REVIEW
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Progress in the study of treatment using Chinese medicine for metabolism-related fatty liver disease in children

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Xiao-Xuan Lin conceived the study, collected literature, and prepared the manuscript. Sheng-Jie You and Xiao-Xui Zhang collected literature and critically revised the manuscript. Qiang He conducted critical revisions of the manuscript. All authors have read and approved the final manuscript.

Competing interests
The authors declare no conflicts of interest.

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Abbreviations
MAFLD, Metabolism-associated fatty liver disease; TCM, Traditional Chinese medicine.

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Abstract
Metabolism-associated fatty liver disease (MAFLD) is a disease of hepatic fat accumulation resulting from metabolic disorders. Currently, MAFLD is the most common cause of chronic liver disease in children and adolescents. No effective or safe drugs for treating children with MAFLD are available. The traditional Chinese medicine used for treating MAFLD in children is characterized by being holistically regulated, multileveled, multi-targeting, and very safe. In this paper, the progress in research involving treatment using traditional Chinese medicine for MAFLD in children is reviewed.

Keywords: metabolism-related steatohepatopathy; traditional Chinese medicine; liver complex disease theory; complex-passing method

Introduction

Metabolism-associated fatty liver disease (MAFLD) is a hepatic fat-accumulating disease closely associated with metabolic disorders. In July 2021, an international panel of gastroenterology-related experts published a relevant expert consensus in the *Journal of Hepatology*, proposing the adoption of pediatric MAFLD to replace the original nomenclature pediatric NAFLD [1]. The new nomenclature defines childhood fatty liver as an independent disease that can coexist with other pediatric diseases; it also emphasizes that the pathogenesis of fatty liver is closely related to abnormal metabolic factors. Currently, MAFLD is the most common cause of chronic liver disease in children and adolescents [2]: A meta-analysis[3] showed that the prevalence of MAFLD in children with obesity or overweight was 52.49% and 39.17%, respectively. Most scholars believe that MAFLD is related to hepatic fat accumulation caused by a combination of factors such as insulin resistance, stress in the endoplasmic reticulum, oxidative stress, mitochondrial dysfunction, and dysbiosis of the intestinal flora. No effective and safe drugs are available to treat MAFLD in children. For children with MAFLD, lifestyle modifications that promote dietary changes to create a negative energy balance, as well as reduced sugar consumption and increased physical activity to optimize body mass index, are the only preventive and therapeutic approaches [4 ,5]. Traditional Chinese medicine (TCM) treatment for MAFLD in children is characterized by being holistically regulated, multileveled, and multi-targeting, with a high degree of safety. Herein, we consolidate and review the literature on such treatment.

Recognition of MAFLD names in Chinese medicine

The phrase *fatty liver* does not exist in ancient Chinese medical literature; however, based on its pathogenesis and clinical symptoms, it can be attributed to plumpness and dystocia in Chinese medicine, including liver fetish, liver plumpness, liver attachment, accumulation, fat qi, fatty liver, fatty gas, accumulation of evidence, and other categories [6]. As early as the Nei Jing text, the description of “accumulation in the liver, the name is fat qi,” refers to the accumulation of lesions in the liver; overindulging fat, sweet, and intense flavors; food and grain that do not liquefy; and fat accumulation in the liver. These lead to the loss of drainage function in the liver, stagnation of phlegm and stasis stagnation, and qi and blood dysregulation. In the Eleventh Five-Year Plan, the TCM Liver Disease Collaboration Group of the State Administration of Traditional Chinese Medicine identified the TCM name for NAFLD as Liver Fetish [7]. The Consensus Opinions on TCM Diagnosis and Treatment of Non-alcoholic Fatty Liver Diseases, released in 2009, identified the name of the disease as liver fetish, dystocia, and accumulation. The 2017 version of the Consensus Opinion then followed [8]. After the concept of MAFLD was proposed, the teams of academician Tong Xiaolin and Professor Zhang Shengsheng proposed the corresponding name spleen fetish. Professor Zhang Shengsheng’s team proposed the concept of disease names corresponding to spleen disease and liver disease [9 ,10].

Understanding within TCM of the etiology and pathogenesis of MAFLD

Due to the characteristics of MAFLD—for example, multiple symptoms and multiple complications, which make it a complex and diversified disease—successive generations of medical practitioners have developed their own understanding of the etiology and pathogenesis of fatty liver in Chinese medicine. Through the continuous summarization of TCM practitioners over time, at present most medical practitioners believe that this disease is related to the causative factors of diet, exertion, emotion and spirituality, physical deficiency, obesity, and other pathogenic factors. These factors in turn lead to the loss of liver qi of sparring, loss of healthy movement in the spleen, phlegm and dampness, stasis of blood, and deficiencies of the spleen and kidneys. In Chinese medicine, MAFLD is believed to be a disease of the liver and kidney. According to TCM, MAFLD is characterized by the liver, spleen, and kidney, With weakness of the spleen qi, weak transportation, easy injury incurred by food and drink, and the evil of dampness and heat. Under pathological conditions, the liver body is damaged and excretion and regulation are dysfunctional, leading to the production of pathological products (such as phlegm) and blood stasis. Phlegm, heat, blood stasis, turbidity, and dampness compete with each other, accumulating in the liver and spleen; the qi and blood of the body flow abnormally, finally leading to the occurrence of this disease. According to Zhou Zhongying, a master of Chinese medicine, the pathogenesis of fatty liver is spleen deficiency and dampness, which over time become phlegm; phlegm and stasis are intertwined [11]. Luo Lingjie, a famous national veteran practitioner of TCM, believes the pathogenesis of the disease is liver depression and spleen deficiency, and that the disease is related to phlegm, stagnation of qi, and blood stasis [12]. Feng Chonglian, a famous Chinese medicine practitioner in Guangdong Province, also attributes the disease mechanism to liver depression and spleen deficiency, and the interconnection of phlegm and blood stasis [13].

TCM treatment ideas

Pathogenic factors

MAFLD is often caused by patients eating too much fat, sweet foods, and intense flavors, more food thick, phlegm and dampness are born, phlegm and dampness within the birth of a long time waterway, stagnant qi, irregular blood flow, the water stops the drink gathering, coagulation and fat; therefore, the onset of obesity in the body ensues. Professor Gao Yueqiu believes that emotional and dietary disorders, labor and leisure, and other reasons result in the deficiency of the spleen to transport and transform powerlessness; phlegm and turbidity result from long term congestion and blockage of the meridians and blood stasis; and phlegm–dampness stasis and blood stagnation. These lead to the occurrence of MAFLD. Treatment of dampness and activation of the blood is based on the main [14]. Professor Liu Guangwei believes that the key to the pathogenesis of MAFLD is internal obstruction of phlegm–dampness, and has achieved good clinical efficacy by treating patients with MAFLD with Er Chen Wan [15]. A clinical study [16] showed that, when treating patients with dampness and turbidity internal obstruction-type MAFLD, using TCMs that have efficacy in clearing and removing dampness and turbidity can effectively reduce lipid metabolism disorders, improve insulin resistance, and help to reduce weight in these patients. Experiments conducted using a rat model [17], showed that the formula for regulating qi and eliminating dampness could reduce the body weight and levels of liver enzymes, regulate the degree of dyslipidemia, improve insulin resistance to regulate abnormal glucose and lipid metabolism, and regulate abnormal serum concentrations of adipokines and inflammatory factors of rats with MAFLD.

Treatment of the internal organs

The liver is the main regulator of excretion, regulating the qi of the whole body, whereas the spleen is the main regulator of transportation. The liver excretion and spleen transportation functions complement each other, although the liver’s storage of blood and the spleen’s regulation of blood are in harmony with each other. The liver's sparing function depends on the spleen’s transportation and clearing functions to facilitate the flow of qi, whereas the liver’s sparing function contributes to the spleen’s transportation and clearing functions to ensure the digestion and absorption of the essence of water and grains. Under pathological conditions, the liver and spleen transmitters also influence each other. The Essentials of the Golden Chamber states “When you see a disease of the liver, you know that the liver transmits to the spleen, and you should first strengthen the spleen.” This indicates the importance of liver–spleen co-regulation when treating MAFLD. According to Professor Zhang Chao, MAFLD treatment should not only treat the liver, but also regulate the spleen and stomach. The spleen and stomach are the foundations of the human body, the source of qi and blood

biochemistry. If the spleen qi is healthy, the spleen will be strong and free from evil, and it can maintain normal functioning to increase clearness and lower turbidity [18]. Academician Tong Xiaolin believes that "congestion of the earth and depression of the wood, disharmony of the liver and spleen" are at the core of the pathogenesis of MAFLD; treatment must therefore be based on dredging the liver and regulating the spleen, harmonizing the liver and spleen [19].

Treatment from the San Jiao

Warm disease, In the Warm Disease Articles, Wu Jutong said: "treat the upper jiao like feathers, if it is not light, it cannot lift; treat the middle jiao like a balance, non-ping uneasy; treat the lower jiao like a power, if it is not heavy, it cannot sink." Professor Chang Zhanjie believes that the etiology of MAFLD lies in the malfunction of the triple jiao fluid metabolism; turbid evil accumulates in the middle jiao, forming abdominal obesity, and the turbid evil enters into the bloodstream to produce fat turbidity, sugar turbidity, et cetera, which in turn cause metabolic disorders [20]. Professor Yu Jiangyi summarized his years of experience and concluded that the pathogenesis of MAFLD is related to stomach strength and spleen weakness, stomach heat and spleen deficiency, and phlegm–heat accumulation in the middle jiao. He recommends treatment that clears the stomach and eliminates phlegm, benefits qi and strengthens the spleen, and regulates qi in the middle jiao: Such treatment involves using Huanglian and Wengdian Tang with additional subtractions [21]. Professor Dong Yun treats the disease from the perspective of the liver and spleen in the middle jiao, and believes that the core pathogenetic mechanism of the disease is spleen deficiency and stagnation of dampness: The key to the pathology is that the spleen loses its healthy movement and phlegm is internally obstructed; the essence of the pathology being that the liver and spleen in the middle jiao are ill at the same time, that the root cause is deficiency of the spleen, and that the symptom is wood [22].

Treatment of MAFLD based on the theory of liver complex disease

Liver complex disease theory and MAFLD

Chinese medicine refers to a series of diseases in which the collaterals are damaged, causing stagnation of qi and blood and leading to dysfunction of the internal organs [23]. Luo is the meridian of the branch of the cross out, is the qi and blood warming the internal organs and tissues of the main pathway. From the liver meridian, liver Luo spreads through the entire body. It maintains both the normal functioning of the liver, and its morphological and structural stability; however, it also communicates between the liver and other organs, and safeguards the liver qi and blood perfusion. The main pathological changes of the liver channels are blockage of the channels and loss of nourishment of the channels. Ye Tianshi stated that the collaterals and meridians, blood collaterals, viscera and internal collaterals of the division clearly indicated that the disease is different. Treatment methods involve prescription drugs that target collaterals of the disease of different positions, the creation of the Xin flavor through the collaterals, and collaterals of the deficiency through the complementary collaterals of the disease. Modern medical academician Wu Yiling further enriched the Chinese medicine complex disease theory system. He proposed that the diagnosis and treatment of a complex disease requires the development of a certain stage of pathological changes to manifest in the symptoms of the complex disease; this ensures that the diagnosis and prescribed treatment are more targeted [24].

Wu Yiling clearly mentioned the term liver disease in his book Liver Diseases. A lesion of the liver complex is the core mechanism of liver complex disease, and the diseases caused by the abnormal structure and function of the liver complex belong to the category of liver complex disease. Pathological changes in the liver channel follow the law of transmission of channel disharmony – channel loss of nourishment – channel stagnation – channel stasis – channel damage [8]. In children, MAFLD—whether it is disorder of the spleen or liver, kidney qi insufficiency, dampness–heat internalization, or qi stagnation and blood stasis—will lead to damage to, obstruction of, and loss of nourishment to the liver channels; ultimately, these will result in loss of nourishment to the liver and liver damage.

Experiences with using the Tonto method to improve glycolipid metabolism in the body

With the attention medical doctors are paying to the theory of complex disease, the method of Tongluo is increasingly used in clinical settings, achieving good clinical therapeutic effects. Nan Yi et al. [25] reported that Yi kidney and Tongluo detoxification soup can regulate the metabolism of glycolipids in rats with diabetic nephropathy. Simultaneously, it can significantly reduce their serum total cholesterol and triglycerides. By benefiting qi, nourishing yin, resolving turbidities, and dispersing collaterals, the glucose–lipid metabolism disorders in mice with spontaneous diabetes mellitus are improved [26]. Similarly, by benefiting qi, nourishing yin, resolving turbidities and clearing collaterals, both medium and large doses of the Chinese herbal compound Kidney Preserving Formula II can regulate lipid metabolism in rats with diabetic nephropathy [27]. A study by Zhang Lu confirmed that Qiqi Gui Tongluo Granules can reduce blood glucose levels in rats [28]. Wang Lijuan et al. [29] administered garcinia cambogia Tongluo granules to treat patients with type 2 diabetes mellitus with lower limb vasculopathy. The results showed that these granules could elevate the serum levels of vaspin—an aliphatic serine protease inhibitor with a strong insulin sensitizing effect—reduce the levels of retinol binding protein 4, and improve lipid metabolism to a certain extent in patients. Professor Chunli Park [30], using liver therapy of thirst as a guide, combined the entry point of the disease mechanism, namely, toxic damage to the collaterals, with many years of clinical experience to formulate a detoxification and regulation of the liver formula. By using this formula in an experimental diabetes mellitus rat model, blood glucose levels and liver damage were gradually be reduced, while the general condition was significantly improved; the formula can also reduce the general condition of rats. Concurrently, the formula can reduce the level of blood lipids, increase insulin sensitivity, reduce insulin resistance, and also have an effect on lowering the body weight of rats. One study has shown that the detoxifying and regulating the liver formula promotes insulin secretion and reduces endoplasmic reticulum stress by increasing the expression of insulin synthesis-related genes, thus regulating intracellular homeostatic balance and reducing glycotoxicity to β-cell damage [31]. The study also confirmed that the detoxifying and regulating the liver formula can reduce the apoptosis of pancreatic islet β-cells in type 2 diabetic rats by enhancing autophagy [32]. By regulating the IRE1/JNK pathway [33], IRE1α/JNK pathway [34], IRE1-related protein expression [35], and serum FGF21 levels [36], this liver formula can ultimately play a role in protecting islet cells and improving insulin resistance.

Experiences with using the Tonto method in pediatric liver disease

In clinical practice, based on the theory of liver and complex disease of Chinese medicine, it has certain advantages in treating liver disease in children. By applying the theory of liver and complex disease in infant cholestatic liver disease, certain therapeutic effects can be obtained, with significant advantages being gained in improving liver function and promoting the relief of cholestasis [37, 38]. The effect of combining the theory of liver complex disease in treating children's bile duct disappearance syndrome in clinical practice is remarkable [39]. We formulated Tongluo Lichuan Tang based on the theory of liver and complex disease, summarized herein, to treat infantile cholestatic liver disease, and obtained a national patent (patent number ZL 2020 1 0829228.7).

Liver complex disease theory and modern medical research

Modern medical research has determined that the collaterals and microcirculation have similarities in distribution, structure, function, and physiopathology. This means that most of the lesions of collaterals

in TCM are closely related to microcirculation. Microcirculation disorder is an important cause of MAFLD. The hepatic sinusoids, the cavities between adjacent liver plates, are the basic units of hepatic microvasculature and constitute the intrahepatic microvascular circulation network. As a major component of the hepatic sinusoids, hepatic sinusoidal endothelial cells have immune and barrier functions, and are involved in the exchange of blood and other substances; they are the initiating and critical link in hepatic microcirculatory disorders [40]. Dysfunction of hepatic sinusoidal endothelial cells can cause abnormal blood flow in the hepatic sinusoids, lipid metabolism disorders, and structural and functional abnormalities of the liver. When liver injury occurs due to various acute and chronic stimuli, hepatic sinusoidal endothelial cells lose their window holes. Simultaneously, they form organized subendothelial basement membranes, that is, hepatic sinusoidal capillarization occurs. This results in hepatocellular ischemia and hypoxia, which exacerbates liver injury. A study has shown that hepatic sinusoidal endothelial cells regulate lipid and lipoprotein transport between blood and liver parenchymal cells, attenuating the inflammatory response caused by fatty acid accumulation [41]. Hepatic sinusoidal capillarization occurs in the early stages of steatosis to steatohepatitis and steadily worsens over time, ultimately affecting the development of hepatitis, hepatic fibrosis, and cirrhosis [42].

Summary

In children, MAFLD is associated with the loss of detachment in the liver, loss of tonicity in the spleen, phlegm–dampness, blood stasis and internal obstruction, spleen and kidney deficiencies, and more. In TCM, MAFLD is treated from different perspectives, such as those of the internal organs, pathological factors, and the San Jiao. In clinical practice, treating children with MAFLD using the theory of liver complex disease as a guide can effectively improve the symptoms and signs of disease. Both the theories of TCM and foundations of Western medicine support the intrinsic connection between liver complex disease, liver microcirculation, and fatty liver. The practice of TCM has confirmed the role of the Tongluo method in improving glucose and lipid metabolism in a rat model. The overall regulation and multileveled, multi-targeted action of TCM, as well as its good safety profile, are the main advantages of using it to treat MAFLD. However, current studies involving the use of TCM to treat MAFLD have certain shortcomings. These shortcomings include relatively few systematic studies being conducted that specifically focus on the etiology and pathogenesis of MAFLD, the small sample sizes of randomized controlled trials, and a lack of evidence in evidence-based medicine. Therefore, in the future, on the basis of in-depth research on the basic theories of MAFLD, formulating precise individualized treatment plans for children and expanding clinical research is necessary. Doing so will provide diagnostic and therapeutic solutions for the use of TCM in the clinical treatment of children with MAFLD that are more scientific and effective.

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