Treatment and prevention of diabetes complicated with non-alcoholic fatty liver disease by integrated traditional Chinese and Western medicine

Xu He1*, Xi-Ping Chen1**, Qi He1, Zhong-Fa Wang1, Jian-Hua Zhong2, Kui Wang1**

1Guangdong Provincial Center of Integrated Traditional Chinese and Western Medicine for Metabolic Diseases, Guangdong Pharmaceutical University, Guangzhou 510006, China. 2Integrated Traditional Chinese and Western Medicine Internal Medicine Center, Dingnan Southern Integrated Traditional Chinese and Western Medicine Hospital, Ganzhou 341900, China. 3Department of Integrated Traditional Chinese and Western Medicine Rehabilitation, Jiangxi Province Leping Traditional Chinese Medicine Hospital, Leping 333300, China. 4Department of Integrated Traditional Chinese and Western Medicine for Geriatric Diseases, Guangxi Shanglin Limin Hospital, Nanning 530500, China. 5Department of Cardiovascular Medicine, Poyang Lake Hospital Affiliated to Fuzhou Medical College, Nanchang University, Shangrao 333100, China.

*These authors contributed equally to this work and are co-first authors for this paper.

**Corresponding to: Kui Wang, Department of Cardiovascular Medicine, Poyang Lake Hospital Affiliated to Fuzhou Medical College, Nanchang University, Futian Avenue, Shangrao 333100, China. E-mail: wangkui202109@163.com.

Author contributions
Xu He and Xi-Ping Chen jointly contributed to the design, data analysis, data interpretation, and paper writing of the article, making it a joint effort. Qi He provides technical consultation and chart drawing, while Zhong-Fa Wang and Jian-Hua Zhong perform language translation, character modification, grammar correction, etc. on the article. Corresponding author Kui Wang coordinated the overall design, revision, spelling correction, and personnel allocation of the article.

Competing interests
The authors declare no conflicts of interest.

Acknowledgments
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Peer review information
TMR Integrative Medicine thanks Sheng Ding and all anonymous reviewers for their contribution to the peer review of this paper.

Abbreviations
NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus; IR, insulin resistance; TCM, traditional Chinese medicine; TG, triglycerides; TC, total cholesterol; FFA, free fatty acids; ROS, reactive oxygen species; NAFLD, non-alcoholic steatohepatitis; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose transport protein 2; GA, glycerated albumin; PQ-MGR, malonyl ginsenosides in Panax quinquefolius L.; HGP, Huanqi powder; ZQR, Zhenqing recipe.

Citation

Abstract
Today’s social economy and science and technology levels are developing rapidly. Type 2 diabetes mellitus (T2DM) is increasing in incidence, and T2DM promotes non-alcoholic fatty liver disease (NAFLD) through some mechanisms. The pathogenesis of T2DM and NAFLD is interconnected, interacted with, and promoted. While increasing the economic burden on patients, it also affects the quality and life of patients themselves. In the world, the current treatment methods include exercise and diet control, drugs (including sugar reduction, lipid-lowering drugs, etc.), weight loss surgery, etc., but currently, researching drugs can only control the progress of the disease. At present, there is no drug for T2DM combined with NAFLD treatment. Therefore, it is necessary to find and study effective drugs for NAFLD. Based on the principle of “syndrome differentiation,” traditional Chinese medicine (TCM) played an important role in treating this disease. The theory of TCM believes that the cause of NAFLD is mostly diet disorders and imbalances in daily life, leading to liver Qi stagnation, spleen dysfunction, and liver and kidney deficiency, producing phlegm and stasis. During the treatment process, we must pay attention to the goal of phlegm turbidity, but also pay attention to the source of phlegm turbidity, strengthen the spleen and stomach, nourish the liver and kidney, and restore the physiological function of the body. The ingredients of Chinese medicine extracts have the effects of antagonist oxidation stress, protecting liver cells, improving fibrous soluble systems, and promoting lipid metabolism, thereby reducing inflammatory factors to release damage to liver cells. By combining the diagnosis of TCM syndromes with Western medical disease diagnosis, the model of disease diagnosis combined with syndrome differentiation can compensate for some of the limitations of TCM’s sole reliance on syndrome differentiation, allowing for a better grasp of the disease. In treatment, a dual approach using traditional Chinese and Western medicine can enhance efficacy and reduce toxicity, leveraging both complementary strengths. Chinese medicine explains its treatment of NAFLD from a macro and micro level, providing a safer and more effective method for treating the disease.

Keywords: traditional Chinese and Western medicine; non-alcoholic fatty liver disease; type 2 diabetes mellitus
Introduction

Epidemiological research shows that non-alcoholic fatty liver disease (NAFLD) has become the world's most common chronic liver disease, with a prevalence of 25% [1], while the prevalence of NAFLD in my country is as high as 32.5% [2]. However, due to the general lack of NAFLD's understanding of NAFLD and weak early prevention and control intervention, most of them will develop into advanced liver cirrhosis and even induce liver cancer. Its harm has seriously threatened people's health and caused a substantial economic burden on society [3]. NAFLD's pathogenesis is very complicated, usually closely related to metabolic risk factors such as obesity, abnormal blood lipids, hypertension, and diabetes [4]. More than 70% of patients with type 2 diabetes mellitus (T2DM) are accompanied by NAFLD [5].

So far, the pathogenesis of T2DM combined with NAFLD has yet to be fully clarified. Research reports that the relevant factors of T2DM combined with NAFLD's onset are obesity, lipid metabolism disorders, inflammation, abnormal blood lipids, hyperglycemia, insulin resistance (IR), oxidation stress, etc. [6]. Protein kinase activated, peroxiredoxin proliferation activation receptor, fetal globulin, insulin-like growth factor-1 and insulin-like growth factor-1, protein-1, TNF-α, C1Q tumor necrosis factor-related proteins three and other molecules involved in the relevant [7].

Studies have confirmed that insulin resistance plays an important role in developing NAFLD. Once diagnosed as NAFLD, fat deposition in the liver will cause insulin resistance to increase, affecting the liver output. In addition, insulin resistance and lipid metabolism disorders increase, and the interaction between the two will aggravate the patient's condition. There is no effective way to treat T2DM with NAFLD [8, 9]. Western medicine therapy has a unique advantage in the aspects of early prevention, improvement of patients' survival quality, delaying the progress of the disease in the domestic and foreign medical community, and the progress of the medical community in the medical community of the medical community with a high degree of side effects, high dependence. There are low cost, good efficacy, and fewer adverse reactions. Therefore, finding a Chinese medicine to treat the disease is even more urgent.

Our review systematically returns to the pathogenesis of T2DM combined with NAFLD, the treatment methods and approaches of integrated traditional Chinese and Western medicine, and the advantages of traditional Chinese medicine (TCM) treatment, as shown in Figure 1.

The pathogenesis of T2DM combined with NAFLD involves insulin resistance, oxidative stress, inflammatory response, and dysbiosis of intestinal flora. Currently, there is a lack of targeted drug therapy for this disease. Chinese medicine has multiple pathways and targets to improve lipid metabolism inhibit MAPK/P13K/AKT signaling pathway to reduce IR, lower triglycerides (TG), and total cholesterol (TC), etc. Western medicine treatment includes GLP1 agonist, SGLT-2 agonist, pioglitazone, etc., to improve liver loss and lower blood sugar by improving inflammation, lipid synthesis, IR, etc. The combination of Chinese and Western medicine has significant advantages and may become the first choice for treating T2DM combined with NAFLD in the future.

T2DM With NAFLD pathogenesis research

Type 2 diabetes with NAFLD pathogenesis is not independent of each other. The two pathogenesis are mutually causal and promote each other's development. These mechanisms including the insulin resistance, oxidation stress, inflammatory response, intestinal flora, etc., are common mechanisms.

Insulin resistance

Due to the defects of insulin target tissue (skeletal muscle, liver, adipose tissue, etc.) and islet beta cells in patients with type 2 diabetic patients, causing an increased insulin level of fasting plasma and chronic hypertrophy mia further damaged insulin sensitivity, a vicious cycle [10]. Insulin resistance and high insulin media are important in non-alcoholic fatty liver. IR is the leading cause of liver fat accumulation. Due to insulin resistance, insulin inhibitory inhibition on fat-mobilization of fat mobilization has weakened, and trotyomycin cin has been decomposed in large quantities to release more free fatty acids (FFA). Too much FFA is transferred to the liver, and another fatty in the liver, causes tripedal glycycin to accumulate in the liver. On the other hand, a large number of fatty acids can activate the apoptosis pathway of hepatocytes and promote the further development of NAFLD [11]. Insulin resistance caused by high insulinemia can promote fatty acid synthesis, inhibit fatty acid degradation, and cause liver cell lipid deposition [12].

![Figure 1 Combined Chinese and Western medicine treatment and prevention of T2DM combined with NAFLD. T2DM, type 2 diabetes mellitus; NAFLD, non-alcoholic fatty liver disease.](https://www.tmrjournals.com/im202307027.png)
Oxidation stress
When the body of T2DM patients is in a high sugar state for a long time, the number of reactive oxygen species (ROS) increases. When the oxidation and antioxidant ability in the cells are imbalanced, the body's oxidation should cause tissue cell damage. ROS in the body can also further promote IR through skeletal muscle insulin resistance, insulin β cell apoptosis, endoplasmic mesh stress, GLUT4 expression decline, and local IR of fat tissue. The body of a T2DM patient experiences an increase in inner ROS, leading to oxidative stress and further exacerbating the progression of NAFLD. When the body is in oxidation stress, it increases UPC2 expression to promote liver cell necrosis. ROS can promote liver cell destruction through the FAS pathway and activate liver star cells and other liver fibrosis [13]. Oxidation stress can induce internal quality network stress, and the internal quality network stress can not only promote liver fat changes but also promote the expression of inflammatory factors, increase the response of liver inflammation, and promote the transformation of cocaine cells' hepatic stellate cells to the muscle fiber. Transform the fat liver degeneration to non-alcoholic fatty hepatitis [14].

Inflammation response
IR in the body of T2DM patients makes insulin unable to play a normal hypoglycemic effect, promotes troyl glycérin decomposition, increased fatty acids in the blood, and enters the liver. Due to the reduction of FFA oxidation and reduction of the liver, the FFA is lipidized in the liver, resulting in the liver, resulting in the liver Increased lipid load, intrahepatic macrophages are activated. The activated macrophages not only release inflammatory factors, exacerbate inflammatory couplet reactions, further promote liver star cell activation, and promote non-alcoholic steatohepatitis (NASH) progress. And when the FFA increases, its metabolic products have increased citric acid. In the skeletal muscle cells, the oxidation absorption of glucose of skeletal muscle cells to glucose is reduced in skeletal muscle cells, which leads to the resistance of skeletal muscle cell insulin resistance. The cell tissue in patients with T2DM has been in high sugar state for a long time, and the excessive generation of ROS has damaged the function of the cells in the cells. The oxidation stress state in the body of T2DM, causing dysfunction and damage to tissue cells, triggering inflammation reactions in the body, and inflammatory reactions will further stimulate free radicals and form a vicious cycle [15]. Oxidation stress, endoplasmic mesh stress, liver fat accumulation, insulin resistance cause inflammation, which can promote the increase of TGF-β-α, transform hepatic stellate cells into muscle fibroblasts, and promote liver fibrosis.

Intestinal flora disorders
Studies have found that the intestinal flora of diabetic patients has mild disorders, and the interaction of high-fat diet and intestinal microorganisms can induce intestinal inflammation. Intestinal inflammation increases intestinal permeability. On the one hand, bacterial fat polysaccharides, lipopolysaccharide in blood or tissue and inflammatory factors produced with receptor recognition cause insulin resistance of the liver, fat, and muscles [16]. Studies have shown that the excessive growth of intestinal bacteria leads to increased intestinal permeability, resulting in the inching blood of bacterial components to form chronic endotoxemia and mediating hepatocyte damage. Furthermore, lead to liver inflammation through a series of channels to promote liver fat deformation [17].

T2DM combined with NAFLD western medicine treatment and exercise intervention
It has not been formally approved for NAFLD treatment, which is closely related to the heterogeneity of NAFLD patients. Different individuals have a large fluctuation in their response to NAFLD treatment drugs [18]. T2DM with NAFLD is a comprehensive management. It must use drugs to control blood sugar, blood lipids, IR, and other abnormal indicators and intervene in lifestyle (such as controlling diet, exercise, weight loss, etc.). The risk of cardiovascular incidents increased, so monitoring and preventing cardiovascular risk factors is necessary [9].

Motion control
T2DM combined with NAFLD needs to be controlled. Regular exercise can activate the active receptor of the liver fat content, increase the β-oxidation of fatty acids, induce liver protective autophagy, and excessively express peroxidase proliferation. γ (PPAR-γ), reducing liver cytoplasty and increasing insulin sensitivity to improve NAFLD. Sports training also increases several antioxidant enzymes and anti-inflammatory media to inhibit ROS's excessive generating and oxidation stress in NAFLD [19]. Exercise can reduce the accumulation of liver fat, and the lower physical quality can be reduced (5%–10%) can improve the fat liver degeneration and inflammation of patients with NAFLD patients. The lower body quality reduced (more than 10%) can reduce the liver fiber to reduce the liver fiber [20].

Drug treatment
Glucagon-like peptide-1 (GLP-1) receptor agonist. A large number of studies have shown that the GLP-1 receptor agonist can reduce weight, reduce blood sugar and blood lipids, improve IR and liver function, improve liver oxidation stress and inflammatory damage, and some products benefit cardiovascular benefits [21]. Leralugin has been widely studied in patients with T2DM combined with NAFLD. Licolitiz peptide treatment T2DM combined with NAFLD can significantly reduce liver fat content and body quality, subcutaneous adipose tissue, and visceral adipose tissue. Studies have shown that CD36 is one of the FFA receptors that promote FFA intake. Leralugin peptide can inhibit STAT5/CD36 to improve fat liver degeneration by significantly increasing serum prolactin. A low level of serum lipo plasma may make NAFLD play an essential pathological and physiological role in the process of NASH. After treating the Licolita peptide, serum lipopside levels can be significantly increased [22].

Sodium-glucose transport protein 2 (SGLT-2) inhibitor. SGLT-2 inhibitors can improve NAFLD by improving IR, are anti-inflammatory, lower liver lipid synthesis, promote lipid decomposition, and reduce fibrosis [23]. Related studies have shown that rising serum uric acid levels are an independent risk factor for NAFLD in patients with T2DM [24]. The SGLT-2 inhibitor also reduces blood uric acid while reducing sugar, possibly related to SGLT-2 permeability diuretic effects. Furthermore, SGLT-2 inhibitors can improve cardiovascular and the ending of the kidney [25].

Pioglitazone. Increasing fat tissue to insulin is increased insulin and promotes fatty acid intake and storage. It may be the primary mechanism of such drugs to improve fat liver degeneration [26]. Meta analysis results show that pioglitazone can significantly improve sugar metabolism, liver function, and liver tissue changes. For example, the degree of fatty liver degeneration, inflammation, and balloon sample change can also alleviate NASH in patients with T2DM combined with NAFLD. There is no significant difference in fibrosis. However, because peritoneal increases the risk of heart failure in patients with T2DM, and adverse reactions such as edema and physical quality, the clinical application of the drug is limited [27]. When inadvertent failure and other omeprazole dione tabs, pioglitazone is T2DM combined with NASH ideal drugs, and pyrrolidone is the only drug that can be used for patients with NAFLD [28].

Metformin. Metformin has demonstrated its ability to enhance fat synthesis and metabolism, lower total cholesterol and low-density lipoprotein cholesterol levels, while maintaining or slightly increasing high-density lipoprotein cholesterol levels. Although it cannot improve the pathological changes associated with non-alcoholic fatty liver disease, metformin can ameliorate insulin resistance, reduce blood sugar levels, and aid in weight loss. Several studies have shown the significant benefits of metformin in improving liver inflammation, steatosis (fatty degeneration), and fibrosis. In clinical practice, obese individuals are divided into two groups: obese individuals with diabetes and obese individuals without diabetes. Extensive and long-term research conducted by the Diabetes Prevention Program in
the United States has found that metformin is effective for obese individuals with type 2 diabetes, not only in reducing blood sugar levels but also in facilitating weight loss. However, it does not significantly affect body fat ratios in individuals with impaired glucose tolerance and no obvious signs of diabetes, resulting in limited effects on weight reduction in such populations.

**Weight loss surgery.** Weight loss surgery can improve the liver tissue of NASH patients, including NASH secondary liver fibrosis. In addition, it can improve the symptoms of T2DM, blood lipid abnormalities, and hypertension and reduce the incidence and mortality of cardiovascular disease [29]. Essentially in a forward-looking study, 180 cases of severely obese patients confirmed by the biopsy for NASH were performed, and a weighing surgery was followed up for five years. The patient’s NASH was relieved (n = 64; 95% CI was 73.1%–92.2%), fibrosis did not deteriorate (P < 0.001), and the relief of NASH was not affected by the severity or fibrosis of the NASH baseline [30].

**Chinese medicine treatment of T2DM combined with NAFLD**

The Chinese medicine in T2DM combined with NAFLD

The Chinese medicine has a deep understanding of diabetes mellitus since ancient times, and it is classified under the category of “thirst” and “disease of elimination” [31], fatty liver is one of the complications of T2DM mellitus. The earliest description of this disease is found in the Classic of Questioning (Eastern Han dynasty), which states, “the accumulation of liver is called fatty gas”. Additionally, the *Plain Questions* (722 B.C.–221 B.C.) explicates, “when the liver is congested, the two hypochondriacs have pain” [32]. Consequently, this condition is categorized within the realms of dystocia, liver amassment, and the accumulation of evidence. According to Chinese medicine, the basic causes of this disease are congenital endowment deficiency, dietary disorder, emotional and mental disorder, and excessive exertion [33]; the pathogenesis is most closely related to the liver and spleen. Insufficient innate endowment, deficiency of the five viscera, deficiency of the innate Yin and Yang (Yin and Yang refer to the two basic properties of things and things that are opposed to each other) of the internal organs, loss of transmission and transportation of Qi (Qi refers to the basic substance that constitutes the human body and maintains life activities, and is the unity of substance and function), blood, and fluids, and injury of fluids and dryness lead to thirst [34].

The Qing dynasty physician Yuan-Yu Huang pointed out in *Su Ling Wei Yun - Extraction of Thrust* that “the disease of extinction of thirst is solely blamed on liver wood”, and based on the clinical manifestations of the disease, the root of the disease is “extinction of thirst”, which can be classified as “liver gang” and “liver fetish” [35]. According to the clinical manifestations of this disease, the disease is rooted in “thirst” and can be classified as “liver pang”, “liver fetid”, “accumulation”; etc.

**TCM etiology of T2DM combined with NAFLD**

The etiology of the disease can be analyzed from the following points: (1) Insufficient congenital endowment and lack of nurturing in later life, resulting in insufficient essence and blood and loss of nourishment of tendons and veins. (2) Fatty food, laziness, prolonged lying down and injury to the Qi, poor diet, over-eating sweet and greasy things, easily injure the spleen, spleen injury, spleen injury, spleen deficiency of water and grain loss of transformation, essence does not spread, phlegm and dampness, turbid fat accumulation, metabolic disorders, so the disease. (3) Emotional and mental disorders, the five wills are too extreme, liver Qi is depressed, Qi is not smooth, depression and fire, decocation of fluids, phlegm and stagnation of each other. (4) Excessive exertion, Yin deficiency in the body, repeated depletion of the innate essence, Yin deficiency and fire, Yin injury and heat victory. This is a sign of deficiency of the essence and the symptoms. Qi deficiency, Yin deficiency and Yang deficiency are the essence, while phlegm, dampness, stasis, heat, toxicity and stagnation are the symptoms.

T2DM combined with NAFLD in Chinese medicine

The concept of “disease” and “evidence” in Chinese medicine has been used for a long time. The differentiation of disease is to understand the disease mechanism, location, nature and development of disease from a macroscopic perspective, which is equivalent to grasping the basic contradictions of the disease.

It is equivalent to grasping the basic contradiction of the disease; identifying the evidence is to determine the pathological essence of the disease at a certain stage, which is equivalent to grasping the contradiction of the current stage of the disease. The combination of the two is to combine the basic contradiction of the disease with the main contradiction of the current stage, so as to understand the essence of the disease more comprehensively and improve the effect of diagnosis and treatment. Discriminatory treatment is the essence of traditional medicine. Each doctor in TCM has its own strengths, and a hundred schools of thought have continuously explored and practiced, putting forward a variety of theoretical treatment views. Most of the medical practitioners task the deficiency of the spleen and stomach, and the spleen is trapped by dampness, which is the initiating link of diabetes mellitus combined with fatty liver, and the accumulation of phlegm, turbidity, dampness, stasis and other pathological products in the liver, and the loss of drainage of the liver are common pathological changes.

Chinese medicine classifies diabetic fatty liver into five types of symptoms: liver deficiency, spleen deficiency, phlegm-dampness internal obstruction, damp-heat internal accumulation, and phlegm-stasis interconnection [36]. The Chinese herbal formulas were Sijunzi decoction combined with Chaihu Shugan powder; Shenling Baizhu powder; Longdian Xiegan decoction; and Wendan decoction plus Taohong Siwu decoction. For patients with typical clinical manifestations, the medicine can be reasonably identified and used according to the clinical symptoms, starting from adjusting the deficiency of the internal organs.

Advantages of Chinese medicine for T2DM combined with NAFLD

With the continuous development of modern Chinese medicine pharmacology, the hypoglycemic and lipid-regulating effects of many single herbs and related extracts have been discovered. Therefore, on the basis of evidence-based treatment, with reference to modern pharmacological research results, the addition of a few targeted Chinese medicines can significantly improve the therapeutic effect. In recent years, the group of patients with diabetes mellitus combined with fatty liver has been expanding, and Chinese herbal remedies for the treatment of this disease have been released, and clinical observation and research have shown that Chinese medicine has long-term safe and effective clinical efficacy for patients with diabetes mellitus combined with fatty liver, giving full play to the advantages of Chinese herbal compound, and effectively The clinical observations and studies have demonstrated the long-term safe and effective clinical efficacy of TCM for patients with diabetes mellitus combined with fatty liver.

**Herbal monomers with clear therapeutic effect on T2DM combined with NAFLD**

We classify the monomer of TCM for T2DM with NAFLD, as show in Table 1. Abnormal glucose metabolism and abnormal lipid metabolism can cause common disorders or complications of glucolipid metabolism. In response to the complex etiology of glucose and lipid metabolism disorders and the need for clinical prevention and treatment, Professor Guo Jiao’s team at Guangdong Pharmaceutical University innovatively proposed the theory of glucose and lipid metabolism disease and achieved a major breakthrough in the treatment of this disease by applying TCM evidence-based treatment [3].

Diabetes mellitus combined with fatty liver is a typical representative of glycolipid metabolic disease. The research team of Cui et al. found that *Schotalaria Radix* improved glucose and lipid metabolism in T2DM rats by regulating hepatic lipid generation and
Table 1 Chinese herbal monomers with clear therapeutic effect on diabetes combined with fatty liver

<table>
<thead>
<tr>
<th>Drug names</th>
<th>Mechanisms</th>
<th>Treatment effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scutellariae Radix</td>
<td>Regulation of hepatic lipid generation and MAPK/P38/Akt signaling pathway</td>
<td>Lower blood sugar, blood lipids, improve inflammation and insulin resistance</td>
<td>[7]</td>
</tr>
<tr>
<td>Cassiae Semen</td>
<td>Activation of Akt and ERK1/2 signaling pathways</td>
<td>Reduce serum levels of ALT, AST, TG, TC</td>
<td>[8]</td>
</tr>
<tr>
<td>Dendrobium nobile Lindl</td>
<td>Significantly affects the insulin-mediated signaling cAMP-PKA and Akt/FoxO1 signaling pathways</td>
<td>Promotes hepatic glycogen synthesis and inhibits hepatic glycogen degradation and hepatic gluconeogenesis</td>
<td>[9]</td>
</tr>
<tr>
<td>Coccis Semen</td>
<td>Activation of GFI/P38/AKT signaling pathway</td>
<td>Increase serum insulin and HDL, decrease TG, TC, LDL levels</td>
<td>[10]</td>
</tr>
<tr>
<td>Ginseng Radix et Rhizoma Rubra</td>
<td>Activation of Akt and ERK1/2 signaling pathways</td>
<td>Reduces TC, HDL-C, GLU and FINS levels</td>
<td>[11]</td>
</tr>
<tr>
<td>Trigerygi Radix</td>
<td>Inhibition of PERK/Eif2alpha signaling pathway</td>
<td>Increase leptin sensitivity and improve capacity balance</td>
<td>[12]</td>
</tr>
<tr>
<td>Gynostemmatis Herba</td>
<td>Activation of PI3K/AKT signaling pathway</td>
<td>Reduce blood glucose, ALT, AST, BUN and CREA levels</td>
<td>[13]</td>
</tr>
<tr>
<td>Artemisiae Scopariae Herba</td>
<td>Regulation of NF-kB signaling pathway</td>
<td>Lower TG, TC levels</td>
<td>[14]</td>
</tr>
<tr>
<td>Galla Turcica</td>
<td>Up-regulation of β-oxidation and ketogenesis</td>
<td>Lower blood sugar, TG, TC levels</td>
<td>[15]</td>
</tr>
<tr>
<td>Panaxis Quinguefolii Radix</td>
<td>Activation of IRS1/P38/Akt and AMPK/ACC signaling pathways</td>
<td>Reduces FBG, TG, TC, LDL-C, NEFA, ALT and AST levels</td>
<td>[16]</td>
</tr>
<tr>
<td>Striatiae Prucrus</td>
<td>Activation of AMPK signaling pathway</td>
<td>Lower FBG levels and alter insulin resistance</td>
<td>[17]</td>
</tr>
<tr>
<td>Captidis Rhiasona</td>
<td>Activation of LKB1-AMPK-TORC2 signaling pathway</td>
<td>Reduced fasting plasma insulin and insulin resistance</td>
<td>[18]</td>
</tr>
</tbody>
</table>

IR, insulin resistance; TG, triglycerides; TC, total cholesterol; FBG, fasting blood glucose; LDL-C, low-density lipoprotein cholesterol.

MAPK/P38/Akt signaling pathways, significantly improving hyperglycemia, dyslipidemia, inflammation and insulin resistance [38]. Zhang et al. investigated and found that cassia seed extract was effective in reducing serum levels of ALT, AST, TG, TC, and cell survival signals triggered by Akt and ERK1/2 effectively improved myocardial function and reduced M/R-induced injury in diabetic but not normal animals [39]. Liu et al. experimentally demonstrated that Dendrobii Caulis can significantly affect the glucagon-mediated signaling pathways cAMP-PKA and Akt/FoxO1, which further promote hepatic glycogen synthesis and inhibit hepatic glycogen degradation and hepatic gluconeogenesis, thus improving hepatic glycogen structure and improving hepatic glucose metabolism in diabetic mice [40]. The results of Xia et al. team showed that Coix lacryma polysaccharide could increase the level of short-chain fatty acids through the intestinal microbiota, thereby stimulating the IGFI/P38/AKT signaling pathway and producing hypoglycemic effects [41]. Cui et al. demonstrated that Ginseng Radix et Rhizoma Rubra extract could improve islet tissue damage, regulate lipid levels, and exert therapeutic effects through amino acid metabolism, glycerol-phospholipid metabolism, and fatty acid metabolism [42]. He et al. found that Radix et Rhizoma regulates proper weight maintenance and glucose metabolism through ERK/Eif2α signaling pathway, revealing a new mechanism of Radix et Rhizoma reduct for metabolic diseases including weight loss [43]. Xu et al. discovered the latest mechanism of action study of giberellins regulating P38/Akt signaling pathway and key node genes of fatty acid metabolic signaling pathway to exert hypoglycemia in vivo [44]. Qin et al. applied network pharmacology and basic experimental studies to validate the protective effect of Gynostemmatis Herba on T2DM-NAFLD and its ability to improve T2DM combined with NAFLD by regulating NF-kB signaling pathway, and their results not only laid the foundation for understanding the active compounds and mechanisms of action of Gynostemmatis Herba, but also provided a reference for studying the mechanism of one herbal medicine for the treatment of multiple diseases [45]. Experimental validation by Chao et al. revealed specific effects of galaxin on diabetes combined with fatty liver, glycated albumin (GA) is a simple polyphenol present in food and TCM. By combining physiological assessments, pathological examinations, metabolomic studies of blood, urine, liver and muscle, and measurements of gene expression, GA treatment was found to alleviate high blood glucose levels and decelerate the development of nonalcoholic fatty liver in mice. Furthermore, the results suggest that the hepatoprotective effect of GA in diabetic mice occurs in part by partially preventing the disordered metabolic pathways associated with glucose, lipids, amino acids, purines and pyrimidines. Specifically, its mechanism through the alleviation of lipid accumulation was associated with the upregulation of β-oxidation and ketogenesis. These findings suggest that GA alleviates metabolic disorders through novel mechanisms [46]. Liu et al. found that malonyl ginsenosides in Panax quinguefolius L. (PQ-MGR) significantly reduced fasting blood glucose, TG, TC, low-density lipoprotein cholesterol, non-esterified fatty acids, ALT, and AST levels in mice with high lipid factor-induced T2DM, and improved glucose tolerance and insulin resistance. The results showed that PQ-MGR could improve glucose and lipid metabolism and insulin resistance in T2DM by modulating the IR53/P38/Akt and AMPK/ACC pathways. These findings suggest that PQ-MGR could be used as an adiabetic candidate for the treatment of T2DM [47]. Zhang et al. experimentally found that rooibos showed good effects on obese T2DM rats, including significant reduction of fasting blood glucose levels and alteration of insulin resistance. Also, they significantly reduced serum triglycerides, total cholesterol, low-density lipoprotein cholesterol (and free fatty acids) and increased high-density lipoprotein cholesterol levels in T2DM rats. In addition, rosmarinic acid significantly increased GLP-1 levels and decreased IL-6 levels in the serum of rats, and rosmarinic acid exerted hypoglycemic and lipid-regulating effects by upregulating AMPK activity [48]. Jiang et al. experimentally found that berberine improved glucose tolerance and reduced plasma hyperlipidemia in high-fat diabetic mice. In addition, berberine, a major component of Phellodendron, reduced fasting plasma insulin and insulin resistance. Berberine increased the protein expression of liver kinase B1, AMP-activated protein kinase and phosphorylated AMPK. The level of phosphorylated TORC2 protein in the cytoplasm of the berberine group was higher than that of the model group, while the level of total TORC2 protein was not significantly different. Immunohistochemical staining showed that the
berberine group had more TORC2 localized in the cytoplasm than the model group. The results showed that berberine inhibited hepatic gluconeogenesis by modulating the LKB1-AMPK-TORC2 signaling pathway [49].

**Chinese herbal compound with clear therapeutic effect on T2DM combined with NAFLD**

We classify the clear efficacy of traditional Chinese herbal compound therapy for T2DM combined with NAFLD, as shown in Table 2. Animal experiments showed that Fufang Zhenzhu Tiaozi formula treatment significantly reduced serum TG, TC, low-density lipoprotein cholesterol and fasting blood glucose levels, increased serum high-density lipoprotein cholesterol levels, improve systemic IR, and reduce liver damage. On histopathological features such as hematoxylin and eosin, Oil Red O staining and electron microscopy, Fufang Zhenzhu Tiaozi formula treatment had a significant favorable effect on hepatic steatosis and hepatic lipid accumulation. Mechanistically, Fufang Zhenzhu Tiaozi formula improves liver metabolism by increasing the phosphorylation of PI3K-AKT and decreasing the expression of HIF-1α [50]. Li et al. demonstrated that raw vin drink combined with Shengmaii formula and Gannmai Dazao decoction affected metabolism-related signaling pathways, including PI3K-Akt, AMPK, and PPAR. In validation experiments, Shengmaii formula and Gannmai Dazao decoction treatment of KKAY mice reduced serum levels of glucose, TC, TG, and FFA, decreased the number of corpuscles in visceral adipose tissue, reduced the size of adipocytes, and decreased the fat deposition in the liver. In addition, Shengmaii formula and Gannmai Dazao decoction improved liver metabolism by increasing the expression of PPARα, HSL and PI3K/Akt, decreasing the expression of SREBP-1 and FASN, inhibiting lipid biosynthesis, and improving insulin sensitivity [51]. Fang et al. showed that Sanhuang decoction reduced food intake, body weight, blood glucose levels and insulin resistance and improved glucose tolerance in obese and Odb1-deficient mice. Mechanistically, it was confirmed that Sanhuang decoction protects against NAFLD by activating PGC-1α and its downstream signaling pathways, as evidenced by attenuation of hepatic lipogenesis and lipid accumulation, increase in hepatic fatty acid oxidation, regulation of plasma lipid parameters, and increased energy expenditure and metabolic function of fat and muscle [52]. Li et al. experimentally demonstrated the protective effect of Huangqi powder (HPQ) against obesity-induced hepatic steatosis in rats fed a high-fat diet. HPQ reduced plasma TC, TG, FFA, and FABP4 levels, normalized glucose and insulin levels, and improved glucose tolerance. RNA-Seq analysis combined with qPCR showed that some important genes related to glucose and lipid metabolism, the including mRNA expression of Acat2, Apoc4, Bhmt, Cyp3a62, Cyp51, Egln3 (Phn3), Fads1, Fads2, Gmct, Hmgs1 and Pemt were significantly altered after HPQ treatment. The results suggest that HPQ has beneficial effects on glycolipid metabolism and hepatic steatosis, and the mechanism may be related to the function of genes that regulate glycolipid metabolism [53]. The experimental results of Fan et al. showed that in NAFLD combined with T2DM rats, TNF-α, IL-6, IL-1β, CRP and MDA decreased significantly after treatment with Tiagogan decoction, and the levels of superoxide dismutase and glutathione peroxidase increased significantly. The results suggested that Tiagogan decoction could treat NAFLD in T2DM rats by improving the inflammatory response and oxidative stress capacity [54]. The results of Song et al. suggested that the serum glucose, TG, TC, and liver TG decreased after treatment with Zhengjiao decoction [QQJ] in mice with diabetes mellitus combined with fatty liver. Reduced expression of SIK1 was observed in the liver of high-fat diet and streptozotocin-induced diabetic rats. Overexpression of SIK1 in the liver alleviated hyperglycemia, hyperlipidemia and fatty liver. The mRNA and protein levels of CREB-regulated transcriptional co-activator 2, phospho-enolpyruvate carboxylase and glucose-6-phosphatase were dramatically decreased in the liver, while the levels of SIK1 were significantly increased in the QQJ group compared with the diabetes mellitus group. The results suggested that QQJ improved hepatic glucose metabolism and lipid storage in high-fat diet and streptozotocin-induced diabetic rats through activation of the SIK1/CRTC signaling pathway. Upregulation of hepatic SIK1 by QQJ may represent an effective strategy for the treatment of diabetes mellitus combined with NAFLD [55].

**Chinese medicine treats T2DM combined with NAFLD from the spleen theory**

According to TCM, the etiology and main symptoms of thirst and hepatic fever are closely related to the spleen. The spleen is located in the middle jiao, which is the basis of the latter part of the body, is responsible for transporting water and grain essence, and is the source of biochemical energy and blood. The *Classic of Questioning* states when one consumes liquids, they enter the stomach, where the essence overflows. This essence then ascends to the spleen, where the spleen’s Qi disperses the essence. Subsequently, the essence returns upwards to the lungs, travels through the water channel, and then descends to the bladder. This process results in the widespread distribution of water essence, with five meridians running in parallel. This passage underscores the significance of the spleen’s role in transferring and dispersing essence, which is pivotal for the absorption and distribution of nutrients throughout the body.

### Table 2 Chinese herbal compounds with clear therapeutic effect on diabetes mellitus combined with fatty liver

<table>
<thead>
<tr>
<th>Drug names</th>
<th>Mechanisms</th>
<th>Treatment Effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fufang Zhenzhu Tiaozi formula</td>
<td>Increased phosphorylation of PI3K-AKT and decreased expression of HIF-1α</td>
<td>Lower TG, TC, LDL-C and FBG levels, increased serum HDL-C levels, improve IR and reduce liver damage</td>
<td>[19]</td>
</tr>
<tr>
<td>Shengmaii formula and Gannmai Dazao decoction</td>
<td>Increased expression of PPARα, HSL and PI3K/Akt and decreased expression of SREBP-1 and FASN</td>
<td>Reduced serum levels of glucose, TC and FFA</td>
<td>[20]</td>
</tr>
<tr>
<td>Sanhuang decoction</td>
<td>Activation of PGC-1α signaling pathway</td>
<td>Reduced body weight, blood glucose levels and insulin resistance, improved glucose tolerance</td>
<td>[21]</td>
</tr>
<tr>
<td>Huangqi powder</td>
<td>Regulation of expression of glycolipid metabolism genes such as Acat2, Apoc4, Bhmt, Cyp3a62</td>
<td>Lowed plasma TC, TG, FFA and FABP4 levels</td>
<td>[22]</td>
</tr>
<tr>
<td>Tiaogan decoction</td>
<td>Reduced expression of TNF-α, IL-6, IL-1β, CRP</td>
<td>Improves inflammation and oxidative stress</td>
<td>[23]</td>
</tr>
<tr>
<td>Zhengqing decoction</td>
<td>Activation of SIK1/CRTC2 signaling pathway</td>
<td>Lowering serum glucose, TC, and hepatic TG</td>
<td>[24]</td>
</tr>
</tbody>
</table>

TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; FFA, free fatty acids.
Diabetes and fatty liver are disorders of glucose-lipid metabolism. Blood glucose, blood lipids, and other tangible substances in the blood are produced by the spleen and stomach transporting water and grain. Injuries to the spleen and stomach are caused by poor diet and excessive consumption of fat and sweets. With the change in people’s diet structure, high sugar, high fat, high protein food, over-eating is easy to cause the spleen and stomach transport and transformation of unfavorable water and grain can not be with the food and transformation of the vein, lewd essence in the pulse, gathered for phlegm, fat by phlegm, and accumulate in the liver and develop fatty liver. The spleen is the master of muscles and limbs, so too much rest and laziness to exercise and reduced physical exertion will affect the function of the spleen and stomach. If the spleen and stomach are out of order, the food and water do not return to the right but become fat, overflowing the muscle, overflowing in the skin, outside for the fat problem, internal gathering in the liver is the development of the disease. In old age and with physical decline, there is a weakening of the spleen and stomach. As stated in Plain Questions- Yin and Yang should be the elephant in the room, it is mentioned that at the age of 40, Yin and Qi begin to decline, leading to a gradual deterioration of health. As individuals enter middle age, the functions of internal organs gradually decline, and various metabolic processes slow down. Conditions such as diabetes and fatty liver are commonly associated with middle-aged individuals. As age One, the transportation functions of the spleen and stomach weaken, leading to inefficient metabolism of sugars, fats, and other nutrients, resulting in their excessive accumulation and potential harm. Li Dong Yuan’s Spleen and Stomach Theory - The Spleen and Stomach in Full and in Low further emphasizes that all diseases originate from spleen and stomach dysfunction.

In cases of diabetes combined with fatty liver, despite the condition manifesting in the liver, the fundamental mechanism underlying the disease is spleen deficiency. Hence, the core issue related to liver congestion and thirst can be traced back to spleen dysfunction. As the saying goes, “when we observe liver-related ailments, we understand that the liver’s function is closely connected to the spleen’s function. Therefore, our primary focus should be on fortifying the spleen.” The ultimate goal is to promote overall well-being and restore health.

**Discussion**

Today, with the increasing incidence rate of T2DM combined with NAFLD, diagnostic methods and means are increasingly rich, and treatment ideas are constantly widened and optimized. But the more troublesome the method, the more complex the choice. Making the best and most direct plan to maximize the benefits of patients is the difficulty we need to solve. Although a large number of TCM prescriptions have achieved significant clinical efficacy, there need to be more large samples, a large number of data collection research, and case observation data, and the lack of solid data support has become the consensus of diagnosis and treatment. TCM has the advantages of multi-target and multi-directional treatment. However, there needs to be more research on the mechanism of NAFLD in the role of TCM. The evaluation criteria of T2DM combined with NAFLD are still limited to biochemical and imaging examinations. The TCM basis for differentiation and treatment of T2DM with NAFLD needs to be standardized, and it is difficult to find a single treatment plan suitable for all patients with T2DM and NAFLD. In the future, individualized T2DM combined with NAFLD treatment is needed. In terms of treatment, T2DM patients with NAFLD should adjust their diet structure and living habits in time, actively achieve early treatment of fatty liver, and continuously improve their quality of life. In the foreseeable future, TCM will become a rich source of candidate drugs for treating T2DM combined with NAFLD.

The realization of this vision will also overcome major challenges. We are faced with many complex problems. The first problem is establishing an international standard language of TCM so that Chinese and western medicine can better understand and communicate. The second point is how to scientifically conduct clinical research on treating NAFLD with TCM to prove the advantages of evidence-based NAFLD with TCM. The third point is how to deeply study the mechanism of action of TCM compound preparation on T2DM combined with NAFLD through a scientific, practical, and recognized verification platform and confirm the significant effect of TCM on T2DM combined with NAFLD. On the issue of T2DM combined with NAFLD, TCM has obvious advantages over Western medicine.

TCM has a history of thousands of years. It is also an outstanding representative of the world’s most systematic traditional medical theory, the richest connotation, the most comprehensive application, and complete preservation. After thousands of years of clinical practice, it has been proved that TCM is conclusive, effective, and feasible in treatment, disease prevention, and health preservation. For the treatment of T2DM with NAFLD, combining traditional Chinese and western medicine can improve the curative effect, improve the quality of life of patients and reduce adverse reactions. TCM syndrome differentiation combined with the western medicine treatment system is the best treatment for T2DM combined with NAFLD. The etiology and pathogenesis of T2DM with NAFLD differ, so developing individualized diagnosis and treatment strategies is important. Under the guidance of the syndrome differentiation and treatment system of TCM, combined with the objective evidence provided by the auxiliary means of western medicine, we can deeply understand the pathological mechanism of T2DM combined with NAFLD and optimize the medication plan pertinently, which can accelerate the recovery and prevent the recurrence of symptoms.

However, although various studies have confirmed the significant advantages of TCM in the treatment of T2DM with NAFLD, it is still in the initial stage, and its therapeutic effect needs more verification. Overcome and solve the common problems in the current clinical research of T2DM combined with NAFLD treated by TCM, give full play to the advantages and great potential of TCM treatment, innovate and break through the challenges faced by TCM treatment, and promote the development of TCM treatment. TCM has become the first choice for treating T2DM combined with NAFLD, which is a goal we need to strive for.

**References**


Integrative Duan Z, Cai et Wang in 2023;7:e23027
Xia Cichorium in Metabolic al. Diabetic et C, 2022;146:112495.
Jiang J of Sci diet-fed Mouse metabolomics Pharmacother China attenuates Z, in Review

http://doi.org/10.1172/jci.insight.145306
http://doi.org/10.3389/fphar.2018.00235
Glucose http://doi.org/10.3390/ijms19113634
Mater https://doi.org/10.2174/187153032066620091015612


47. Liu Z, Qu CY, Li JX, et al. Hypoglycemic and Hypolipidemic Effects of Malonyl Ginsenosides from American Ginseng (Panax quinquefolius L.) on Type 2 Diabetic Mice. ACS Omega 2021;6(49):33652–33664. Available at: http://doi.org/10.1021/acsomega.1j02273


