-gallate (EGCG) and (−)-epicatechin-3-O-gallate (ECG) , from the herbal medicine Rhodiola kirilowii (Regel) Maxim (Xiaye Hongjingtian) exhibited potent inhibitory effect against HCV NS3 serine protease with low cytotoxicity (Zuo, G et al., 2007)Polyphenols extracted

from green tea also exhibited potent activity against HCV viral entry and replication. In one study, a single oral administration of green tea extract containing 94% pure EGCG was safe and well
-tolerated by all 11 patients with cirrhosis associated with chronic HCV infection (Halegoua-De et al., 2012).

Glycyrrhizin

The major component of the root of Glycyrrhiza glabra (Yanggancao), inhibited expression of the HCV full-length viral particle and HCV core gene synergistically with IFNα . Treatment with glycyrrhizin acid reduced hepatic inflammation through
regulation of CD4+ T cell response in a JNK-, ERK-, and PI3K-Akt-dependent manner in mice with liver injury , Glycyrrhizin acid prevented apoptosis and inflammatory infiltrates induced by LPS/GaIN injection through disturbing the binding of HMGB1 protein to the promoter of Gsto1 (Kuroda, N et al., 2014).

Curcumin

Curcumin is a polyphenol compound from the Chinese herb, Curcuma longa. hose mechanisms include suppressing the proinflammatory cytokines, lipid perodixation products, PI3K/Akt and hepatic stellate cells activation, as well as ameliorating cellular responses to oxidative stress such as the expression of Nrf2, SOD, CAT, GSH, GPx and GR. Taking together, curcumin itself acts as a free radical scavenger over the activity of different kinds of ROS via its phenolic, β-diketone and methoxy group (Farzaei, MH et al., 2018)

Genistein

Genistein is a type of isoflavone first isolated from Hydrocotyle sibthorpioides (Tianhusui) and considered a potent chemopreventive agent with estrogenic activities against breast cancer . Treatment with genistein decreased levels of inflammation mediators, including IL-6, TNF-α, and myeloperoxidase, through downregulation of NF-κB in alcohol- and CCl4-induced liver fibrosis in rats (Ullah, M.F et al ., 2011).

CONCLUSION

In conclusion, this review amply demonstrates that the potent natural products and herbal medicines are used for treating liver fibrosis.

The use of plant and natural products offer an extensive and safe alternatives but a drawback is the insufficiency of in vivo results to confirm the clinical efficacy of these natural product.

It should be expected that the laboratory success of clinical trials with botanical pharmaceuticals would pave the way to successful treatment of liver fibrosis.

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