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Research Progress on the Regulation of Intestinal Flora by Traditional Chinese Medicine in the Treatment of Metabolic Associated Fatty Liver Disease

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Abstract: Metabolic associated fatty liver disease (MAFLD) is a metabolic syndrome manifestation in the liver, and its pathogenesis has not been fully elucidated. Numerous studies have shown that the development of MAFLD is closely related to intestinal flora dysbiosis, and intestinal flora is considered a new target for clinical treatment of MAFLD. At present, the efficacy of traditional Chinese medicine (TCM) in treating MAFLD based on intestinal flora is widely recognised, and the authors summarised the research on the regulation of intestinal flora by TCM in the treatment of MAFLD in recent years, in the hope that it will be helpful to the treatment and research of MAFLD.

1. Introduction

With the improvement of people's living standards, dietary habits and structures have also changed, which has led to the increasing prevalence of metabolic associated fatty liver disease (MAFLD) globally, and it has rapidly become the world's largest chronic liver disease [1]. MAFLD, formerly known as non-alcoholic fatty liver disease (NAFLD), is a metabolic disorder in which dysfunction of hepatic fat metabolism causes excessive accumulation of fat [2-3]. Patients with MAFLD may have no obvious discomfort in the early stage, so they do not pay attention to it, so that some of them develop into cirrhosis, and even evolve into hepatocellular carcinoma (HCC) [4], as shown in Figure 1. At present, there is still a lack of targeted drugs for the treatment of MAFLD, which mainly focuses on symptomatic treatments such as diet control, exercise and weight loss, lipid and glucose lowering, and hepatoprotection. Combined with relevant studies at home and abroad, it has been found that intestinal flora disorders play an important biological function in a variety of pathological and physiological processes such as MAFLD, and are involved in the occurrence and development of MAFLD through a variety of pathways, and intestinal flora is considered to be a new target for the clinical treatment of MAFLD. The authors summarised and reviewed the studies on the regulation of intestinal flora by Chinese medicine for the treatment of MAFLD in recent years.

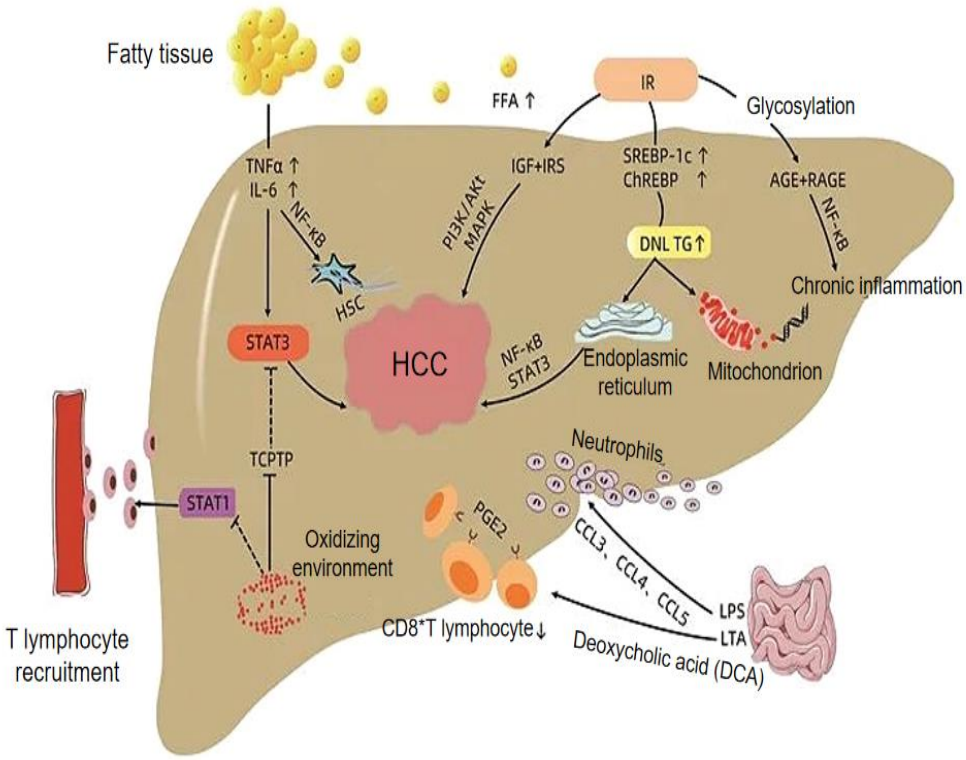

Figure 1: The pathogenesis of NAFLD related HCC

2. MAFLD and intestinal flora

2.1. The pathogenesis of MAFLD

The pathogenesis of MAFLD is very complex, and there is no clear medical statement on this, which still needs to be explored in depth. The "second strike" theory was widely accepted in the early days [5], but since the "second strike" theory has not fully elucidated the pathogenesis of MAFLD, many scholars have begun to accept the "multiple strikes" theory. Many scholars have begun to accept the "multiple-strike" theory, which suggests that the pathogenesis of MAFLD involves multiple aspects, including intestinal flora disorders, lipid metabolism disorders, lipotoxicity, mitochondrial dysfunction, endoplasmic reticulum stress disorders, and other mechanisms that act on the population and synergise with each other to participate in the occurrence and development of MAFLD [6]. With the deepening of research, it has been found that intestinal flora plays an important role in the occurrence and development of MAFLD [7].

2.2. Gut-liver axis

Marshall proposed the concept of "gut-liver axis" in 1998, and since then the relationship between the gut and the liver has received widespread attention [8]. The gut and liver are closely related in biology and anatomy. Biologically, the common origin of the two is the anterior intestinal endoderm, and anatomically, the two are connected through the portal vein [9]. Therefore, food antigens, bacteria, bacterial metabolites and toxins produced in the gut may directly flow into the blood circulatory system through the digestive barrier, and then reach the liver through the portal vein, thus leading to the immune-inflammatory response of liver function and accelerating the occurrence and

development of MAFLD [10-11]. Metabolic disorder caused by intestinal microbial imbalance is one of the main causes of MAFLD, and the gut-liver axis is an important part of it [12].

2.3. Relationship between intestinal flora disturbance and MAFLD

There are hundreds of millions of microflora in the human gut, which is characterized by diversity, dynamics and complexity. Intestinal microflora is an important part of the gastrointestinal microecology, which can digest food, regulate immunity, participate in metabolism and other processes [13]. Under normal circumstances, the microbes in the gut are dynamically balanced, with both beneficial bacteria and pathogenic bacteria, and each bacteria community checks and balances with each other. Intestinal flora is easily affected by many factors such as diet, drugs, alcohol, environment and genetics. If the balance among various flora is broken, the intestinal flora will be disrupted, further resulting in intestinal mucosal barrier damage and increased permeability [14].

Through animal experiments, Chu [15] found that the imbalance of intestinal flora significantly affected the development of MAFLD. Bacteria, endotoxins and metabolites in the intestine entered the liver along with the portal vein, resulting in impaired liver function, while the liver would release a series of inflammatory factors, which in turn caused intestinal damage, and so on, resulting in a vicious cycle.

3. The effect of TCM on regulating intestinal flora on MAFLD

TCM believes that the small intestine has a function of secreting and clearing turbidity, and its "secreting function" corresponds to the "intestinal barrier", "clearing turbidity function" and "clearing intestinal endotoxins". Chinese herbs are mostly taken orally in the form of decoction, granules, pills, etc. Although the ingredients are not easy to enter the blood, many studies have found that Chinese herbs produce metabolic reactions with various intestinal microorganisms. The monomer, active ingredient and compound of Chinese herbs can regulate intestinal flora, restore the diversity of intestinal microorganisms, and maintain intestinal microecological balance. It plays a crucial role in the treatment of MAFLD, revealing that the regulation of intestinal flora by TCM is an important way to treat MAFLD [16-19].

3.1. TCM monomers and active ingredients regulate intestinal flora in the treatment of MAFLD

Some studies have summarized the mechanism of cassia seed to protect the liver. The alcohol extract of cassia seed and total aglycoid extract of cassia seed were given to MAFLD mouse model, and it was found that they can increase the diversity of intestinal flora, increase the relative abundance of beneficial bacteria, and reduce the relative abundance of harmful bacteria based on the gut-liver axis. Promote the expression of Occludin, ZO -1mRNA, and ZO-1 protein in the intestinal tissue of MAFLD mice, improve the imbalance of intestinal microorganisms, protect the intestinal wall barrier, reduce the inflammatory response, and thus improve the further peroxidation accumulation of liver lipids [20]. Berberine is a typical Chinese herbal ingredient with antimicrobial activity, which is present in drugs such as cypress and yellow dock, and is commonly used clinically against intestinal bacterial infections. Berberine has the ability to regulate hepatic metabolism by promoting the expression of the colonic mucosal tight junction proteins claudin-1 and ZO-1 mRNA, decreasing the expression of MLCK mRNA, inhibiting the translocation of claudin-2, and protecting the epithelial barrier of the intestinal mucosa, and thus exerting a protective effect on the liver [21-22].

The main active ingredient of Ganoderma lucidum is total naphthoquinone. Gong [23] found through experiments that total naphthoquinone in Ganoderma lucidum can regulate the intestinal flora of mice with MAFLD induced by high fat diet. The abundance of firmicutes in MAFLD mice given

total naphthoquinone increased, while the abundance of Bacteroidetes decreased, which improved the diversity and richness of intestinal microorganisms. The microecological structure of intestinal flora in MAFLD mice was improved.

Diammonium glycyrrhizate is the main component of licorice root extract, which has anti-inflammatory and liver protective effects. Study [24] found that diammonium glycyrrhizate can significantly change the composition of intestinal microflora in MAFLD mice, reduce the abundance of endotoxin-producing bacteria and the ratio of harmful bacteria, and increase the abundance of probiotic lactobacillus and short-chain fatty acid producing bacteria. Thus, it can promote the production of short-chain fatty acids, strengthen the intestinal barrier, and further prevent and control MAFLD.

The main active ingredient of gypenoside is the total saponins of gypenoside, which exerts its efficacy through the interaction between the host gut and intestinal flora. Zhong [25] found that the diversity of intestinal microbes in MAFLD rats induced by high fat diet was restored after the intervention of the total saponin of gypenoenoside, and the total saponin of gypenoenoside could promote the proliferation of beneficial bacteria, inhibit the growth of harmful bacteria, decrease the relative abundance of firmicutes by increasing the relative abundance of Bacteroidetes, and then reduce its ratio. At the genus level, gypenosides can promote the growth of SCFAs producing bacteria, regulate the metabolism of short-chain fatty acids, and effectively protect the occurrence and development of MAFLD. (Table 1)

Table 1: TCM monomers and active ingredients regulate intestinal flora

TCM Monomers	Active ingredient	Related Findings	Reference
Cassia seed	Alcohol extract of cassia seed and total aglycone extract of cassia seed	Promote the expression of Occludin, ZO-1mRNA, ZO-1 protein, and regulate the abundance and composition of intestinal microorganisms with specific metabolic functions.	[20]
Cypress and yellow dock	Berberine	Elevate the expression of claudin-1 and ZO-1 mRNA, decrease the expression of MLCK mRNA, and inhibit the translocation of claudin-2.	[21-22]
Ganoderma lucidum Licorice root	Total naphthoquinone	The abundance of firmicutes increased and Bacteroidetes decreased, which increased the diversity and richness of intestinal microorganisms.	[23]
Gypenoside	Diammonium glycyrrhizate	Improve the composition of intestinal flora, increase the abundance of beneficial bacteria, reduce the abundance of harmful bacteria, and strengthen the intestinal barrier.	[24]
Gypenoside	The total saponins of gypenoside	Restore the diversity of intestinal flora, promote the proliferation of beneficial bacteria, inhibit the growth of harmful bacteria, and regulate the metabolism of short chain fatty acids.	[25]

3.2. TCM compounds regulate intestinal flora in the treatment of MAFLD

Chaihushugang powder, a famous formula in ancient China, is often used to treat diseases of the

liver, hepatobiliary system, such as "dystocia" and "gallbladder distension", etc. Xie [26] found that Chaihushugang powder can significantly improve the intestinal flora of patients with MAFLD, and the treatment of Chaihushugang powder significantly increased the abundance of Bifidobacterium and Lactobacillus. Lactobacillus abundance increased significantly, while Enterobacteriaceae and Enterococcus abundance decreased significantly, increasing the beneficial flora and decreasing the harmful flora for the treatment of MAFLD.

Li [27] applied 16SrRNA technology and metabolomics to jointly analyse the intestinal flora of MAFLD model rats, and found that yinchenhao decoction could regulate the intestinal flora disorders in high-fat diet-induced MAFLD model rats. This experiment demonstrated that yinchenhao decoction had an ameliorative effect on the abnormal expression of glycerophospholipid metabolic pathway, reduced the number of Staphylococcus and Streptococcus, and increased the content of glutathione in rats with MAFLD, which confirms that yinchenhao decoction has a bi-directional effect on the treatment of MAFLD, and that it can improve the diversity of intestinal microorganisms through the increase in the number of probiotics. The study confirmed that yinchenhao decoction could have a bidirectional effect on the treatment of MAFLD by increasing the number of probiotics and improving the diversity of intestinal microorganisms, as well as having a significant retuning effect on a number of genera, which proved that yinchenhao decoction could have a therapeutic effect on MAFLD by interfering with the relevant intestinal flora. A study found [28] that the relative abundance of intestinal thick-walled bacillus phylum would decrease and anaphylactic bacillus phylum would increase in patients after treatment through Added yinchenhao decoction, which suggested that Added yinchenhao decoction might improve MAFLD by regulating intestinal microorganisms and further regulating the body's liver function and inflammation.

Yan [29] found that the abundance, homogeneity and diversity of intestinal flora of MAFLD rats were significantly decreased by high-throughput histological techniques such as 16SrRNA, and the use of Huangqin Decoction showed a significant improvement in the body mass, blood lipids and liver function of MAFLD rats, and it could increase the abundance, homogeneity and diversity of the intestinal flora, and promote the restoration of their intestinal flora to the normal level, and this study confirmed the the relevance of Huangqin Decoction to the therapeutic effect of MAFLD through the improvement of intestinal flora dysbiosis in MAFLD rats.

Huazhirougan Granules are commonly used in the clinical treatment of MAFLD. Liu [30] found that Huazhirougan Granules could change the composition of the intestinal flora of MAFLD model mice, and reduce the ratio of the thick-walled bacillus phylum to the anaplastic bacillus phylum. Zhu [31] found that high-dose Huazhirougan Granules could significantly regulate the bacterial abundance in the intestinal flora of MAFLD rats and reduce the pathogenic factors associated with MAFLD, which confirms that Huazhirougan Granules can improve the hepatic lipid accumulation by regulating the intestinal flora and further regulating the metabolic pathways such as bile acid metabolism and cholesterol, so as to ameliorate the occurrence and development of MAFLD.

Zhang [32] found that Qinggan Qushi Huoxue formula increased the number of Bifidobacterium and Lactobacillus colonies significantly, reduced the number of E. coli and enterococci, and improved the intestinal flora in MAFLD rats, thus treating MAFLD. Ling [33] found that Cangju Qinggan prescription improved the pathological state as well as lipid deposition by improving the number of species in the intestinal community of MAFLD rats fed with a high-fat diet, and by gradually restoring the composition and structure of the disordered intestinal flora to normal, thus improving the pathological state as well as lipid deposition of the rats. (Table 2)

Table 2: TCM compounds regulate intestinal flora

TCM compounds	Drug composition	Related Findings	Reference
Chaihushugang powder	Radix bupleurum, Radix Paeoniae alba, Ligusticum Chuanxiong, Citrus peel, Fructus aurantii, licorice	The abundance of Bifidobacterium and Lactobacillus was significantly increased, and the abundance of enterobacterium and enterococcus was significantly decreased, which increased the beneficial flora and reduced the harmful flora.	[26]
Yinchenhao decoction	Wormwood, gardenia, rhubarb	Reduce the number of Staphylococcus and Streptococcus, increase the number of probiotics, regulate the diversity of intestinal microorganisms.	[27]
Added yinchenhao decoction	Wormwood, salvia miltiorrhiza, Rhubarb, Pulsatilla pulsatilla, Patrinia, grilled licorice	Reduce the relative abundance of the thick-walled bacterial phylum, regulate the level of inflammation and the composition of the intestinal flora.	[28]
Huangqin Decoction	Scutellaria, Paeoniae, jujube, scorched licorice	Enhancement of the abundance, homogeneity and diversity of the intestinal flora of MAFLD rats, increasing the abundance of beneficial bacteria and decreasing the abundance and ratio of harmful bacteria.	[29]
Huazhirougan Granules	Cassia seed, wormwood, rhubarb, Hawthorn, white art, Ligustrine seed, ink lotus	Reduce the ratio of the thick-walled phylum to the anaplasma phylum modulates the genus abundance of the intestinal flora and reduce the pathogenic factors associated with MAFLD.	[30-31]
Qinggan Qushi Huoxue formula	Prunella, cockscomb, cockscomb seed, wormwood, plumb pot, salvia miltiorrhiza, plumb gold	Promote the proliferation of Lactobacillus and Bifidobacterium in the intestinal tract of rats and reduce the number of Escherichia coli and Enterococcus.	[32]
Cangju Qinggan prescription	Atractylodes, white art, chrysanthemum, lotus leaf, cassia seed	Improve the number of species in the intestinal community and gradually normalise the composition and structure of the intestinal flora in MAFLD rats.	[33]

4. Summary and prospect

MAFLD is a disease of abnormal lipid metabolism associated with obesity, and the regulation of intestinal flora by TCM provides new ideas and methods for the treatment of metabolic diseases.

TCM monomers and TCM compounds have made some progress in treating MAFLD by regulating the intestinal flora and have shown good clinical effects. However, it is still necessary to combine with a series of high-throughput histological techniques, such as macrogenomics and macro-metabolomics, to systematically reveal the exact relationship and mechanism of the interactions between TCM, the intestinal flora, and human body, in the perspective of the intestinal flora's composition, function, and interactions with the host's metabolism. The relationship and mechanism

between TCM, intestinal flora and human body can only be revealed systematically from the perspectives of composition, function and interaction with host metabolism. We should take the intestinal flora as the target point to explore its role in the pathogenesis of MAFLD more deeply, and fully apply the unique advantages of TCM in regulating the intestinal flora to develop safer, more effective and standardised diagnostic and therapeutic methods and treatment measures.

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