DOI: 10.66069/ojspub.27450733

A Study on the Intervention of the 'Soothing the Liver and Strengthening the Spleen' Approach in T2DM complicated by MAFLD via the Lipid Droplet–Mitochondrial Axis mediated by Signalling Pathways

Wei Liu[1], Yang Xiao[2,*]

[1]Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Shaanxi Provincial Hospital of Chinese Medicine, Xi'an 710003, Shaanxi, China
Correspondence Author

Abstract: ***Diabetes is rising rapidly worldwide. According to WHO data, there were 422 million people with diabetes globally by 2014, with developing countries accounting for 77 per cent of the global total; the risk of related complications and all-cause mortality has also increased accordingly [1]. This is accompanied by a continuous deterioration in metabolic function. Amongst these, metabolic-associated fatty liver disease (MAFLD), which is closely linked to metabolic dysfunction, has become the world's leading chronic liver disease of the 21st century. Research statistics indicate that the global prevalence of MAFLD has reached as high as 25.24 per cent. MAFLD acts as a trigger for the progression from steatosis to non-alcoholic steatohepatitis (NASH), cirrhosis and even liver cancer. Currently, MAFLD has risen to become the most prevalent liver disease in China. Statistics indicate that over the past decade, the proportion of patients with fatty liver disease in China has risen from 18 per cent to 29.2 per cent. As a common liver condition, MAFLD frequently co-occurs with type 2 diabetes mellitus (T2DM) [2]. They contribute to the development of cardiovascular disease, chronic kidney disease, cirrhosis, liver cancer and other malignant tumours, imposing a significant disease burden and economic impact on patients and society.***

Keywords: Liver-soothing and Spleen-strengthening Formula, Type 2 diabetes, Metabolic-associated fatty liver disease, IRS/PI3K/Akt signalling pathway.

1. The Relationship Between T2DM and MAFLD

Type 2 diabetes mellitus (T2DM) is a global chronic metabolic disease characterised by hyperglycaemia, insulin resistance and pancreatic β-cell dysfunction [3]. With changes in lifestyle and an ageing population, the prevalence of T2DM continues to rise worldwide and has become a serious public health issue. According to data from the International Diabetes Federation (IDF) for 2021, approximately 537 million adults worldwide have diabetes, of whom over 90 per cent have T2DM. Metabolic-associated fatty liver disease (MAFLD) is a liver condition closely associated with insulin resistance and metabolic syndrome. Firstly, insulin resistance is considered one of the key factors in the development of MAFLD. Insulin resistance leads to reduced insulin sensitivity in adipose tissue and skeletal muscle, which in turn results in increased lipogenesis and reduced glucose uptake, elevated levels of free fatty acids (FFAs) in the blood, and ultimately hepatic steatosis. Secondly, abnormalities in lipid metabolism also constitute an important pathogenic mechanism of MAFLD. This high rate of comorbidity not only reflects their shared metabolic background but also reveals their interaction in terms of pathophysiological mechanisms [4].

The core pathological features of T2DM are insulin resistance and β-cell dysfunction, leading to impaired blood glucose regulation [5]. Insulin resistance results in reduced sensitivity to insulin in tissues such as muscle, adipose tissue and the liver, thereby affecting glucose uptake and utilisation. In the liver, insulin resistance leads to increased glucose output and enhanced fatty acid synthesis, resulting in the accumulation of hepatic fat—a key step in the development of MAFLD. Furthermore, insulin resistance exacerbates hepatic inflammation and lipid metabolism disorders by activating a series of signalling pathways, such as the IRS/PI3K/Akt pathway.

The pathological process of MAFLD primarily involves the accumulation of lipid droplets within hepatocytes, an inflammatory response and fibrosis. The accumulation of lipid droplets is mainly due to excessive fatty acid intake and synthesis, as well as reduced fatty acid oxidation. In patients with T2DM, hyperglycaemia and hyperinsulinaemia further promote fatty acid synthesis and the formation of lipid droplets. Mitochondrial dysfunction within hepatocytes is also one of the key mechanisms underlying the development of MAFLD. Mitochondria are the centres of cellular energy metabolism and fatty acid β-oxidation. In patients with T2DM and MAFLD, mitochondrial function is impaired, manifesting as a reduction in mitochondrial number, morphological abnormalities and functional dysfunction. Mitochondrial dysfunction leads to disturbances in energy metabolism, which further exacerbates the accumulation of lipid droplets and the inflammatory response. Furthermore, mitochondrial dysfunction also leads to increased production of reactive oxygen species (ROS), causing oxidative stress and further damaging hepatocytes [6].

2. The Role of the IRS/PI3K/Akt Signalling Pathway in T2DM and MAFLD

The IRS/PI3K/Akt pathway plays a key role in the pathogenesis of T2DM and MAFLD. Insulin activates the IRS/PI3K/Akt signalling pathway by binding to the insulin receptor, thereby promoting glucose uptake and utilisation, and inhibiting gluconeogenesis and lipogenesis [7]. In patients with T2DM, insulin resistance leads to impaired activation of the IRS/PI3K/Akt pathway, which in turn affects glucose and lipid metabolism. In MAFLD, impaired activation of the IRS/PI3K/Akt pathway not only exacerbates fatty acid synthesis and the accumulation of lipid droplets, but also promotes the development of inflammatory responses and fibrosis. Furthermore, the activation of the IRS/PI3K/Akt pathway is also associated with the maintenance of mitochondrial function; its impairment leads to mitochondrial dysfunction, which further exacerbates the pathological process of MAFLD.

Insulin receptor substrates (IRS) are a class of multifunctional adaptor proteins, primarily comprising IRS-1 and IRS-2. Upon binding to its receptor, insulin activates the receptor's tyrosine kinase activity, leading to the tyrosine phosphorylation of IRS proteins [8]. Phosphorylated IRS proteins act as a platform to recruit and activate PI3K. PI3K is a lipid kinase capable of converting phosphatidylinositol bisphosphate (PIP2) into phosphatidylinositol trisphosphate (PIP3). This is a key step in the activation of Akt; it promotes the translocation of Akt from the cytoplasm to the cell membrane and, through the phosphorylation of PDK1 and PDK2, leads to the full activation of Akt. Activated Akt further phosphorylates various downstream target proteins, such as mTOR, GSK3β and FoxO, regulating cellular processes including metabolism, growth, survival and apoptosis [9].

In type 2 diabetes mellitus (T2DM) and metabolic-associated fatty liver disease (MAFLD), dysfunction of the IRS/PI3K/Akt signalling pathway constitutes a common pathophysiological basis. Insulin resistance is a core feature of T2DM, manifested as impaired insulin-mediated glucose uptake and utilisation. Under conditions of insulin resistance, the phosphorylation levels of IRS proteins are reduced and PI3K activity is diminished, leading to insufficient activation of Akt. This, in turn, affects the translocation of the glucose transporter GLUT4, reducing glucose uptake by muscle and adipose tissue and resulting in elevated blood glucose levels [10]. Furthermore, insufficient activation of Akt also leads to increased activity of gluconeogenic enzymes in the liver, further exacerbating hyperglycaemia. However, in patients with MAFLD, due to the presence of insulin resistance, activation of the IRS/PI3K/Akt signalling pathway is inhibited, leading to reduced fatty acid uptake and increased lipogenesis, ultimately resulting in the accumulation of lipid droplets within hepatocytes and the development of steatosis [11].

In summary, the IRS/PI3K/Akt signalling pathway plays a significant role in the pathogenesis of T2DM and MAFLD. By regulating this signalling pathway, it is possible to improve insulin resistance, reduce the accumulation of lipid droplets within hepatocytes and restore mitochondrial function, thereby providing new therapeutic strategies for these two conditions.

3. The Role of the Lipid Droplet – Mitochondrial Axis in Carbohydrate and Lipid Metabolism

Lipid droplets are neutral lipid reservoirs enclosed by a single-layer phospholipid membrane, primarily responsible for the storage and metabolism of intracellular lipids. Under normal conditions, lipid droplets are able to convert stored lipids into free fatty acids (FFAs) through lipolysis; these FFAs are subsequently taken up by mitochondria for β-oxidation, thereby generating ATP to meet the cell's energy requirements. However, in cases of T2DM complicated by MAFLD, due to insulin resistance and dysregulated lipid metabolism, lipolysis in the droplets is enhanced, leading to the release of large quantities of FFAs into the cytoplasm. These excess FFAs not only increase the burden on the mitochondria but may also lead to mitochondrial dysfunction, manifested as abnormal mitochondrial morphology, impaired respiratory chain function and increased ROS production [12].

Mitochondria are the cell's powerhouses, responsible for generating ATP through the process of oxidative phosphorylation. When mitochondrial function is normal, they can efficiently utilise FFAs for β-oxidation to produce energy. However, when mitochondria are overwhelmed by excessive FFA, their oxidative capacity is exceeded, leading to disruption of the electron transport chain and, consequently, excessive ROS production. The increase in ROS not only damages the structure and function of the mitochondria themselves but also induces oxidative stress in other cellular components, further exacerbating cellular damage. Furthermore, mitochondrial dysfunction leads to reduced ATP production, affecting the cell's energy supply and thereby exacerbating insulin resistance and lipid metabolism disorders.

In the progression of T2DM complicated by MAFLD, dysfunction of the lipid droplet–mitochondrial axis manifests as a vicious cycle of excessive lipid droplet accumulation and mitochondrial dysfunction. On the one hand, excessive accumulation of lipid droplets leads to the over-release of FFA, increasing oxidative stress on the mitochondria; on the other hand, mitochondrial dysfunction in turn affects lipid droplet metabolism, forming a positive feedback loop that accelerates disease progression. This process not only affects the function of liver cells but may also extend to other organs, such as the heart and muscles, leading to systemic metabolic disorders.

In response to this issue, recent studies have shown that modulating the IRS/PI3K/Akt signalling pathway can effectively intervene in the dysfunction of the lipid droplet–mitochondrial axis. The IRS/PI3K/Akt pathway is a key route in insulin signalling and is involved in regulating multiple physiological processes, including glucose metabolism, lipid metabolism and cell survival. In T2DM complicated by MAFLD, abnormal activation or inhibition of the IRS/PI3K/Akt pathway is one of the key mechanisms leading to insulin resistance and lipid metabolism disorders. By

activating the IRS/PI3K/Akt pathway, normal lipid droplet metabolism can be promoted, the excessive release of free fatty acids (FFA) reduced, whilst simultaneously improving mitochondrial function and lowering reactive oxygen species (ROS) production [13], thereby breaking the vicious cycle of the lipid droplet–mitochondrial axis and achieving therapeutic outcomes.

4. The Traditional Chinese Medicine Perspective on Diabetes and Fatty Liver Disease in Traditional Chinese Medicine.

Diabetes is classified under the category of 'xiao ke' (thirst and wasting syndrome). This concept first appeared in the *Huangdi Neijing* (The Yellow Emperor's Classic of Internal Medicine), which describes the symptoms of xiao ke—such as excessive thirst, excessive appetite, frequent urination and weight loss—as corresponding to those of type 2 diabetes mellitus (T2DM) in modern medicine. According to TCM theory, the spleen is the foundation of postnatal life; it governs the transformation and transport of the essence of food and drink, and is the source from which qi and blood are generated. Spleen deficiency leads to qi deficiency; qi deficiency results in inadequate distribution of blood, causing the viscera and meridians to be undernourished and their functions to weaken. Deficiency of qi also impedes the circulation of blood, leading to poor blood flow; over time, this results in blood stasis. Spleen deficiency can also lead to an imbalance in fluid metabolism, giving rise to phlegm-dampness; phlegm-dampness is both a product of liver qi stagnation and an aggravating factor in blood stasis, creating a vicious cycle [14]. The liver is the organ of the Jueyin channel; it governs the free flow of qi and regulates qi dynamics. If liver qi becomes stagnant, it will impair the spleen's transformative and transport functions, leading to impaired qi dynamics and further exacerbating spleen deficiency. Failure of the liver to regulate the free flow of qi also leads to obstruction of blood circulation, resulting in blood stasis; this blood stasis, in turn, further impedes the liver's regulatory function, creating a pathological state characterised by liver qi stagnation and spleen deficiency.

Traditional Chinese Medicine classifies metabolic-associated fatty liver disease (MAFLD) under the categories of 'accumulation' (jiju), 'excessive qi' (feiqi) and 'flank pain' (xietong), holding that its pathogenesis is fundamentally rooted in spleen-kidney deficiency, with phlegm-dampness and blood stasis being secondary manifestations. Diminished spleen and kidney function leads to abnormal distribution of the essence of food and drink, resulting in the internal generation of phlegm-dampness [15]. Over time, this transforms into heat, which injures yin fluids, giving rise to pathological states such as internal obstruction by phlegm-dampness and internal accumulation of damp-heat. These conditions further impair liver function, leading to abnormal accumulation of fat within liver cells and the development of MAFLD.

From a Traditional Chinese Medicine perspective, the pathogenesis of T2DM complicated by MAFLD is closely related to the failure of the liver to regulate the flow of qi and the failure of the spleen to perform its transport and transformation functions. The failure of the liver to regulate the flow of qi leads to impaired qi circulation, which in turn affects the transport and transformation functions of the spleen and stomach. This prevents the normal distribution of the essence of food and drink, thereby leading to the internal generation of phlegm-dampness, obstructing the circulation of qi and blood, and exacerbating insulin resistance. Impaired spleen transport and transformation, in turn, leads to a failure in the transformation and transport of the essence of food and drink; as these essential substances cannot be properly distributed, excess lipids become retained in the liver, forming fat deposits which further impair liver function and lead to the development of MAFLD [16]. Consequently, the 'Liver-Regulating and Spleen-Strengthening Formula', by regulating liver and spleen function to improve insulin resistance and lipid metabolism disorders, has become an important therapeutic approach for treating T2DM complicated by MAFLD.

5. Theoretical Basis and Mechanism of Action of the Liver-Soothing and Spleen-Strengthening Formula

Modern research has shown that the Liver-Soothing and Spleen-Strengthening Formula can intervene in the pathological process of T2DM complicated by MAFLD through multiple pathways. Firstly, the formula improves insulin resistance by regulating the IRS/PI3K/Akt signalling pathway. IRS (insulin receptor substrate) is a key molecule in insulin signalling, whilst the PI3K/Akt pathway is one of the primary routes of insulin signalling [17]. When liver and spleen function is disrupted, the activity of the IRS/PI3K/Akt pathway is reduced, leading to impaired insulin signalling and decreased insulin sensitivity. By regulating liver and spleen function, the Liver-Soothing and Spleen-Strengthening Formula restores the activity of the IRS/PI3K/Akt pathway, thereby improving insulin resistance, glucose uptake and utilisation.

The Liver-Soothing and Spleen-Strengthening Formula can alleviate hepatic inflammatory responses by regulating the expression of inflammatory factors in the liver, such as tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6) [18]. Overexpression of these inflammatory factors interferes with the normal function of the IRS, leading to impaired insulin signalling. Studies have shown that the Liver-Soothing and Spleen-Strengthening Formula can significantly reduce serum levels of TNF-α, IL-1β and IL-6 in rats with T2DM and MAFLD, thereby alleviating liver inflammation and restoring IRS function. Furthermore, the Liver-Soothing and Spleen-Strengthening Formula can improve the function of the lipid droplet–mitochondrial axis by regulating lipid metabolism in the liver. The lipid droplet–mitochondrial axis plays a key role in maintaining cellular energy metabolism and lipid homeostasis [19]. In patients with T2DM complicated by MAFLD, impaired function of the lipid droplet–mitochondrial axis leads to lipid accumulation and mitochondrial dysfunction. The herbs in the Liver-Soothing and Spleen-Strengthening Formula can improve lipid metabolism, reduce lipid droplet formation and restore mitochondrial function by upregulating the expression of genes related to lipid metabolism, such as the sterol regulatory element-binding protein-1c (REBP-1c), fatty acid synthase (FASN) and acetyl-CoA carboxylase 1

(ACC1). The Liver-Soothing and Spleen-Strengthening Formula not only inhibits the formation of lipid droplets but also promotes their breakdown. The breakdown of lipid droplets relies primarily on the action of lipases, such as adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) [20].

From the perspective of spleen deficiency, spleen deficiency is closely associated with mitochondrial abnormalities in various organs throughout the body. In particular, the maintenance of gastrointestinal motility requires a substantial supply of energy from mitochondria, and normal mitochondrial function is crucial for ensuring gastrointestinal peristalsis and digestion and absorption. In a state of spleen deficiency, the homeostasis of mitochondrial autophagy is disrupted, leading to cumulative mitochondrial damage, which in turn triggers energy metabolism disorders [21]. Studies have shown that in rats with a spleen deficiency syndrome model, mitochondria in the gastric antrum tissue exhibit swelling, abnormal shapes, and a significant reduction or deformation of cristae-like structures, accompanied by the absence of autophagosomes, suggesting mitochondrial autophagy impairment. The 'Liver-Soothing and Spleen-Strengthening Formula' exerts its therapeutic effect by regulating mitochondrial autophagy and improving spleen function

MAFLD is a common chronic liver disease characterised by excessive fat accumulation in the liver, which can progress to cirrhosis or even hepatocellular carcinoma. According to Traditional Chinese Medicine theory, MAFLD falls under the categories of 'accumulation' (jiju), 'excessive fat' (feiqi) and 'flank pain' (xietong), with its primary pathogenesis being spleen deficiency with excess dampness and liver stagnation with spleen deficiency. Based on this, the Liver-Soothing and Spleen-Strengthening Formula aims to treat MAFLD by regulating the functions of the liver and spleen and alleviating dampness within the body. Numerous clinical studies have demonstrated that the Liver-Soothing and Spleen-Strengthening Formula is highly effective in the treatment of MAFLD. Furthermore, the Liver-Soothing and Spleen-Strengthening Formula may exert a positive therapeutic effect on MAFLD by regulating bile acid metabolism, modulating TGR5 receptor activity, thereby influencing the secretion of brain-gut peptides, reducing visceral hypersensitivity, improving intestinal permeability, and repairing the intestinal mucosal barrier [22]. Bile acid metabolism is closely linked to the gut microbiota; by regulating this metabolic process, the Liver-Soothing and Spleen-Strengthening Formula not only improves hepatic lipid metabolism but also exerts a distal protective effect on the liver via interactions through the gut-liver axis [23].

Lifestyle interventions are a vital component of the management of T2DM and MAFLD, encompassing dietary control, physical exercise and weight management [24] The combined use of the Liver-Soothing and Spleen-Strengthening Formula with lifestyle interventions can more effectively regulate patients' metabolic status. The formula improves patients' appetite and digestive function, promoting nutrient absorption, whilst lifestyle interventions help to control weight and reduce fat intake; the synergistic action of both approaches collectively improves patients' metabolic status [25].

6. Current Issues and Shortcomings in Research

Shugan Jianpi Formula is effective in treating type 2 diabetes mellitus combined with metabolic dysfunction-associated fatty liver disease (MAFLD), yet existing studies have multiple limitations that need to be addressed. First, current pathway research only detects a small number of protein markers and fails to fully illustrate the regulatory mechanisms of upstream and downstream molecules in the IRS/PI3K/Akt pathway. Omics technologies are needed to carry out systematic analysis on this pathway. Second, the active substances responsible for the therapeutic effects of this compound remain unidentified. Most studies adopt administration of the complete formula, and further efforts are required to isolate and identify its core active ingredients and validate their individual pharmacological effects. Third, existing research mainly focuses on short-term monitoring of glucose and lipid indicators, lacking long-term investigations into patients' quality of life, long-term complications and populations suitable for individualized medication [26].

In conclusion, this compound possesses promising clinical application potential. Future research shall supplement clinical trials, further explore signaling pathway mechanisms, identify its pharmacodynamic substances and conduct long-term comprehensive evaluations, so as to provide evidence for clinical medication.

References

[1] Chinese Diabetes Society. Guideline for the prevention and treatment of type 2 diabetes mellitus in China (2020 edition) (Part 1). Chinese Journal of Practical Internal Medicine. 2021;41(8):668-695.

[2] Fu TT, Ding H. An excerpt of liver ultrasound elastography: an update to the World Federation for Ultrasound in Medicine and Biology guidelines and recommendations. Journal of Clinical Hepatology. 2019; 35(1):59-63.

[3] Chinese Diabetes Society, Zhu DL. Guideline for the prevention and treatment of type 2 diabetes mellitus in China (2020 edition). International Journal of Endocrinology and Metabolism. 2021;41(5):482-548.

[4] Zhao PP, Li Q. Research progress on correlation between serum bilirubin and type 2 diabetes mellitus combined with metabolic associated fatty liver disease. Chinese Journal of Practical Internal Medicine. 2019; 39(6): 568-571.

[5] Zhou ZH, Wang LT, Gao YQ. Role of hepatocyte mitophagy in pathogenesis of metabolic associated fatty liver disease. Journal of Clinical Hepatology. 2019; 35(12): 2809-2811.

[6] Jiang LJ, Li YG, Cui W, et al. Research progress on PI3K/Akt signaling pathway involved in traditional Chinese medicine improving insulin resistance in type 2 diabetes mellitus. China Journal of Traditional Chinese Medicine and Pharmacy. 2021;36(9):5405-5408.

[7] Yang Y, Qin ZG. Research progress on correlation between Helicobacter pylori infection and the

pathogenesis of metabolic associated fatty liver disease. Journal of Pathogen Biology. 2025;20(9):1230-1233.
[8] Xue SY, Liu C, Jiang YB, et al. Pathogenesis and treatment of type 2 diabetes mellitus combined with metabolic associated fatty liver disease. Chinese Journal of Gerontology. 2025;45(3):756-762.
[9] Zhang ZN, Jin WF, Jiang HG, et al. Mechanism of insulin resistance and research status of active components of mume fructus in ameliorating insulin resistance. The Chinese Journal of Clinical Pharmacology. 2025;41(2):274-278.
[10] Wang Q, Yang M, Zhao Q, et al. Research status of traditional Chinese medicine intervening PI3K/Akt signaling pathway for the prevention and treatment of metabolic associated fatty liver disease. Liaoning Journal of Traditional Chinese Medicine. 2025; 52(9): 209-213,237.
[11] Li Y, Cao WF, Li JD. Effects of Shenmai Lanling Decoction on liver fat content and hepatic fibrosis in patients with type 2 diabetes mellitus combined with metabolic associated fatty liver disease. Chinese Archives of Traditional Chinese Medicine. 2022;40(6):144-148.
[12] Bai CM, Yang HJ, Wu B. Research progress on correlation between adipokine adipsin and type 2 diabetes mellitus. The Journal of Practical Medicine. 2023;39(2):133-136.
[13] Xu Z, Ni XM, Li S, et al. S-Equol improves type 2 diabetes mellitus combined with metabolic associated fatty liver disease in rats via regulating SREBP pathway and PPARγ. Journal of Army Medical University. 2022;44(22):2266-2274.
[14] Wang J, Hu TX. Progress in drug therapy of type 2 diabetes mellitus combined with metabolic associated fatty liver disease. Zhejiang Medical Journal. 2024;46(6):561-565,571.
[15] Liu YR, Yang M, Tian XC, et al. Research progress on metabolic associated fatty liver disease combined with type 2 diabetes mellitus. Guizhou Medical Journal. 2022;46(8):1188-1190.
[16] Maan M, Peters JM, Dutta M, et al. Lipid metabolism and lipophagy in cancer. Biochemical and Biophysical Research Communications. 2018;504(3):582-589.
[17] Zhou YQ, Luo H, Dong XT, et al. Research progress on integrated traditional Chinese and western medicine for metabolic associated fatty liver disease combined with type 2 diabetes mellitus. Chinese Journal of Integrated Traditional and Western Medicine on Liver Diseases. 2025;35(2):250-254.
[18] Wang Y, Song JY, Wang L, et al. Exploration on intestinal flora-bile acid axis improving insulin resistance of type 2 diabetes mellitus based on qi collateral regulation from liver treatment. Modernization of Traditional Chinese Medicine and Materia Medica-World Science and Technology. 2024; 26(11): 2914-2920.
[19] Liu T, Xu QL. Theoretical discussion on invigorating spleen and eliminating dampness regulating methylation of hepatic lipid export genes for treatment of metabolic associated fatty liver disease. Journal of Clinical Hepatology. 2019;35(3):661-664.
[20] Lu YN, Liu LJ, Li W. GA/HbA1c ratio is associated with type 2 diabetes mellitus combined with metabolic associated fatty liver disease. Basic & Clinical Medicine. 2020;40(12):1636-1639.
[21] Huang KZ, Jiang KP, Li JH, et al. Prescription medication strategy for metabolic associated fatty liver disease based on relationship between intestinal microecology and spleen-stomach ascending and descending. Chinese Journal of Experimental Traditional Medical Formulae. 2020;26(3):43-52.
[22] Jin HX, Qi ZT, Ding SZ. Research progress on lipophagy-mediated metabolic associated fatty liver disease and its exercise regulation. Chinese Journal of Sports Medicine.
[23] Yin YX, Hu YY, Peng JH. Origin of phlegm-dampness theory and its application research progress in metabolic associated fatty liver disease. China Journal of Traditional Chinese Medicine and Pharmacy. 2023; 38(4): 1689-1692.
[24] Riazi K, Azhari H, Charette JH, et al. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. The Lancet Gastroenterology & Hepatology. 2022;7(9):851-861.
[25] Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology. 2023;77(5):1797-1835.
[26] Chang K, Hong F, Liu H, et al. FTO aggravates podocyte injury and diabetic nephropathy progression via m6A-dependent stabilization of ACC1 mRNA and promoting fatty acid metabolism. Biochemical Pharmacology. 2025;235:116819.