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Research Progress of Traditional Chinese Medicine in Regulating Intestinal Flora in the Treatment of Liver Injury

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Abstract: ***Liver injury can be divided into three types: physical liver injury, viral liver injury and chemical liver injury, and the pathogenesis of each type of liver injury is related to the imbalance of intestinal flora. Traditional Chinese medicine can treat liver injury by improving the structure of microflora, regulating the number of microflora and adjusting the homeostasis of intestinal flora. This article provides a basis for a general review of the mechanism of traditional Chinese medicine in the treatment of liver injury by regulating intestinal flora in recent years.***

Keywords: Traditional Chinese medicine, Intestinal flora, Liver injury, Liver protection**.**

1. Introduction

The liver is not only the main place of human metabolism, but also the main organ for detoxification and excretion of endogenous and exogenous compounds, and it is also a way to completely decompose drugs and excrete them out of the body through a series of biological transformations such as oxidation, reduction, hydrolysis and binding, in order to ensure resistance to the invasion of harmful substances and the normal operation of human function, so as to achieve the so-called liver "detoxification" function [1,2]. Liver injury can be divided into three categories: physical liver injury, viral liver injury and chemical liver injury. Physical liver damage includes liver rupture caused by car accidents and fights, while viral liver damage is mainly caused by abnormal liver function caused by hepatitis B, hepatitis C and other viruses; chemical liver injury is caused by alcohol, some chemicals and drugs and other hepatotoxic substances. On the other hand, liver injury is enough to pose a threat to human life and health, and effective control such as mild liver injury through drugs is expected to return to normal, while a series of discomfort symptoms or abnormal changes in liver function indexes caused by a variety of pathogenic factors can lead to liver failure. The mechanism of liver injury is complex, and the final liver injury caused by different pathological factors will also cause apoptosis and necrosis of hepatic parenchyma cells in different degrees, including the synergistic participation of liver microenvironment and multiple pathways. Its pathogenesis is mainly concentrated in the repeated "second blow" caused by hepatocyte inflammation induced by alcohol and chemicals, toxic bile acid accumulation, bile duct activation and oxidative stress, inflammatory reaction leads to bile duct obstruction and excessive drug intake leads to oxidative stress leading to abnormal liver metabolism [3]. Liver is not only the main pathway of drug metabolism, but also the main organ of drug injury. If liver damage develops further, it will cause hepatocyte death, liver cirrhosis and even liver cancer and other serious diseases. How to effectively treat liver damage caused by various injury factors has become the focus of pre-research [4].

2. The Relationship between Liver and Intestinal Flora

The intestinal tract not only functions as a digestive organ, but also has a huge complex system of more than 1014 microbes. According to related studies, intestinal flora can be divided into three types, including symbiotic flora (dominant bacteria), conditional pathogenic bacteria and pathogenic bacteria. Under normal physiological conditions, each intestinal microflora plays its physiological role in co-existence with the host. The two are in a state of relative balance, but once this physiological balance is broken, the imbalance of flora will lead to disease. Modern medicine believes that the liver and the intestinal tract are two important organs, and there is a two-way communication pathway between them, which is called "enterohepatic axis". Due to the existence of enterohepatic axis, there is a close relationship between the occurrence and development of chronic liver disease and flora imbalance [5]. With the development of modern medicine for hepatointestinal axis One-step research, It is found that there is a close relationship between chronic liver disease and intestinal flora, and intestinal bacteria play an important role in maintaining immune and metabolic homeostasis and resisting pathogens. The imbalance of flora is related to the pathogenesis of many inflammatory diseases and infections [6], so it has become a potential target to treat liver diseases by regulating intestinal flora. In modern medicine, there are no specific drugs for the treatment of liver injury, and most of them take the improvement of dietary structure, drug treatment (hepatoprotective drugs, anti-inflammatory drugs), exercise and so on. The patients with serious symptoms should stop taking drugs so as not to further aggravate the irreversible harm caused by liver injury. Compared with western medicine in the treatment of liver injury, traditional Chinese medicine, as a treasure of our country, has obvious advantages in the treatment of diseases, such as high degree of cooperation of patients, less clinical adverse reactions and low treatment cost [7]. Traditional Chinese medicine and its active components have unique advantages in the prevention and treatment of liver injury by regulating intestinal flora, with obvious curative effect and certain safety. Therefore, focusing

on the relationship between intestinal flora and liver injury, this paper reviews the regulation of intestinal flora by traditional Chinese medicine to improve liver injury, in order to provide more reference for the research and development of drugs for regulating intestinal flora and anti-liver injury.

3. Understanding of Liver Injury in Traditional Chinese Medicine

According to the surface of relevant research, there is no specific record of the name of liver damage in traditional Chinese medicine, but it can be classified as "hypochondriac pain on both sides", "jaundice", "liver", "ascites" and so on. In the *Inner Canon of Huangdi* of *plain Questions · six sections of the Tibetan image theory*: "the liver is strong, the master is strong, he can not only defend against foreign aggression, but also be resourceful, just like a general, so he is the official of a general." *Miraculous Pivot*: "the liver stores blood…… Liver qi leads to anger, liver qi leads to subcostal pain". *Shennong's Classic of Material Medical*: "the pain under the two sides of the liver disease leads to less abdomen, which makes people afraid, but if they are empty, they have nothing to see and hear, and fear is like being arrested. " In the Qing Dynasty, Li Guanxian *knowing the doctor must distinguish*" said: "the five internal organs of a man, but the liver is easy to move and difficult to rest. The only disease of the liver, that is, it extends to his dirty. Its unpredictable, can not be fully described, its exchanges are capricious, incredible. " The liver is the official of the general, such as the chess car, let it run rampant, do not dare to be. The diseases of the five internal organs are most common, especially liver qi. *Synopsis of the Golden Chamber*: "if the husband treats those who are not sick, when he sees the disease of the liver and knows that the liver spreads to the spleen, he should first consolidate the spleen. " Here focus on the relationship between the liver and spleen, liver disease spread the spleen to describe the treatment of liver deficiency, in order to treat the liver tonifying the spleen to describe the treatment of liver deficiency. The loss of liver qi is easy to invade the spleen, so the treatment should also pay attention to enrich the spleen soil while soothing the liver, if the time is when the temper is prosperous, or meet the person with a strong temper, it is another matter. Most of the patients with liver injury have insufficient body endowment or irregular diet and rest for a long time, resulting in long-term strain and damage to the liver. Based on many years of clinical experience, Professor Zhao Xueyin believes that the imbalance of liver and spleen is an important pathological feature in the development of liver disease. combined with the particularity of patients' symptoms and signs, he puts forward that the key to the pathogenesis of drug-induced liver damage (DILI) is the loss of liver leakage and spleen movement [8]. In the development of DILI, pathological factors such as qi stagnation, blood stasis, phlegm-dampness, dampness and heat influence each other. Internal and external evil toxin accumulates in the body, which can lead to liver failure and liver cirrhosis for a long time. Zhang Yiyi et al[9] thought that the main pathogenesis of drug-induced liver injury was drug depression and heat, fumigation of liver, gallbladder, spleen and stomach, and abnormal movement of spleen and stomach. Guo Zhonghua [10] believes that for drug-induced liver damage that has not been cured for a long time, in addition to taking into account the main syndrome of yellowing of dampness-heat in the liver and gallbladder, At the same time, we should also know that liver disease spreads to the spleen, the connection between the liver and spleen, long-term illness does not heal at the same time to take into account the situation of liver-yin, overall thinking in order to prevent the further development of liver disease.

4. Effect of Traditional Chinese Medicine Extract on Regulating Intestinal Flora on Liver Injury

4.1 Dendrobium Candidum

Dendrobium candidum is the dry stem of Dendrobium officinale Kimura et Migo, which belongs to Dendrobium of Orchidaceae. It has the functions of anti-aging, anti-tumor, reducing hypoglycemia and improving immune function [11]. ZhangJ et al. [12] in order to study the mechanism of extract of Dendrobium candidum (DOFE) on alcoholic fatty liver, the extract of Dendrobium candidum (DOFE) was used to treat alcoholic fatty liver in mice. The composition of intestinal flora in feces of mice was analyzed by 16SrRNA gene sequencing. The results showed that there was no significant difference between CTRL group, AFLD group and low dose group after supplementation of DOFE, but the Chao index of intestinal flora in middle dose group and high dose group increased significantly. DOFE increased the species richness of intestinal microbiota in mice, and DOFE significantly increased the relative abundance of mucoprotein Ackermania, indicating that DOFE can improve the composition of intestinal microorganisms, which may be a potential target for the protective effect of DOFE. It is further demonstrated that Acetobacter mucinophilus plays an important role in preventing alcohol-induced liver injury and improving intestinal screen barrier function by degrading intestinal mucin and improving intestinal barrier function.

4.2 Yanzhou Selaginella Officinalis

Yanzhou Selaginella officinalis is the whole grass of Selaginella officinalis, which has the functions of clearing heat and dampness, relieving cough, detoxification and so on. Yanzhou Selaginella officinalis is often used as a folk drug against hepatitis and pneumonia [13]. Wen Yangmin et al. [14] after the aqueous extract of Selaginella officinalis was applied to mice with acute alcoholic liver injury induced by absolute ethanol, it was found that Yanzhou Selaginella group could increase the relative abundance of lactic acid bacteria, mycobacteria and Ekmania, while reduce the relative abundance of Helicobacter and Erysipelatoclostridium to restore intestinal flora imbalance, and reduce the release of inflammatory factors such as TNF-α by inhibiting the activation of NF-κ B in liver tissue. To achieve the effect of relieving liver inflammation and protecting liver.

5. Effect of Active Components of Traditional Chinese Medicine on Regulating Intestinal Flora on Liver Injury

5.1 Tripterygium, also known as Pleurotus ostreatus, is a flaky algae of the genus Candida of Cyanophyta, which has the functions of heat-clearing and detoxification, antibacterial and anti-inflammatory, immune regulation and so on.

Polysaccharide of Tripterygium wilfordii (NCVP) is one of the biological activities of Tripterygium, which has many biological activities, such as anti-tumor, promoting wound healing, probiotics and so on [15]. In order to further analyze the effect of polysaccharides from Tripterygium wilfordii on intestinal flora of mice with alcohol-induced liver injury, Liu Shuo [16] found that NCVP could inhibit the production of transaminase, inhibit lipid peroxidation, enhance antioxidant activity and protect L02 cells from alcohol injury. At the same time, NCVP can alleviate the disorder of intestinal flora caused by alcohol. at the family level, NCVP group can effectively inhibit the overgrowth of Helicobacteraceae and Ruminococcaceae. In addition, NCVP group could increase the relative abundance of Prevotellaceae, lactobacillaceae and lachnospiraceae. At the generic level, the relative abundance of harmful bacteria Helicobacter decreased significantly, and promoted the growth of Prevotellaceae-UCG-003 and Desu lfovibrio. This study further proved that NCVP can reduce the relative abundance of harmful bacteria, promote the growth of probiotics and increase their species diversity, thus regulating the balance of intestinal flora has a protective effect on alcoholic liver injury. It is suggested that Tripterygium polysaccharide can reduce liver inflammation by regulating intestinal flora disorder and inhibiting lipid peroxidation.

5.2 licorice, Xingping, return to the heart, lung, spleen and stomach meridian, the main efficacy is to tonify the spleen, expectorant and cough, and reconcile various drugs. It can not only ease the intensity of the drug or reduce the toxic and side effects, but also reconcile the spleen and stomach. Glycyrrhizic acid is the main active component of licorice. According to modern medicine, it has been found that glycyrrhizic acid has the pharmacological effects of anti-virus, anti-tumor, anti-inflammation and sterilization [17]. Yang Biqian et al. [18] through the action of Glycyrrhiza uralensis on cisplatin-induced liver injury in rats, it was found that Glycyrrhiza uralensis increased the richness of Bacteroides and decreased the ratio of thick-walled bacteria to Bacteroides, indicating that Glycyrrhiza uralensis can regulate the intestinal flora of cisplatin-induced liver injury and down-regulate the expression of IL-1 β, IL-6, TNF- α-related proteins to alleviate cisplatin-induced liver injury. To provide more basis for the clinical application of Glycyrrhiza uralensis and the development of anti-DILI drugs. Wang Jing [6] after the action of glycyrrhizic acid on the rat model of CCl4 liver injury, it was found that glycyrrhizic acid could reduce the levels of AST and ALP in the serum of rats, and found that the high and middle dose groups of glycyrrhizic acid could significantly increase the relative abundance of beneficial bacteria such as Lactobacillus, Lactobacillus and Lactobacillus, while significantly reduce the relative abundance of pathogenic bacteria into Bacteroides, Pseudomonas and Pseudomonas. On the contrary there was little change in intestinal flora structure in low dose glycyrrhizic acid group glycyrrhetinic acid group and positive control group. It is further concluded that glycyrrhizic acid can improve the abundance and evenness of flora, gradually improve the intestinal microflora diversity and species composition of rats with chronic liver injury, and alleviate liver inflammation. Then Wang Jing [19] further studied the effects of total saponins of licorice and aqueous extract of licorice on intestinal flora of rats with liver injury on the basis of the above experiments. After acting on the rat model of liver injury induced by CCl4, it was found that total saponins of licorice, water extract of licorice and biphenyl diester could reduce the levels of ALT and AST in serum of rats with liver injury induced by CCl4. The intestinal microflora of rats in the total saponins group and water extract group were different from those in the model group, in which the microflora of Spirillaceae, Bacteroides S24-7 and Lactobacillaceae changed significantly in the total saponins group, because they could produce short-chain fatty acids and scavenge free radicals, which further confirmed that licorice could alleviate the imbalance of intestinal flora and intestinal and liver inflammation caused by liver injury.

5.3 Salvia miltiorrhiza is the dry root and rhizome of Radix Salviae Miltiorrhizae, which is slightly cold and bitter in taste, entering the heart and liver meridians, as a commonly used medicine for promoting blood circulation and removing blood stasis, as well as cooling blood, clearing the heart and relieving annoyance, dredging menstruation and relieving pain. Salvianolic acid B is one of the main active components in the water-soluble extract of Salvia miltiorrhiza, which has the effects of anti-liver fibrosis, anti-oxidation, anti-tumor, anti-apoptosis and so on [20]. Tian Li et al. [21] implanted hepatoma H22 cells into mice and induced hepatoma H22 mice to form hepatoma H22 mice. It was found that Salvianolic acid B could regulate the expression of TLR4, MyD88 and NF- κ B genes and proteins, Inhibition of tumor grow; Compared with the model group, the diversity of intestinal flora in the high dose Salvianolic acid B group was significantly higher than that in the model group. At the gate level, the relative abundance of Bacteroides in the experimental group was significantly increased, while the relative abundance of Bacteroides in the experimental group was significantly lower than that in the model group. In the experimental group, bacteria such as Rumen Bacteriaceae and Spirillaceae increased significantly. The results showed that Salvianolic acid B could increase the relative abundance of intestinal beneficial bacteria and reduce the relative abundance of harmful bacteria, indicating that Salvianolic acid B could improve the changes of intestinal flora caused by tumor, regulate intestinal flora and improve intestinal environment. it has a positive regulatory effect on intestinal microflora. It is suggested that Salvianolic acid B can alleviate the liver injury induced by H22 by regulating the abundance of intestinal flora and regulating the gene and protein expression of TLR4, MyD88 and NF- κ B.

5.4 Alginate oligosaccharide (AOS) is a kind of acidic oligosaccharide, which is the product of degradation of fucoidan. According to modern research, algal oligosaccharides have anti-tumor, enhance immune regulation function, antioxidant activity, anti-inflammatory activity, promote the metabolism and proliferation of beneficial bacteria and antibacterial activity [22]. Wang Yutian et al. [23] after AOS was applied to the liver injury of mice induced by emetic toxin (DON), it was found that the addition of AOS could improve the symptoms of pathological injury. The content of MDA in liver of DON group was significantly higher than that of C ON group, while AOS could inhibit the increase of MDA content and increase the activity of T-SOD in liver. Therefore, AOS can reduce the secretion of inflammatory factors caused by DON, alleviate the inflammatory injury of the body, neutralize the oxidative

stress toxicity of DON, and promote the balance of redox metabolism in mice to reduce liver inflammation.

5.5 Gardenia, cold in nature, return to the Heart and Lung Sanjiao Meridian, its main effects are clearing heat and dampness, cooling blood and detoxification, purging fire and eliminating annoyance. Polysaccharides from Fructus Gardeniae (GPS) is the main active component of Gardenia jasminoides. It has been found that it has a variety of pharmacological effects, such as anti-inflammation, anti-oxidation, anti-tumor, enhanced immunity and so on [24]. Fang Shuo [25] Gardenia jasminoides polysaccharides was applied to mice with acute cholestasis induced by ANIT. At the gate level, the dominant bacteria such as Bacteroides and thick-walled bacteria in the experimental group increased significantly, and the abundance of Proteus and verruca was inhibited. The composition of intestinal flora in the experimental group was more similar to that in the normal group, while the relative abundance of intestinal flora in the model group changed significantly. At the genus level, the abundance of Acetobacter, Alloprevotella, norank_f_Bacteroides and norank_f_Lachnospiraceae increased in the experimental group, and the metabolism of bile acid in hepatocytes was accelerated by up-regulating the expression of liver nuclear receptors FXR and PXR and metabolic enzyme Cyp3a11. It is suggested that Zhizi polysaccharide can also promote the excretion of bile acid from hepatocytes to reduce cholestasis and regulate the microflora to reduce liver injury.

6. Effect of Traditional Chinese Medicine Compound Prescription on Regulating Intestinal Flora on Liver Injury

6.1 Jiedu Hugan Tongluo Recipe

Li Sitong et al. [26] added and subtracted Yinchenhao decoction, Xiaoyao Powder and Xiao Chaihu decoction, and made "jiedu Hugan Tongluo prescription", which was composed of Bupleurum, raw licorice, Schisandra, wine and Scutellaria baicalensis, Radix Astragali, fried Radix Paeoniae Alba, Radix Paeoniae Alba, Yinchen, Radix Salviae Miltiorrhizae, Radix Salviae Miltiorrhizae, Radix et Rhizoma Rhei. After "jiedu Hugan Tongluo recipe" was used in mice with liver injury induced by APAP, the results showed that "jiedu Hugan Tongluo recipe" could significantly alleviate the liver function of mice and the pathological injury of liver and intestine, increasing the relative abundance of Bacteroides, S24-7 and Spirillaceae, and regulating the expression levels of occludin and ZOmur1 protein, and further speculating that "jiedu Hugan Tongluo recipe" may achieve the purpose of treating DILI by restoring the imbalance of intestinal flora, repairing the injured intestinal mucosa and reducing intestinal permeability.

6.2 Jiedu Hugan Recipe

Hu Weiwei et al. [27] on the basis of Yinchenhao decoction, Xiao Chaihu decoction and Xiaoyao pills, add and subtract the self-made "detoxification and liver protecting prescription". Its drug composition: Bupleurum, Schisandra chinensis, raw licorice 10g each, fried peony, fried Atractylodes macrocephala, Salvia miltiorrhiza, raw astragalus, Fructus Rehmanniae, Yinchen 15g each, Tianji yellow 30g. The "jiedu Hugan recipe" was used to treat the mice with drug-induced liver injury induced by APAP. The results showed that the jiedu Hugan recipe could significantly reduce the contents of ALT and AST in the serum of mice, thus improving the pathological injury of the liver. At the same time, it was found that the relative abundance of Bacteroides increased significantly in the experimental group, while the relative abundance of Streptomyces and Proteus and the value of Fmax B decreased significantly in the experimental group, indicating that jiedu Hugan recipe may regulate the structure of intestinal flora, slow down the inflammation of the liver and play a role in protecting the liver.

6.3 Decoction of Herba Artemisiae Scopariae and Four Drugs with poria

Wang Manfei [28] used decoction of Herba Artemisiae Scopariae and Four Drugs with poria to study alcohol-induced liver injury in rats. Decoction of Herba Artemisiae Scopariae and Four Drugs with poria is composed of seven herbs: **Herba Artemisiae Scopariae, Rhizoma Atractylodis Macrocephalae, tuckahoe, alisma alisma, Polyporus umbellata, gardenia fruit and Fructus Aurantii.** It was found that Decoction of Herba Artemisiae Scopariae and Four Drugs with poria could reduce hepatic inflammatory reaction, improve intestinal permeability, repair intestinal mucosal barrier function, reduce endotoxin accumulation and improve liver function by regulating the expression of Occludin and ZO-1 protein and increasing the content of sIgA and pIgR in jejunal mucosa of ALD rats.

6.4 Jiawei Xiaozhi Ligan Recipe

Liao Xiaomei et al. [29] the rat NAFLD model was established by high-fat diet induction (high-fat feed, HFD) to explore the mechanism of non-alcoholic fatty liver disease induced by high fat. Jiawei Xiaozhi Ligan recipe: Coptis 6g, Bupleurum 30g, Radix Paeoniae Alba 10g, Guangyujin 15g, Rhizoma Curcumae 10g, Hawthorn 10g, Salvia miltiorrhiza 10g, rhubarb 15g, fried Fructus Aurantii 10g, alisma alisma 10g, fried Atractylodes macrocephala 15g and Poria 15g. The results show that Jiawei Xiaozhi Ligan recipe can protect liver injury in rats, and its mechanism may be related to increasing the abundance and diversity of intestinal flora, regulating the balance of species proportion, improving intestinal permeability, regulating dyslipidemia and improving liver injury, thus inhibiting the further development of NAFLD.

6.5 Four-Ingredient Decoction for Spleen Qi Deficiency

You Hongjuan et al. [30] induced alcoholic liver injury in mice with ethanol solution and treated with four-Ingredient Decoction for Spleen Qi Deficiency. The results showed that the decoction group could reduce the levels of ALT, AST, ALP, T-BIL and TG, improve the pathological damage of liver and spleen, increase the content of beneficial bacteria Dubosiella, Bifidobacterium, Allobaculum and reduce the pathogen. It is suggested that the protective mechanism of four-Ingredient Decoction for Spleen Qi Deficiency decoction in improving alcoholic liver injury is mainly manifested in regulating lipid metabolism, restoring liver function and increasing the abundance of beneficial microflora in

regulating microflora disorder.

To sum up, at present, the research on the regulation of traditional Chinese medicine on intestinal flora of liver injury is increasing day by day. The active components of traditional Chinese medicine, the extract of traditional Chinese medicine and the compound prescription of traditional Chinese medicine have been proved to improve the structure of intestinal flora, regulate the number of microflora and restore the homeostasis of microflora so as to protect the liver injury. Because traditional Chinese medicine has obvious advantages such as multi-components and multi-targets, and intestinal flora is a huge microorganism, the application of traditional Chinese medicine to inhibit intestinal mucosal permeability and improve liver inflammation to alleviate liver injury has become a new treatment model. However, at present, there are still the following problems in this study: There is a lack of objective and unified standard for TCM syndrome differentiation of each classification of liver injury, which hinders the formation of a unified diagnosis and treatment system; 2) Most of the compound prescriptions of traditional Chinese medicine are empirical prescriptions, which lack the support of a large number of clinical observation data and are not convincing enough, and their scientific nature still needs to be studied. 3)The dosage of traditional Chinese medicine varies from person to person, and different doses also have an effect on intestinal flora. The problem of how to control the dose of traditional Chinese medicine remains to be further improved. 4) There are still some problems in the research in this area, such as insufficient sample size, significant individual differences, imperfect experimental design, inconsistency between syndrome differentiation standard and syndrome model, and the study of characteristic flora of different syndromes remains to be improved. The research on targeted treatment of intestinal microflora and its metabolites has opened up a new idea and a new method for the treatment of liver disease in the future. It is hoped that there will be more extensive and in-depth studies to clarify the more detailed effects of intestinal microflora and their metabolites in liver injury, so as to establish a specific treatment suitable for individual intestinal microflora targeting.

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