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## Potential of traditional Chinese medicine in the treatment of nonalcoholic fatty liver disease: A promising future

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### Abstract

In this editorial, we provide insights into the publication by Niu *et al* featured in the latest edition of the *World Journal of Gastroenterology*. Specifically, our focus was on exploring the potential of traditional Chinese medicine (TCM) in treating nonalcoholic fatty liver disease (NAFLD) induced by a high-fat diet through various mechanisms. NAFLD is a common liver condition, affecting approximately 25% of the world's population. It is closely linked to metabolic syndrome, insulin resistance, excessive body weight, and irregular lipid processing, leading to fat accumulation in the liver, as well as oxidative stress and inflammation. While maintaining a healthy diet and active lifestyle are essential for managing NAFLD, treatment options are limited due to undefined pathogenesis and a lack of specific medications. TCM, rooted in traditional Chinese practices, presents a promising alternative through its "syndrome differentiation and treatment" principles, enhancing liver lipid metabolism, reducing inflammation, and addressing fibrosis. Certain herbs, such as *Poria cocos*, *Puaria lobata*, and *Salvia miltiorrhiza*, have shown significant efficacy in reducing fat deposition and improving liver function. Due to systematic research and analysis of mechanisms, TCM is anticipated to yield new approaches to prevent and treat NAFLD, increasing its clinical application.

**Key Words:** Nonalcoholic fatty liver disease; Traditional Chinese medicine; High-fat diet; Potential; Prospects

**Core Tip:** Nonalcoholic fatty liver disease has the highest global prevalence among chronic liver diseases, and to date, treatment options have been limited. Owing to their multicomponent and comprehensive conditioning characteristics, traditional Chinese medicine has garnered attention for its potential to improve liver lipid metabolism, alleviate liver oxidative stress damage, and mitigate the inflammatory response. In recent years, a growing body of research has demonstrated the efficacy of traditional Chinese medicine in treating nonalcoholic fatty liver disease induced by a high-fat diet, making it a significant area for new drug development and an indispensable component of modern medicine.

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## INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a medical condition in which there is an abnormal buildup of fat in the liver resulting from various factors unrelated to alcohol consumption or other well-defined causes of liver damage[1]. The range of diseases includes hepatic steatosis without alcohol involvement, nonalcoholic steatohepatitis, cirrhosis of the liver, and hepatocellular carcinoma[2]. Currently, metabolic syndromes, such as systemic hypertension, dyslipidaemia, insulin resistance (IR), and overt diabetes, are widely recognized as significant contributors to the development of NAFLD[3]. With the global increase in obesity and diabetes rates joining a growing prevalence of metabolic syndrome, NAFLD has emerged as a significant global health issue, impacting approximately 25% of the global population. NAFLD begins as a simple accumulation of fat in the liver, and if left untreated, it may be the primary reason for end-stage liver disease, which places increasing pressure on global health care systems[4]. Currently, the double-whammy theory is widely as accepted regarding the aetiology of NAFLD. In this theory, the buildup of fatty deposits in the liver (the initial impact) heightens vulnerability to risk factors (the subsequent impact), which triggers the progression from NAFLD to a more serious form referred to as nonalcoholic steatohepatitis. Furthermore, it can even lead to cirrhosis and hepatocellular carcinoma[5]. It is now widely believed that a high-fat diet has become an important contributing factor to the first hit, leading to liver fat accumulation and, subsequently, liver steatosis[6]. Therefore, the underlying mechanism of its induction may be used to elucidate the pathogenesis of high-fat diet-induced NAFLD.

When a high-fat diet is maintained for an extended period, it disrupts the body's equilibrium and results in an overabundance of energy being stored as lipids in the liver, thus exerting a profound effect on the structure and function of hepatic cells[7]. The consumption of a high-fat diet often induces a state of IR, wherein the inhibitory effect of insulin on lipolysis is attenuated, resulting in the breakdown of adipose tissue and the subsequent release of significant amounts of free fatty acids (FFAs)[8]. Then, excess FFAs are taken up by liver cells and stored in the liver as triglycerides, forming ectopic lipid deposits[9]. Moreover, the accumulation of FFAs in the liver can disrupt  $\beta$ -oxidation and impair mitochondrial function. This leads to an overproduction of reactive oxygen species (ROS), which ultimately triggers an inflammatory response[10]. If the clearance of ROS is delayed, it can result in the oxidation of fat deposits and the release of lipid peroxides, which can cause damage to hepatocytes. Within hepatocytes, both ROS and lipid peroxides have the potential to disrupt the respiratory chain, thereby leading to either direct or indirect oxidative damage to mitochondria. This process further triggers an increase in ROS production, thus establishing a detrimental cycle[11,12]. In addition, there is a strong correlation between endoplasmic reticulum (ER) stress and the progression of NAFLD, which can dysregulate fatty acid metabolism, stimulate the inflammatory response, trigger cell death, and exacerbate liver fibrosis through the activation of multiple signalling pathways[13]. In summary, excessive levels of FFAs in plasma induce lipotoxicity, leading to hepatocyte mitochondrial damage, increased production of ROS, ER stress, oxidative stress, and inflammation. These aforementioned processes ultimately play pivotal roles in the progression of hepatic disorders.

Owing to the intricate pathogenesis of NAFLD, there is currently a lack of clinically approved pharmaceutical interventions. Presently, clinicians commonly employ pharmacotherapy to treat type 2 diabetes, as lipid-lowering agents, and as antihypertensive agents to ameliorate NAFLD. Clinical research has led to the development of a series of targeted drugs with the goal of accurately delaying the development of liver lesions. Although these new drugs have achieved good results in clinical trials, they are limited by having only a single target effect[14]. However, traditional Chinese medicine (TCM) prescriptions consist of a specific proportion of various Chinese medicinal herbs, each possessing unique efficacies. Through balanced compatibility, they can yield enhanced efficacy and minimized side effects. As a globally recognized complementary and alternative therapy, TCM presents promising opportunities for the prevention and management of NAFLD because of its multitarget properties. Diverging from Western medicine's reliance on chemical synthetic drugs, TCM emphasizes a "holistic view" and "dialectical treatment", focusing on individual differences and the diverse causes underlying diseases. This diversified approach also grants TCM distinct advantages in regulating the body, boosting immunity, and ameliorating chronic ailments[15].



With the progress of modern science and technology, the active components and mechanisms of action of TCM are being deeply studied, which enable its standardization and modernization. In addition, the individualized treatment concept of TCM enhances its applicability, especially in the prevention and overall management of NAFLD. In general, TCM provides safe and effective treatment options for NAFLD patients, promotes the international development of TCM, promotes related scientific research and new drug development, and contributes to global health.

## TCM IN THE TREATMENT OF NAFLD: NEW DIRECTIONS AND INNOVATIONS

As a common liver disease in modern society, NAFLD has a complex pathogenesis involving metabolic disorders, inflammatory reactions and liver cell damage. TCM has shown broad prospects and innovative potential in the treatment of NAFLD. Many TCM components can intervene in the development of NAFLD in multiple ways.

TCM prescriptions contain many different ingredients. In summary, Ji *et al*[16] reported that TCM prescriptions containing *Potentilla discolor* Bunge (PDB) have emerged as promising TCM treatment options. The main components of PDB include flavonoids, terpenes, organic acids, steroids and tannins. Flavonoids have demonstrated potential in enhancing lipid metabolism and IR, mitigating oxidative stress and ER stress, and regulating the gut microbiota. Terpenoids have the potential to ameliorate lipid metabolism and inhibit ER stress, whereas steroids can improve IR. Among the 88 prescriptions for NAFLD screened by Ding *et al*[17], the top 5 most common single herbs were hawthorn, *Rhizoma Alismatis*, *Radix Salvia miltiorrhiza*, *Radix Bupleuri* and *Semen Cassiae*. The activation of the AMPK pathway by vitexin and maslinic acid in hawthorn has been reported to potentially improve insulin signalling and reduce lipogenesis in mice fed a high-fat diet[18,19]. An additional constituent, hawthorn peel polyphenol, does not impact MDA levels or T-SOD and GSH-Px activities in the liver. However, it has a potent ability to modulate the expression of Nrf-2/ARE, thereby demonstrating significant efficacy in safeguarding against oxidative stress[20]. The content of *Rhizoma Alismatis* was found to regulate autophagy through the AMPK/mTOR/ULK1 pathway and to inhibit ROS and inflammation in mouse models of MCD[21]. In addition, salvianolic acid in *Salvia miltiorrhiza* can play a role in lipid metabolism regulation, antioxidation and antifibrosis by regulating multiple targets, such as PPAR $\alpha$ , CYP1A2 and MMP2[22]. These are the only therapeutic effects of the three Chinese herbs used for the treatment of NAFLD alone. When they are used in combination to treat diseased liver cells in registered clinical trials, their effectiveness has been shown in the treatment of patients, and there have been few side effects[23].

In the latest issue of the *World Journal of Gastroenterology*, Niu *et al*[24] demonstrated through *in vitro* cell experiments and animal studies that treatment with the Fanlian Huazhuo Formula (FLHZF) effectively mitigated nonalcoholic fatty liver induced by a high-fat diet by modulating autophagy and lipid synthesis signalling pathways. Researchers first verified that FLHZF can reduce lipid accumulation and liver cell damage caused by a high-fat diet *in vitro* and *in vivo*. At the molecular level, they confirmed that FLHZF effectively inhibits the accumulation of toxic lipid substances in NAFLD by regulating various mechanisms, including oxidative stress, signalling pathways involved in lipid synthesis, autophagy, and apoptosis. This was achieved through the detection of changes in molecules associated with oxidative stress, proteins related to triglyceride synthesis and breakdown pathways, and proteins involved in autophagy and apoptosis through both *in vivo* and *in vitro* experiments. The effects of each component of FLHZF on FFA-treated HepG2 cell lines and high-fat diet-induced mouse models and their potential mechanisms were not analysed separately but were comprehensively studied as a whole, demonstrating the effectiveness of its overall therapeutic effect. These results provide new evidence for the treatment of NAFLD by FLHZF and provide strong support for further research into its therapeutic potential.

Niu *et al*'s study presents diverse perspectives and methodologies for the treatment of NAFLD[24]. First, they employed FLHZF, a TCM prescription, to address NAFLD, surpassing previous studies that relied on single compounds or synthetic drugs. By attenuating oxidative damage, activating AMPK- $\alpha$ -associated autophagy and lipid synthesis signalling pathways, and inhibiting hepatocyte apoptosis, FLHZF has demonstrated its potential to intervene in multiple ways related to NAFLD and offers innovative alternatives to conventional therapeutic strategies. Second, the study validated the combined effects of FLHZF in terms of weight loss, improvement in fatty liver marker levels, and reduction in liver damage; thus, FLHZF is a favourable treatment for NAFLD. These findings not only support the application of TCM in metabolic disease treatment but also lay a foundation for future exploration in related fields. Finally, this study suggests further investigations into how FLHZF specifically influences metabolic pathways *via* the use of metabolomic methods to determine its extent of impact on NAFLD and other metabolic diseases. This perspective enriches research on integrating TCM with modern medicine while providing novel strategies for preventing and treating metabolic issues. Therefore, it holds scientific value and innovative significance both theoretically and practically while guiding future developments in clinical applications of TCM.

## CLINICAL IMPLICATIONS

The practical clinical application of TCM for the treatment of NAFLD presents diverse possibilities. First, the use of TCM to treat NAFLD can ensure an individualized treatment plan. Chinese medicine doctors can make a comprehensive assessment of patients' specific symptoms, mental state, tongue coating, and pulse to determine the compatibility and combination effectiveness of treating with the right. Individuals with different symptoms are prescribed different formulations, some of which help reduce moisture in the body, while others protect liver cells and improve liver function. Second, TCM emphasizes the flexibility adjustable drug dosage and treatment duration on the basis of the development

of the disorders and how the individual reacts to treatment. In clinical practice, it is possible to initiate treatment with a smaller dose while observing the patient's response and gradually increase the dose after confirming drug tolerance. In addition, regular follow-up and testing should be performed, and the treatment time should be adjusted according to the liver function indicators and imaging results of patients to ensure safe and effective treatment. Third, Chinese medicine treatment is not limited to the use of prescription but can also be combined with the patient's lifestyle for comprehensive intervention. Fourth, doctors can gradually form TCM treatment plans suitable for local characteristics or specific populations through the accumulation of a large amount of clinical experience. This method of combining TCM theory with modern medicine can provide patients with systematic and convenient treatment. In general, TCM prescriptions for the treatment of high-fat diet-induced NAFLD have shown good clinical value and practical significance through individualized treatment on the basis of the specific syndrome, appropriate matching of medicine with ailment, outcome monitoring, and adjusting the treatment process. This multilevel treatment approach not only focuses on liver health issues but also considers the overall condition of the patient and involves the construction of a systematic and comprehensive treatment plan.

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## CONCLUSION

In conclusion, Chinese medicine shows great potential in addressing NAFLD induced by a high-fat diet. Our research not only broadens the application of various TCMs but also provides additional treatment options for NAFLD. These findings suggest that TCM, through its integrated regulatory mechanisms of targeting pathways, is more effective than all other chemical drugs or active ingredients in the management of liver disorders.

However, a complete understanding of the precise mechanisms by which TCM treats NAFLD is still lacking. Elucidating the comprehensive activity and mechanism of TCM compounds holds important guiding significance for the future development of NAFLD treatment drugs based on TCM.

In recent years, omics areas of study such as metabolomics, transcriptomics, network pharmacology, and gene sequencing have been extensively applied to provide new research perspectives for an in-depth understanding of the mechanism of action of TCMs[25-28]. Furthermore, the integration of network pharmacology and other disciplines, including systems biology, multidimensional pharmacology, and bioinformatics, paves the way for the innovative construction of complex research frameworks based on "disease-gene-target-medicine" interactive networks within TCM studies[29]. The utilization of these omics analyses aligns with the concept of a "holistic view" and is expected to offer a systematic theoretical framework for future investigations into the mechanism behind TCM's actions, thereby promoting its modernization and application in medical practice. Therefore, future studies should continue exploring the mode of action employed by TCM in treating NAFLD to provide more effective therapeutic strategies for patients.

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