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Research Progress on the Mechanism of Baicalein in Scutellaria Baicalensis Against Liver Fibrosis

Chenyang Wu[1], Guotai Wang[2,*]

[1]Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712000, Shaanxi, China
**Correspondence Author*

Abstract: ***Baicalein is a flavonoid extracted from the dried root of Scutellaria baicalensis, family Labiatae, which can inhibit hepatic stellate cell activation, collagen deposition, reduce the release of inflammatory factors, and regulate the cell cycle and apoptosis, thereby controlling the balance between synthesis and catabolism of hepatic extracellular matrix. In this paper, we reviewed the literature on baicalein in the treatment of hepatic fibrosis in recent years and found that baicalein inhibits inflammatory factors such as interleukin and tumor necrosis factor, and regulates the signaling pathways such as transforming growth factor-β, Wnt/β-catenin, nuclear factor-kB, PDGF, MAPK and other related signaling pathways, and then influences the activation of hepatic stellate cells, extracellular matrix deposition, and inhibits the progression of hepatic fibrosis. The aim of this paper is to provide new ideas and a theoretical basis for the treatment of liver fibrosis and the development of new drugs.***

Keywords: Baicalein; Liver fibrosis; Hepatic stellate cells; Extracellular matrix; Mechanism**.**

1. Introduction

Liver fibrosis (LF) refers to the pathological process of diffuse excessive deposition and abnormal distribution of extracellular matrix in the liver, which is also the pathological repair stress response of the liver to chronic injury, and at the same time, it is the inevitable pathological process in the process of chronic liver disease to cirrhosis and liver failure caused by various etiological factors, and it is an essential link in the development of chronic liver disease. If not controlled, further development of hepatic fibrosis may cause structural disorders of liver lobules, nodular regeneration of hepatocytes, formation of pseudo-lobular structure, i.e., cirrhosis, and clinical manifestations of hepatic hypoplasia and portal hypertension [1]. The causes of liver fibrosis are varied, and common causes include hepatitis B, hepatitis C, alcoholic liver disease, non-alcoholic fatty liver disease (known as "fatty liver", which is a kind of chronic liver injury closely related to metabolic syndromes, such as obesity, hypertension, and diabetes mellitus), and pharmacological liver injury. Currently, the prevalence of non-alcoholic fatty liver disease (NALD) in adults is about 25-30%, and the prevalence of hepatitis B is about 6%, which is the main cause of liver fibrosis [2]. Moreover, liver fibrosis will eventually develop into liver cancer if not intervened [2]. Liver fibrosis will eventually develop into liver cancer if not intervened, so early intervention to treat or delay the development of liver fibrosis is especially important to reduce the incidence of cirrhosis and liver cancer. Scutellaria baicalensis was first recorded in the Shennong's Herbal Classic, and is the dried root of Scutellaria baicalensis of the family Labiatae, which is bitter in flavor and cold in nature, and enters the lung, stomach, gallbladder and large intestine meridians. The Shennong's Herbal Classic states that Scutellaria baicalensis is "It is mainly used for the treatment of various kinds of fever, jaundice, dysentery, edema, dysuria, skin malignant sores, ulcers and burns." Correct Treatise on Materia Medica is said "If the herb is dry, it can clear away fire-heat from the upper jiao, dissolve phlegm and regulate qi, relieve wheezing and coughing, stop bleeding, alleviate exchanges of cold and heat, clear away wind-heat and damp-heat, relieve headache, relieve plague, clear the throat, and treat lung impotence, carbuncles, and back sores and ulcers. In addition, it dispels heat from the body's surface, so it can be used to treat symptoms such as spotted rashes, tuberculosis of the lymph nodes in the neck, sores, and red eyes. If the herb is firm in texture, it can clear away fire heat in the lower jiao, clearing away symptoms such as red diarrhea, frequent urination, urgent urination, painful urination caused by damp heat in the bladder, and dysuria, pain, constipation, blood in the stools, and intestinal bleeding caused by diseases of the urinary system." Scutellaria baicalensis has a long history of medicinal use with remarkable efficacy and can be used to treat a variety of diseases such as jaundice, canker sores and poisons. The main chemical components of Scutellaria baicalensis include flavonoids, terpenoids, volatile oils, phenolic acids, polysaccharides, and trace elements. Scutellarin and baicalin are the main active components of flavonoids. Modern pharmacological studies have shown that Scutellaria baicalensis has anti-inflammatory, antitussive, diuretic, anti-microbial, anti-tumor, antioxidant, antifibrotic, cardiovascular, and neurological protection effects [3–5]. This article is a review of studies on baicalein for the prevention of liver fibrosis.

2. Mechanisms of liver Fibrosis Pathogenesis.

The liver is formed by parenchymal cells (i.e., hepatocytes) and other cells that are not parenchymal. The walls of the hepatic sinusoids are lined by three different types of nonparenchymal cells: hepatic sinusoidal endothelial cells (LSEC), Kupffer cells (KC), and hepatic stellate cells (HSC). Both hepatic parenchymal and nonparenchymal cells are involved in the development and progression of liver fibrosis and cirrhosis [6]. Liver fibrosis is caused by liver injury due to a variety of pathologic factors. Liver injury activates the trans-differentiation of hepatic stellate cells (HSC) into collagen-producing myofibroblasts and induces excessive deposition of extracellular matrix (ECM), destroying the liver parenchyma and the normal structure of the liver [7,8]. HSCs are also involved in the development of hepatic fibrosis and cirrhosis [7,8].

The activation of HSC plays a very important role in the occurrence and development of hepatic fibrosis, meanwhile, as the target cell of hepatic fibrosis, HSC, under the joint action of multiple pathogenic factors, HSC is activated and transformed into myofibroblast-like cells, which synthesize and secrete a large number of ECM, such as collagen and fibronectin, etc., meanwhile, the ECM are excessively deposition in the liver, thus promoting the occurrence and development of hepatic fibrosis [9, 10]. There are multiple pathways to activate HSC, which are broadly categorized into two main types of pathway activation, intracellular and extracellular origin. The intracellular pathways include nuclear receptors, reduction of OS, G protein-coupled receptors, cell proliferation and inhibition of apoptosis and fibrogenic pathways, innate immune signaling pathways, adipocytokines and cytokines, and genetics-related signaling [11-14]. Extracellular pathways can also activate HSCs, e.g. KC cells, hepatic sinusoidal endothelial cells, B lymphocytes, biliary epithelial cells, etc. can promote the activation of HSCs through the secretion of various cytokines or the activation of the corresponding signaling pathways, such as the transforming growth factor β (TGF-β), platelet-derived growth factor (PDGF) and inflammatory vesicle (NLRP3) - capase1 signaling pathway, as well as the WNT/β-catenin signaling pathway, which in turn promotes the activation of HSCs. In addition, HSC activation not only involves the above cell types or cytokines, but also promotes the formation of myofibrosis through the production of extracellular matrix such as collagen, and the formation of myofibroblasts also involves inflammation, which not only activates HSCs but also promotes their proliferation and synthesis of ECM, which attracts more inflammatory cells to infiltrate, thus exacerbating liver inflammation, which promotes HSC activation. Thus, exacerbation of liver inflammation promotes the development of myofibrosis. Activation of HSCs is characterized by cell proliferation and migration, contraction after transformation into myofibroblasts, and production of large amounts of collagen and other extracellular substances [6].

3. Mechanism of Baicalein for HSCs

Scutellaria baicalensis, as a traditional Chinese herb, has a wide range of roles in the field of traditional Chinese medicine research and has attracted much attention for its unique medicinal value and anti-disease properties. The main active component of baicalin is (5,7-dihydroxy-8-methoxyflavone), which belongs to flavonoids [3]. The origin of the study of baicalin for liver fibrosis comes from the main active ingredient in the Chinese herbal prescription Nourishing the Liver Pill from Zhu's Collection of Effective Prescriptions and Xiao Chaihu Tang from Cold-Induced Diseases, both of which are commonly prescribed for the treatment of hepatic fibrosis, and both of which are nourishing in preventing and inhibiting hepatic fibrosis and in protecting the liver. Studies have shown that the main active ingredient of liver-supporting pills for the treatment of liver fibrosis is baicalein, which acts through the inhibition of the Wnt signaling pathway to exert epigenetic modification, and through the inhibition of the expression of the PPARγ (peroxisomal proliferator-activated receptorγ) pathway to reverse the activation of HSCs induced by high-glucose culture agents. Inhibition of peroxisomal proliferator-activated receptorγ pathway expression Xiaochaihu Tang inhibits fibrosis by decreasing peroxidation, inhibiting HSC proliferation, decreasing collagen I and α-SMA, and inhibiting dimethylnitrosamine (DMN). Baicalin and baicalein are the main components that resist the oxidative damaging effects of HSCs [18,19] HSC activation is divided into two phases: 1) Initiation or pre-inflammatory phase, which refers to early changes in gene expression shortly after the injury; 2) Permanence corresponds to the maintenance of the activated phenotype and the development of fibrosis [20]. And baicalein inhibits HSC proliferation by inhibiting the early stages of HSC initiation or gene expression [21, 22]. Baicalin inhibits PDGF-BB-induced proliferation, activation, apoptosis, and cell cycle progression of HSC in vitro via miR-3595/ACSL4 axis [23]. Meanwhile, baicalein reduced PDGF-BB-induced epithelial - mesenchymal transition (EMT) in activated HSC-T6 cells. Due to the altered phenotype of intercellular adhesion complexes, epithelial cells lose their polarity. They may then cross the ECM-like mesenchymal cells, a process known as EMT. Activated HSCs exhibit a significant elevation of mesenchymal and epithelial markers, suggesting that they undergo EMT [24, 25]. Meanwhile, TGF-β1 is a key factor in the activation of HSC, and baicalein down-regulates the expression of TGF-β1, preventing the phosphorylation of Smad proteins, while PDGF is an accessory factor of TGF-β1, which promotes the onset and development of liver fibrosis by stimulating the activation and proliferation of HSC. TNF-α plays an important role in HSC proliferation and activation as well as in the synthesis of EC M and the release of matrix metalloproteinases and their tissue inhibitors, whereas baicalein can promote the activation of HSC induced by TGF-β1 by inhibiting the activation of HSC [26, 27]. In addition baicalein in PDGF-BB-induced HSC when antifibrotic properties. miRNA profiles of PDGF-BB-induced activated HSC-T6 cells. acsl4 is a potential functional target of miR-3595. Hambelin does not affect the cycle of activated HSC but regulates apoptosis. Hambelin inhibits the progression of liver fibrosis by promoting apoptosis of activated HSC [28]. Therefore, baicalein has a strong effect on anti-HSC proliferation and inhibition of astrocyte protein synthesis [29].

4. Role of Baicalein in Antioxidant and Anti-inflammatory Properties

Inflammation is the body's response to damaged tissues, and noxious stimuli, aimed at eliminating primary damaging factors and initiating the process of repairing damaged tissues; it is part of the protective mechanism of the immune system [30]. Baicalein; can inhibit the NF-κB/mitogen-activated protein kinase (MAPK) signaling pathway by decreasing the release of prostaglandin E2, nitric oxide. In addition, baicalein inhibits apoptosis and the release of pro-inflammatory cytokines, IL-1β, IL-18, and IL-6, thus baicalein can effectively inhibit HK-2 cell loss and cytotoxicity induced by oxygen-glucose deprivation/reoxygenation. These effects could be realized by the enhanced autophagy of baicalein and the inhibition of COX-2 expression. Finally, baicalein can effectively inhibit the activation of PTEN, which in turn inhibits the phosphorylation of Akt, and improves the inflammatory state of the liver by inhibiting the release of a variety of pro-inflammatory factors, which in turn protects the liver [31]. Baicalein attenuates oxidative damage in

hepatocytes by scavenging reactive oxygen species (ROS) and inhibiting lipid peroxidation. It was found that baicalein up-regulated the expression of the antioxidant protein Sestrin2 and enhanced superoxide dismutase (SOD) and glutathione (GSH) activities, while reducing malondialdehyde (MDA) levels, thereby ameliorating the hepatic injury induced by a high-fat diet or cadmium exposure. In addition, baicalein significantly alleviated hepatic inflammatory responses by inhibiting the activation of NLRP3 inflammatory vesicles and reducing the release of interleukins (IL-1β, IL-18) and tumor necrosis factor-α (TNF-α) [21,32,33].

5. Regulation of Cell Death Mechanism

Baicalein intervenes in the process of liver fibrosis through multiple cell death pathways, and apoptosis signal-regulated kinase (ASK1) belongs to the MAPK pathway, which is involved in liver apoptosis, inflammation, and fibrosis [34]. While it contains iron death, baicalein inhibits hepatocyte iron death and reduces lipid peroxidation injury by regulating ECM1 protein. Scutellaria baicalensis induces iron death in activated HSCs through the SOCS11 / P53 / SLC7A11 pathway via baicalein, thereby alleviating liver fibrosis [28]. Baicalein induces iron death in HSCs by targeting SLC7A11 from the iron metabolism pathway, while baicalein reduces the activation of HSCs by targeting ACSL4 from the lipid peroxidation pathway to reduce lipid peroxidation and inhibiting hepatocyte iron death [10]. Inhibitors of iron death can reduce hepatic injury, decrease the secretion of inflammatory factors, and thus inhibit the activation of HSCs. Sorafenib can induce iron death in HSCs by modulating ZFP36/TTP and ELAVL1/HuR, which affects downstream mRNAs and leads to iron autophagy in HSCs. Therefore, reducing iron death in hepatocytes or inducing iron death in activated HSCs is an effective therapeutic strategy for the treatment of liver fibrosis [28, 35].

6. Synergistic Therapy and Metabolic Regulation

TGF-β signaling is a key cytokine in the promotion of hepatic fibrosis. The TGF-β family has as many as 33 members. Although TGF-β2 plays a very important role in cholangiofibrosis, it is TGF-β1 that has been most widely studied in the study of liver fibrosis [36]. Among them, TGF-β is composed of potential precursors synthesized by a variety of cells, including endothelial cells, macrophages, and hepatocytes. In addition. An important source of TGF-β in the liver is platelets [37]. Inactivated TGF-β molecules bind to latency-associated protein (LAP) and accumulate in the ECM, where they must be cleaved by specific proteases to become active. Endothelial cells are involved in the conversion of TGF-β from the latent to the active form. [38] Oxidative stress (OS) is a key process driving liver injury and the onset of liver fibrosis. It corresponds to a shift in the balance between cellular pro-oxidants and antioxidant factors, which leads to the production of ROS and reactive nitrogen species (RNS) [39] ROS induces important epigenetic changes in HSC, including histone modification-induced chromatin remodeling, DNA methylation, and gene silencing caused by microRNAs (miRs) [158]. In vitro and in vivo approaches have shown that HSC displays global demethylation of fibrogenic genes during transdifferentiation into myofibroblasts, which is associated with the development of liver fibrosis [40].

7. Conclusion and Outlook

Despite the significant efficacy of baicalein in hepatic fibrosis, it also faces some challenges, which are as follows Pharmacological effects: The main active ingredients in baicalin, such as baicalin and baicalein, have a variety of pharmacological effects and can exert anti-hepatic fibrosis effects through antioxidant, anti-inflammatory and anti-hepatic stellate cell activation pathways. Some clinical studies have shown that Scutellaria baicalensis extracts or compound preparations containing Scutellaria baicalensis are effective in improving liver function indices and serological indices of hepatic fibrosis in patients with hepatic fibrosis, and have a good safety profile. Scutellaria baicalensis is often used in compound preparations with other Chinese medicines for the treatment of liver fibrosis, which can exert synergistic effects and improve the therapeutic effects. Meanwhile, it can also be used in combination with conventional Western medicine treatments to provide new ideas and methods for the comprehensive treatment of liver fibrosis. The disadvantage is that the mechanism of action is not fully understood: although it has been shown that some components of Scutellaria baicalensis have anti-hepatic fibrosis effects, the specific molecular mechanisms still need to be studied in depth, which limits its precise application and further research and development.In addition, the quality of Scutellaria baicalensis herbs is highly influenced by factors such as origin, harvesting time and preparation method, and the quality of different batches of the drug may vary, affecting the stability and reproducibility of clinical efficacy. Current clinical trials of Scutellaria baicalensis for the treatment of liver fibrosis suffer from small sample sizes, lack of rigorous study design, and lack of high-quality randomised controlled trials and long-term follow-up studies, making it difficult to accurately assess its long-term efficacy and safety. The metabolism of baicalin in the human body is complex and there are differences in drug metabolism between individuals, which may lead to different responses to baicalin in different patients, making it difficult to predict therapeutic effects and develop individualised treatment plans. Baicalin inhibits liver fibrosis through multidimensional mechanisms such as antioxidant, anti-inflammatory and regulation of cell death and signalling pathways, demonstrating the advantages of multi-target therapy of traditional Chinese medicine. Future studies should focus on improving its bioavailability, elucidating key molecular mechanisms, and exploring synergistic therapeutic options with other drugs such as NAC. The combination of metabolomics and single-cell sequencing technology is expected to provide a more precise theoretical basis for the clinical application of baicalein.

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