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Role of saponins in the prevention and treatment of liver fibrosis

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Abstract: *This paper aims to investigate the mechanism of saponins in the prevention and treatment of liver fibrosis. Based on a comprehensive analysis of relevant literature, the structural characteristics, distribution and main types of saponins were described, and the research progress of saponins in inhibiting lipid peroxidation, reducing hepatic stellate cell activation and proliferation, inhibiting immune inflammatory response, regulating mitochondrial function and other related mechanisms were analyzed in detail. Studies have shown that saponins have multi-target and multi-pathway anti-fibrosis effects, which provides a theoretical basis for their application in the treatment of liver fibrosis.*

Keywords: *Saponins; Liver fibrosis; Action mechanism*

1. Introduction

Hepatic fibrosis is a pathological process caused by a variety of chronic liver diseases, characterized by excessive deposition of extracellular matrix in the liver. If the disease continues to develop, liver fibrosis can further progress to cirrhosis, a serious threat to human health[1]. At present, there are still some limitations in the clinical treatment of liver fibrosis, so it is of great practical significance to find safe and effective anti-liver fibrosis drugs. Saponins exist widely in natural plants and some Marine organisms, and have various biological activities. In recent years, more and more studies have shown that saponins show good potential in the prevention and treatment of liver fibrosis[2]. This article reviews the mechanism of saponins in the prevention and treatment of liver fibrosis in order to provide new ideas and theoretical support for the treatment of liver fibrosis[3].

2. Overview of saponins

Saponins are a class of glycosides with complex structure. The basic structure of saponins is formed by the linkage between aglycones and sugars or uronic acids. The aglycones of steroid saponins usually contain 27 carbon atoms and have a carbon frame structure such as spiral steranes or isospiral steranes[4]. The aglycones of triterpene saponins are composed of 30 carbon atoms, and the common structure types include oleane-type, urusuran-type, lupine-type, etc. Taking ginsenosides as an example, it belongs to triterpenoid saponins, whose aglycones have diverse structures, different sugar chain connection positions, sugar types and amounts, giving ginsenosides rich and diverse activities, which is also an important material basis for ginseng to have a variety of pharmacological effects[5].

Saponins are widely distributed in nature, mainly in higher plants on land and some Marine organisms. Saponins are abundant in legumes, acanthaceae, liliaceae and other genera of higher plants on land[6]. For example, ginseng and Panax notoginseng belong to the same family of plants, which are rich in saponins. There are many kinds of ginsenosides in ginseng, such as Rg1, Rb1, Rg3, etc. Panax notoginseng mainly contains ginsenosides Rg1, Rb1 and panax notosaponin R1. Among Marine organisms, sea cucumber is also an important source of saponins, which have unique structure and biological activity. There are some differences in structure and activity of saponins from different sources, which are closely related to their ecological environment and biosynthetic pathways[7, 8].

Steroidal saponins are mainly found in plants such as Liliaceae and Dioscoreaceae. The aglycones have a steroidal parent structure, and there are two configurations on the C-25 position of the parent steroid, that is, S configuration (L-type) and R configuration (D-type), corresponding to the helical sterane structure and heterohelical sterane structure respectively. Diosgenin in Dioscoreaceae is a typical steroidal saponin, which has many pharmacological activities, such as anti-inflammation,

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anti-tumor, and lowering blood lipids[9, 10]. Triterpenoid saponins are more widely distributed in the plant kingdom, and are found in many families such as Acanthaceae, legumes, and rosaceae. Saikosaponins are a common triterpenoid saponins. As a traditional Chinese medicine, saikosaponins are closely related to their effects of soothing liver and relieving depression. There are various types of saikosaponins, including saikosaponins a, b, c, d, etc. Different types of saikosaponins also have some differences in pharmacological activity[11, 12].

3. The mechanism of saponins in the prevention and treatment of liver fibrosis

3.1. Inhibit lipid peroxidation

Under normal physiological conditions, the oxidation and antioxidant systems in the body are in dynamic balance. However, when the liver is subjected to various damaging factors, such as viral infection, drug toxicity, alcohol stimulation, and so on, it will cause oxidative stress response. At this time, the liver cells will produce a large number of free radicals, such as superoxide anion free radicals , hydroxyl free radicals and so on[13]. These free radicals have strong oxidative activity and can attack polyunsaturated fatty acids on cell membranes, triggering lipid peroxidation. A series of lipid peroxidation products are produced in the process of lipid peroxidation, among which malondialdehyde (MDA) is a commonly used detection index, and the increase of its content reflects the intensification of lipid peroxidation. At the same time, free radicals can also destroy the antioxidant oxidase system in the cell, such as superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), etc., further aggravate the oxidative damage of liver cells, and ultimately lead to the occurrence and development of liver fibrosis[14, 15].

Many studies have shown that saponins can significantly regulate oxidative stress-related indexes, thereby alleviating the damage of lipid peroxidation to liver cells. For example, the total saponin of Panax notoginseng is the main active ingredient extracted from Panax notoginseng, and a number of experiments have confirmed that it can increase the activity of SOD and GSH-Px in liver fibrosis model animals, and reduce the content of MDA. SOD can catalyze the disproportionation of superoxide anion free radicals to generate oxygen and hydrogen peroxide, thus reducing the accumulation of free radicals. Gsh-px can use reduced glutathione (GSH) to reduce hydrogen peroxide to water, further scavenging free radicals. By increasing the activity of these two antioxidant enzymes, the total saponins of panax notoginseng can effectively enhance the antioxidant capacity of the body and inhibit lipid peroxidation[16, 17]. Studies have shown that the total saponins of panax notoginseng can reduce the damage of liver cells caused by oxidative stress by inhibiting lipid peroxidation, and thus play a certain role in the prevention and treatment of liver fibrosis[18].

3.2. Decreased hepatic stellate cell activation and proliferation

Hepatic stellate cells (HSCs) are an important cell type in the liver. In normal liver, HSCs are in A quiescent state and their primary function is to store vitamin A. However, when the liver is damaged, HSCs are activated, undergo a series of biological changes, and transform into myofibroblast-like cells with the ability to proliferate and secrete. After activation, HSCs proliferate and secrete a large amount of extracellular matrix (ECM), including collagen and fibronectin. Excessive deposition of ECM can lead to changes in the structure and function of liver tissue, and gradually form liver fibrosis. Therefore, the activation and proliferation of HSCs play a key role in the occurrence and development of liver fibrosis[19, 20].

Saponins can inhibit the activation of HSCs in various ways. On the one hand, saponins can down-regulate the expression of transforming growth factor-β1 (TGF-β1), platelet-derived growth factor (PDGF) and other pro-fibrotic cytokines. TGF-β1 is a potent pro-fibrotic factor, which can activate HSCs and promote their synthesis and secretion of ECM. PDGF can stimulate the proliferation of HSCs. On the other hand, saponins can also up-regulate the expression of anti-fibrotic cytokines such as bone morphogenetic protein-7 (BMP-7), which can inhibit the activation of HSCs and promote their reversal to a quiescent state. In addition, saponins can also block the signal transduction of HSCs activation by inhibiting mitogen-activated protein kinase (MAPK) signaling pathway and phosphatidylinositol-3 kinase (PI3K)/protein kinase B (Akt) signaling pathway, so as to effectively inhibit the activation and proliferation of HSCs[21, 22]. Ginsenoside Rd can inhibit the activation and proliferation of HSCs induced by OX-LDL-induced liver fibrosis[23].

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3.3. Suppress immune inflammatory response

As an important immune organ of human body, liver can cause immune inflammation when stimulated by various damage factors. Inflammatory cells, such as macrophages and lymphocytes, gather at the site of liver injury and release a large number of inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β). These inflammatory cytokines can not only directly damage liver cells, but also activate HSCs, promote their proliferation and secretion of ECM, thus aggravating the liver injury and fibrosis process. In addition, the inflammatory response can also lead to microcirculation disorders in the liver, further affecting the normal function of the liver, forming a vicious cycle[24, 25].

Saponins can regulate the immune inflammatory response through various mechanisms. First, saponins can inhibit the activation of immune cells and reduce the production of inflammatory cytokines. For example, ginsenoside Rg1 can inhibit the activation of macrophages and reduce the level of their secretion of inflammatory cytokines such as TNF-α and IL-6. Second, saponins also regulate inflammatory signaling pathways, such as the nuclear factor-κb (NF-κB) signaling pathway. NF-κB is an important transcription factor that plays a key regulatory role in inflammatory responses. Saponins can play an anti-inflammatory role by inhibiting the activation of NF-κB and reducing the expression of inflammation-related genes. In addition, saponins can also regulate the function of immune cells and promote the restoration of immune balance[26, 27]. Studies have shown that argenin can protect the liver by inhibiting the release of inflammatory cytokines, reducing the inflammatory response of the liver[28].

3.4. Regulating mitochondrial function

Mitochondria are energy factories within the cell, responsible for aerobic respiration and energy production in the cell. In the process of liver fibrosis, the structure and function of mitochondria will undergo obvious abnormal changes. On the one hand, mitochondrial membrane potential decreases, resulting in impaired mitochondrial respiratory chain function and reduced ATP production. On the other hand, the activity of the mitochondrial respiratory chain complex is reduced, and the electron transport process is blocked, resulting in the production of a large number of reactive oxygen species (ROS). Too much ROS can further damage the mitochondrial membrane and mitochondrial DNA, creating a vicious cycle. The abnormality of mitochondrial function will not only affect the energy metabolism of liver cells, lead to liver cell dysfunction, but also trigger cell apoptosis and promote the development of liver fibrosis[29-31].

Saponins regulate mitochondrial function in a variety of ways. Firstly, saponins can improve the fluidity of mitochondrial membrane and maintain the normal structure and function of mitochondrial membrane. For example, notoginseng saponin Rg1 can increase the fluidity of mitochondrial membrane and improve the respiratory function of mitochondria. Secondly, saponins can also regulate the activity of mitochondrial respiratory chain complex, promote electron transport and ATP production. Studies have shown that ginsenoside Rb1 can increase the activity of mitochondrial respiratory chain complex I, II, III, and enhance the energy metabolism capacity of mitochondria. In addition, saponins can also inhibit the swelling of mitochondria and the release of cytochrome C, thus inhibiting the occurrence of apoptosis[32, 33]. Studies have shown that Notoginseng saponin Rg1 can improve the energy metabolism of liver cells by regulating mitochondrial function, and play a certain role in the prevention and treatment of liver fibrosis[18].

3.5. Other mechanisms

In the process of liver fibrosis, the imbalance of collagen synthesis and degradation is an important reason leading to excessive deposition of ECM. Matrix metalloproteinases (MMPs) are a class of proteases capable of degrading ECM, among which MMP-1 is mainly responsible for degrading type I and type III collagen, and is one of the key enzymes regulating collagen metabolism. Tissue metalloproteinase inhibitors (TIMPs) can inhibit the activity of MMPs and thus regulate the degradation of collagen. Studies have shown that Astragalus saponin can promote the degradation of collagen by up-regulating the expression of MMP-1 and down-regulating the expression of TIMP-1, thus reducing the degree of liver fibrosis. In one experiment, rats with liver fibrosis were randomly divided into model group, astragalus low-dose group, astragalus medium-dose group and Astragalus high-dose group. After different doses of astragalus saponin intervention, the expression levels of MMP-1 and TIMP-1 in liver tissues were detected. The results showed that compared with the model group, the expression level of MMP-1 was significantly increased and the expression level of TIMP-1

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was significantly decreased in all astragaloside administration groups in a certain dose-dependent manner, indicating that Astragaloside can improve liver fibrosis by regulating the expression of collagen metabolism-related enzymes[34-36].

Gypenosides have a unique mechanism of action in anti-liver fibrosis, among which induction of hepatic stellate cell apoptosis is one of its important roles. Apoptosis is a kind of programmed cell death mode, which plays an important role in maintaining the stability of intracellular environment and the normal function of tissues and organs. In the process of liver fibrosis, inhibiting the survival of HSCs and inducing their apoptosis can reduce the production of ECM, thus easing the development of liver fibrosis. Through in vitro experiments, the researchers found that gypenosides can activate the apoptosis signaling pathway in HSCs, promote the release of cytochrome C from mitochondria into the cytoplasm, activate apoptosis-related proteases such as Caspase-3, and ultimately lead to the apoptosis of HSCs. In the experiment, HSCs were divided into normal control group, gypenoside low-dose group, gypenoside medium-dose group and gypenoside high-dose group. After culture for a period of time, the apoptosis rate of HSCs was detected by flow cytometry. The results showed that compared with the normal control group, the apoptosis rate of HSCS in each gypenoside administration group was significantly increased. With the increase of dose, the apoptosis rate increased gradually. At the same time, Western blot results showed that the expression levels of fibrosis-related proteins such as α-SMA were significantly reduced, indicating that gypenosides effectively inhibited the development of liver fibrosis by inducing the apoptosis of HSCs[37, 38].

4. Conclusion and prospect

In summary, saponins have various mechanisms of action in the prevention and treatment of liver fibrosis. They can inhibit lipid peroxidation and reduce the damage of liver cells caused by oxidative stress. Reduce the activation and proliferation of hepatic stellate cells, inhibit the excessive secretion of extracellular matrix; Inhibit the immune inflammatory response and reduce the damage of inflammatory cytokines to the liver; Regulate mitochondrial function and maintain normal energy metabolism of hepatocytes; In addition, it can also play a comprehensive role in anti-liver fibrosis by regulating collagen metabolism and inducing hepatic stellate cell apoptosis.

Although the research of saponins in the prevention and treatment of liver fibrosis has made some progress, there are still many shortcomings. For example, most studies focus on the mechanism of action of a single saponin component, and there are relatively few studies on the synergistic effects between complex saponin mixtures. In addition, although multiple action targets of saponins have been identified, the network regulatory relationship between these targets and their dynamic changes in the overall pathophysiological process are not fully understood. Future studies can further explore the synergistic mechanism between saponins, and comprehensively analyze the molecular network regulation mechanism of saponins in the prevention and treatment of liver fibrosis by combining with multidisciplinary techniques such as systems biology. At the same time, the pharmacokinetics of saponins should be strengthened to clarify their absorption, distribution, metabolism and excretion processes in vivo, so as to provide a more solid theoretical basis for their clinical application. It is believed that with the deepening of research, saponins are expected to become potential drug targets for the treatment of liver fibrosis, and provide new strategies and methods for the prevention and treatment of liver fibrosis.

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