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Review Article

Research Progress of Rhubarb in the Treatment of Liver Fibrosis

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Abstract

Liver fibrosis is the excessive accumulation of extracellular matrix proteins including collagen that occurs in most types of chronic liver diseases.It is a complex disease centered on the activation of hepatic stellate cells and regulated by a variety of cell signal transduction pathways.Advanced liver fibrosis can results in cirrhosis, liver failure, and portal hypertension[1].As a commonly used traditional Chinese medicine, rhubarb is often concerned and studied by scientists. Its pharmacological effects are extensive and can play an important role in the treatment of liver fibrosis. In this paper, the inhibitory effect of rhubarb on the formation of liver fibrosis will be discussed from three aspects: the active components of rhubarb, the protein targets related to liver fibrosis, and the signaling pathway, in order to clarify its specific mechanism of action, and to develop anti-hepatic fibrosis drugs for reference.

Keywords: Rhubarb, Liver Fibrosis, Mechanism, Review.

Active Ingredients of Rhubarb

Rhubarb contains a variety of active ingredients, which have the functions of purging and attacking accumulation, cooling blood and detoxifying, clearing heat and purging fire, removing blood stasis and clearing meridians.According to the current research, there are about 160 definite chemical components of rhubarb, mainly anthracene derivatives, organic acid, naphthalene derivatives, etc.

Anthracene derivatives

The content of anthraquinone in rhubarb medicinal materials is 1.5% ~ 4%,Relevant literature reports that rhubarb anthraquinones can block the process of tissue fibrosis in experimental animals[2].TGF-β1 can activate hepatic stellate cells, promote the survival of activated hepatic stellate cells, and stimulate its transformation, proliferation and synthesis of extracellular matrix, leading to liver fibrosis.A variety of anthraquinones have the effect of protecting the liver, such as rhein, emodin.According to related experiments, rhein can intervention in fibrosis animal modelsthe expression of TGF-β1 and αSMA in liver tissue was significantly reduced, the collagen area in liver tissue was significantly reduced, and the degree of fibrosis was significantly improved through experiments, indicating that rhein may inhibit TGF-β1 and αSMA, inhibiting hepatic stellate cell activation to exert hepatoprotective and anti-fibrotic effects. Through the experiment of Miao-Xian Dong[3], it was known that the experimental liver fibrosis rat model was established by CCl4 injection. After receiving emodin treatment, the level of TGF-β1 protein in serum and the expression of Smad4 and α-SMA in the serum were observed. The protein expression in liver tissue was significantly down-regulated.Zhang Lili[4] and others believed that emodin can reduce oxidative stress, inhibit the proliferation and activation of hepatic stellate cells (HSC) and the expression of collagen, which can reduce TNF-a, malondialdehyde (MDA), nitric oxide (NO), and the content of peroxynitrite (ONOO-) delayed the progression of liver fibrosis.In addition,Emodin can inhibits hepatocyte apoptosis and regulates Th1/Th2 balance in rats[5] So,Emodin and rhein might be a therapeutic antifibrotic agent for the treatment of hepatic fibrosis.

Organic acid

The organic acids contained in rhubarb mainly include palmitic acid, linoleic acid, etc.Palmitic acid is a saturated fatty acid, which is of great significance for the pathogenesis of lipid metabolism-related diseases.Abnormally increased lipids in liver tissue can promote liver fibrosis by affecting lipid metabolism balance and enhancing lipid peroxidation,at the same time, hepatic stellate cell activation is also closely related to lipid metabolism.When the liver is injured, the phenotype and function of hepatic stellate cells change, they can secrete a variety of cytokines to promote their own activation[6], and the vitamin A lipid droplets they contain are gradually lost[7].Palmitic acid can participate in vitamin A metabolism and affect the biological activity of hepatic stellate cells.Abergel[8] found that adding palmitic acid (75uM) and normal dose of vitamin A to the culture medium of hepatic stellate cell line (PAV-1) can increase the number of lipid droplets in PAV-1 cells, significantly inhibit cell proliferation and α-SMA , and significantly reduced the level of collagen I, indicating that palmitic acid can induce the transformation of hepatic stellate cells from activation to quiescence.Linolenic acid is a polyunsaturated fatty acid that reduces lipid deposition and also plays an important role in regulating lipid metabolism[9].

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Targets related to liver fibrosis

TNF

TNF (Tumor Necrosis Factor) is a Protein Coding gene. This cytokine is involved in the regulation of a wide spectrum of biological processes including cell proliferation, differentiation, apoptosis, lipid metabolism, and coagulation. This cytokine is mainly secreted by macrophages,and it has been confirmed that TNF-α can promote the formation of liver fibrosis in liver tissue.Studies have shown that antagonizing inflammatory cytokines released by hepatic macrophages, such as IL-1 and TNF-α, or promoting apoptosis of activated hematopoietic stem cells, can alleviate liver fibrosis[10].

TP53

TP53 acts as a tumor suppressor in many tumor types, and its mutations are prevalent in cancer types.Increased expression of TP53 induces synthesis of connective tissue growth factor (CTGF) in mouse and human hepatocytes and leads to liver fibrosis in mice[11].When liver fibrosis progresses to the later stage, DNA damage is severe, and the expression of p53 protein in the liver tissue of rats is significantly up-regulated, thereby initiating apoptosis-related proteins and causing cell apoptosis[12].In damaged DNA, the expression of p53 protein is up-regulated, mainly by inducing growth arrest and cell death to prevent the malignant transformation of damaged cells[11,13].Studies have shown that TP53 plays a regulatory role in muscle cell differentiation, suggesting that the recognition of new target molecules may bring new implications for the treatment of liver fibrosis[14].

TGF-β1

This gene encodes a secreted ligand of the TGF-beta (transforming growth factor-beta) superfamily of proteins.Among its related pathways are DNA Damage Response (only ATM dependent) and Loss of Function of SMAD2/3 in Cancer.TGFβ1 is the most potent stimulator of the synthesis of collagen I and other matrix components.In fibrotic diseases, TGF-β signaling is continuously transduced leading to chronic activation of fibroblasts and massive accumulation of extracellular matrix[15,16].So inhibition of its effects remains the main focus of anti-fibrotic effects in the liver[17].Emodin and rhein have been confirmed to inhibit the activity of TGFβ1.By inhibiting TGF-β1, it can increase the regeneration of hepatocytes, thereby inhibiting the process of liver fibrosis[18].In addition, liver fibrosis is the most critical link in the "tri-step" of hepatitis-cirrhosis-hepatocellular carcinoma. Dysregulation or defects in the TGFβ apoptotic pathway may underlie hepatocellular carcinoma and many hematological malignancies[19].

Signaling pathways related to liver fibrosis

Liver fibrosis is a complex lesion co-regulated by a variety of cell signal transduction pathways, with duality of repair and injury.It is of great significance to clarify the cell signal transduction pathways related to the occurrence of liver fibrosis to block and reverse the progression of liver fibrosis.

NF-kB signaling pathway

NF-kB is an important nuclear transcription factor whose expression can be detected in hepatocytes, hepatic stellate cells, and endothelial cells. NF-kB has a pleiotropic regulatory effect and can regulate the transcription of various cytokines. Prevents apoptosis of hepatic stellate cells.Current studies have shown that NF-kB is involved in the regulation of immune responses and inflammatory processes, and promotes the expression of inflammatory factors (IL-1, TNF-α, IL-6), chemokines (IL-8) and other inflammatory genes and TGF-β genes. expression, and these cytokines play an important role in the development of liver fibrosis.As an extracellular stimulator, TNF-α can activate NF-kB and further amplify the inflammatory response[20,21] . Therefore, TNF-α-mediated NF-kB signal transduction pathway plays a promoting role in the occurrence and progression of liver fibrosis. And according to related experiments, rhein can down-regulate the release of inflammatory factors such as IL-1β and TNF-α by inhibiting the activation of NF-κB pathway[22,23].

MAPK signaling pathway

There are four main MAPK signal transduction pathways, namely ERK1/2 pathway, p38 pathway, JNK pathway and BMK11 ERK5 pathway. Relevant studies have shown that TGF-β1 can not only transmit through the TGF β/Smad signaling pathway, but also activate the ERK, p38, and JN141-4 signaling pathways in various tissue cells. The activated MAPK signaling pathway has a regulatory effect on the Smad signaling pathway, which may eventually lead to the occurrence of related diseases or cancer[24,25].The activation of MAPK signaling pathway plays a very important regulatory role in the proliferation and activation of hepatic stellate cells and the occurrence and development of liver fibrosis, which has also been confirmed in recent studies[26]. At the same time, Wu Wenjuan[27] detected the changes of p38MAPK mRNA and protein expression in the liver tissue of the experimental rat liver fibrosis model and found that p38MAPK was up-regulated in CCl4-induced rat liver fibrosis, indicating that p38MAPK signal transduction may promote CCl4-induced hepatic fibrosis in rats.The effects of emodin on liposaccharido-induced MAPK signaling pathway related proteins were studied in relevant experiments, and it was clear that emodin could inhibit MAPK signaling pathway[28].

Hedeghog signaling pathway

Hedeghog signaling pathway may play a key role in the occurrence and development of liver fibrosis.The core link of liver fibrosis is the abnormal activation of hepatic stellate cells. The activation of Hedeghog pathway makes hepatic stellate cells become functional fibroblasts, maintains the phenotype of fibroblasts, promotes their proliferation, and inhibits apoptosis.In adults, the severity of portal inflammation and fibrosis correlates with the activity of the Hedgehog pathway[29]. Experiments show that conditional disruption of Hedgehog signaling in myofibroblasts reduces the number of glycolytic myofibroblasts and liver fibrosis in mice[30].The development of hepatic fibrosis induced by hexavalent chromium is also caused by the activation of hepatic stellate cells mediated by the Hedgehog signaling pathway[31].It is therefore inferred that Hedgehog signaling controls HSC fate by regulating metabolism.

Outlook

Traditional Chinese medicine has the advantages of multi-link, multi-level and multi-target in the treatment of liver fibrosis, which provides a new idea for the study of anti-hepatic fibrosis.But there are reports that rhubarb has bidirectional potential, including liver protection and liver toxicity, and the anthraquinones it contains have liver and kidney toxicity and potential carcinogenic risks[32,33].Whether the clinical

safety of anthraquinone-containing traditional Chinese medicines can be improved through syndrome differentiation and drug use attenuated or avoided is a practical problem that needs to be solved urgently[34].It is necessary to strengthen research and improve the level of clinical rational use of traditional Chinese medicine.Liver fibrosis is a major problem affecting human health, and it has received more and more attention in recent years.How to overcome the toxicity of rhubarb to maximize its pharmacological effects is an unexplained problem, and the research on liver fibrosis is only in its infancy. Clinical trial research and demonstration provide clearer theoretical basis and clear ideas for clinical application. It is believed that with the deepening of research, rhubarb will have broader application prospects in the treatment of liver fibrosis, and play an important role in human health, and the treatment of liver fibrosis can also be effectively solved.

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