Research progress of traditional Chinese medicine in the treatment of endocrine metabolic diseases in 2023

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Author contributions
Hai QH conceived the idea for this study. Fan MY, with the support of Wen WB and Cui HT, completed the preparation and revision of the manuscript. Fan MY also made significant contributions to the research on non-alcoholic fatty liver disease, type 2 diabetes mellitus and its complications, as well as thyroid diseases. Ru J contributed to the research on obesity, hyperuricemia, and the abstract and discussion sections of the paper. Wang S and Chen Y contributed to the standardization of disease abbreviations, chart creation, and provided guidance on the revision process of the paper. Zhang XX and Li GL were responsible for the retrieval and screening of all relevant literature. All authors provided critical feedback and assisted in revising the final manuscript.

Competing interests
The authors declare no conflicts of interest.

Acknowledgments
This study was supported by the Yunnan Provincial First-Class Discipline Innovation and Research Fund Key Project (2YXZD202405) and the Yunnan Provincial Science and Technology Department Traditional Chinese Medicine Joint Project (202001A207001-026).

Peer review information
Traditional Medicine Research thanks all anonymous reviewers for their contribution to the peer review of this paper.

Abbreviations
TCM, traditional Chinese medicine; T2DM, type 2 diabetes mellitus; NAFLD, non-alcoholic fatty liver disease; MAS1D, metabolic associated steatotic liver disease; SIRT, Sir2 homolog; CYP1B1, cytochrome P450 family 1 subfamily B member 1; AMPK, AMP-activated protein kinase; SASH, non-alcoholic steatohepatitis; PPARδ, peroxisome proliferator-activated receptor δ; LCN2, Lipocytin-2; SLC6A4, solute carrier family 6 member 4; CHM, Chinese herbal medicine; F/F, Firmicutes-to-Bacteroidetes ratio; HO-1, heme oxygenase-1; GLUT4, glucose transporter 4; IR, insulin resistance; BA, bile acid; DN, diabetic nephropathy; DR, diabetic retinopathy; LSP, Lychee seed polyphenol; DPN, diabetic peripheral neuropathy; HFD, high-fat diet; ED, erectile dysfunction; DED, diabetic erectile dysfunction; DGP, diabetic gastroparesis; ORG, obesity-related glomerulopathy; HUA, hyperuricemia; BFA, Bacillus subtilis-Fermented Astragalus membranaceus; GO, Graves’ ophthalmopathy.

Citation

Executive editor: Jing-Yi Wang
Received: 12 April 2024; Accepted: 25 June 2024; Available online: 28 June 2024.
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environmental factors can be treated by targeting the underlying causes. However, in reality, we encounter the challenge of having a relatively small number of endocrine metabolic diseases with clear causes. Even in diseases with known causes, the pathological changes are often irreversible, leading to a generally low cure rate in clinical practice. Therefore, there is a need to explore new treatment methods and approaches for endocrine metabolic diseases to improve patient therapeutic outcomes and quality of life.

According to TCM, the human endocrine system is closely related to the Yin-Yang (The concept of Yin and Yang in Chinese philosophy encompasses opposing yet complementary forces, with Yin representing negative, feminine, and passive principles, and Yang representing positive, masculine, and active principles. These forces interplay dynamically to maintain a state of balance in all things) and its five elements (the concept of Five Elements encompasses the interacting and transformative cycles among Wood, Fire, Earth, Metal, and Water, forming a fundamental framework for understanding natural phenomena in Chinese philosophy) of nature. Imbalances in endocrinology and metabolism are manifestations of disturbances in the Yin-Yang and Qi-Blood ("Qi" refers to the energetic force that drives bodily functions, regulates metabolism, and sustains life. "Blood" is the nourishing fluid that circulates through the body, vitalizing its tissues) levels within the body. Diseases such as diabetes, thyroid disorders, and obesity are all considered in TCM to be caused by the dysfunction of internal organs and obstructed flow of Qi-Blood. In TCM theory, the belief is that the treatment of endocrine metabolic diseases should be approached from the perspective of a holistic view and syndrome differentiation. The goal is to treat endocrine metabolic diseases by harmonising the Yin-Yang and Qi-Blood, nourishing the functions of the internal organs, and improving lifestyle and dietary habits. In recent years, with the continuous deepening of research on TCM, its advantages in the treatment of endocrine metabolic diseases have gradually become prominent, attracting attention from the medical community, both at home and abroad.

Through an in-depth review and analysis of the literature on TCM for the treatment of endocrine and metabolic diseases in the PubMed database in 2023, we found that the research focus of TCM is still centred on the symptomatic treatment of its pathogenesis. Primarily through methods such as reducing lipid deposition and anti-inflammatory and antioxidant effects, TCM improves the functional defects of target cells/organ, thereby regulating hormone secretion or the reactivity of target cells to hormones and ultimately achieving the treatment goal. In terms of research content, we explored the direct regulatory effects of TCM active ingredients, extracts, or compound prescriptions on lipid metabolism pathway activities involving classical pathways such as SIRT1 and PPARα.

### The risk factors and main classifications of endocrine metabolic diseases

Figure 1 The risk factors and main classifications of endocrine metabolic diseases (by Figdraw)
also focused on research hotspots that have received much attention in recent years, such as intestinal flora and ferroptosis (Figure 2).

The traditional approach in endocrinology involves studying the molecular pathology and pathophysiological mechanisms of diseases based on their phenotypic characteristics. However, research programs guided by various omics technologies have adopted different approaches, providing novel molecular avenues and drug targets for the diagnosis and treatment of endocrine diseases, thus emerging as a cutting-edge field in biological research. Extracts and compounds from TCM exhibit multi-target effects, similar to a ‘shotgun’ approach that can cover as many signalling pathways related to human diseases as possible. This approach holds significant potential for treating endocrine metabolic diseases with complex pathogeneses. In 2023, research on the mechanisms of TCM extracts and compounds in treating endocrine metabolic diseases, and techniques such as pharmacogenomics and metabolomics were employed to elucidate their effects from a network regulation perspective.

In addition, this article also pays special attention to the research progress of some ethnic medicines in treating endocrine and metabolic diseases, aiming to discover more promising treatment methods and drugs and provide new options for the treatment of endocrine and metabolic diseases. This article also focuses on two less-studied complications of diabetes mellitus: diabetic erectile dysfunction (DED) and diabetic gastroparesis (DGP). These two complications are common in patients with diabetes; however, the current treatment methods are limited, and the effect is not satisfactory. Therefore, we hope to explore the potential and advantages of TCM in treating these two complications through in-depth research and provide more comprehensive and effective treatment plans for patients with diabetes.

**Metabolic dysfunction-associated steatotic liver disease**

At the European Association for the Study of the Liver Annual Meeting on June 24, 2023, NAFLD was officially renamed metabolic dysfunction-associated steatotic liver disease (MASLD) [1]. MASLD is currently the most common chronic liver disease, along with non-alcoholic fatty liver and non-alcoholic steatohepatitis (NASH) [2]. It is a major risk factor for diseases such as liver cirrhosis and primary liver cancer [3]. Its pathogenesis is primarily related to lipid metabolism disorders, oxidative stress injury, inflammatory responses, insulin resistance (IR), intestinal flora, and ferroptosis disorders (Table 1) [4–8].

**Improve lipid metabolism disorder**

Excessive accumulation of metabolic substrates, such as fatty acids, in hepatocytes leads to hepatocyte dysfunction, which is a core factor in the development of NAFLD [2]. Therefore, improving lipid metabolism is a key mechanism for the prevention and treatment of NAFLD. SIRT1, a member of the sirtuin (SIRT, silent information regulator) protein family, participates in the regulation of cell metabolism, growth, and ageing through deacetylation. It is closely related to AMP-activated protein kinase (AMPK), which comprises two crucial intracellular energy-sensing and metabolic regulatory systems. Peroxisome proliferator-activated receptor α (PPARα) promotes the synthesis of lipases when activated, catalysing triglycerides in lipoproteins into free fatty acids and promoting lipid metabolism. Similar to previous research findings, TCM extracts and formulas reported in 2023 can also directly participate in regulating the activities of classical pathways involving SIRT1 and PPARα, accelerating fatty acid oxidation, and thus reducing lipid deposition in the liver. mTOR is a serine/threonine protein kinase belonging to the PI3K-related kinase (PIKK) family. AMPK and mTOR have opposing effects on cellular energy and nutritional status, exhibiting antagonistic effects on many common downstream processes, such as autophagy, lipid metabolism, and protein synthesis. Studies have shown that TCM extracts and formulations can improve the functional state of hepatocytes by inhibiting the PI3K/AKT/mTOR pathway.

**Chinese herbal extract**

Formononetin, extracted from *Astragalus membranaceus*, can upregulate the expression of β-oxidation regulatory enzymes Carnitine Palmitoyltransferase 1A (CPT1A) and Acyl-Coenzyme A Dehydrogenase, Medium-Chain (ACADM) by activating the SIRT1/PGC-1α/PPARα pathway, promote fatty acid β-oxidation, alleviate hepatic steatosis, and improve liver function [9]. Bavachinin, extracted from *Psoraleae Fructus*, has anti-inflammatory and anti-lipid effects and can also bind to Proliferating Cell Nuclear Antigen to improve liver injury and promote

![Figure 2 Overview of TCM treatments for endocrine and metabolic diseases in 2023 (by Figdraw)](https://www.tmrjournals.com/tmr)
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<td>Bavachinin</td>
<td>In vivo (hamster), in vitro (HepG2 cell)</td>
<td>It has anti-inflammatory and anti-lipolytic effects, and also binds to proliferating cell nuclear antigen to ameliorate liver injury and promote liver regeneration.</td>
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<td>[8]</td>
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NAFLD, nonalcoholic fatty liver disease; PPARα, peroxisome proliferator-activated receptor α; HFD, high-fat diet.

| Table 1 Study on the mechanism of action of main single TCM and prescriptions in the treatment of MASLD |
|---|---|---|---|---|---|
| Liver regeneration | Procyanidin B2, extracted from *Cranage pinnatifida* and other Chinese herbs, is a natural food colourant that can protect the liver and treat NAFLD by activating the Nrf2/Keap1 and AMPK/GSK-3β pathways while inhibiting the PISK/ACT/mTOR pathway [10]. Protocanaxadil, which is extracted from *Gynostemma pentaphyllum*, regulates lipid metabolism in hepatocytes by activating the AMPK/Sirt1 signalling pathway [11]. Curcumin is extracted from *Curcuma Longa* and resveratrol is extracted from peanuts and berries. When used together, they may improve NAFLD symptoms by inhibiting the PISK/ACT/mTOR axis and the HIF-1/VGEF axis [12]. |

**Chinese herbal compound.** The Sheng Formula, developed by the Shanghai University of Traditional Chinese Medicine for the treatment of NAFLD, consists of *Salviae Millorrihiae Radix et Rhizoma* (Danshen), *Puerariae Lobatae Radix* (Gegen), and other components. It contains 39 active ingredients, including puarin, and achieves its therapeutic purpose by reducing ACX1 activity, activating the PPARα/CPT1A signalling pathway, promoting β-oxidation of fatty acids in liver cells, and inhibiting lipid accumulation [13]. The combination of Sanhuang Xiexin decoction and Baihu decoction with *Atractylodis Rhizoma* (Cangzhu) can treat stomach fires. According to experimental results, it exerts anti-inflammatory and lipid-regulating effects by inhibiting the JNK/NF-κB and ERK/NF-κB signalling pathways [14]. Huangqin decoction is a compound prescription with a long history in TCM and is composed of *Scutellariae Radix* (Huangqin), *Paeoniae Radix Alba* (Baishao), and other Chinese herbs. Huangqin decoction regulates lipid metabolism by inhibiting the Sirt1/NF-κB signalling pathway [15].

**Regulation of gut microbiota**

The basis of the interaction between the gut microbiota and the liver is the gut-liver axis, in which the liver is exposed to metabolites of the gut microbiota through the portal vein. Disturbances in the gut microbiota may lead to metabolic disorders, degeneration, and necrosis of liver cells [16]. External environmental stimuli such as alcohol and high-fat diets (HFDs) can increase the risk of microbial exposure and liver inflammation. Extracts and compound prescriptions of TCM mainly exert their therapeutic effects by improving the distribution of gut microbiota and their metabolites, thereby affecting the activities of classical pathways related to lipid metabolism and energy metabolism, such as the PPARα protein pathway mentioned earlier. At the same time, they can also increase intestinal barrier function by upregulating the expression of tight junction proteins like zonula occudens-1 (ZO-1), reducing the stimulation of lipopolysaccharides, inhibiting the activities of classical inflammatory pathways involving nuclear factor kappa-β (NF-κB), and alleviating NAFLD.

**Chinese herbal extract.** Angelica sinensis polysaccharide, derived from *A. sinensis* (Oliv.) Diels, functions as a health supplement that regulates hepatic lipid metabolism through modulating gut microbiota and activating the propionate/ERα axis [17]. The α-D-1,3-glucan, isolated from radix puerariae, activates the PPARα signalling pathway by upregulating gut microbiota such as *Flintibacter*, *Butyricoccus*, and *Oscillibacter* and their metabolites, thereby improving lipid and energy metabolism. Additionally, it reduces intestinal lipopolysaccharide-induced inflammation by inhibiting the NF-κB signalling pathway and activating the FXR signalling pathway to regulate energy metabolism, ultimately treating NAFLD [5]. *Polypaga japonica* Houtt., which is commonly used in the clinical treatment of inflammatory diseases, significantly improved liver injury and intrahepatic lipid deposition in MCD-NASH mice. The underlying

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mechanism is attributed to the reduction in the Firmicutes-to-Bacteroidetes ratio (F/B) and the concurrent increase in the relative abundance of Dubosiella, Akkermansia, and Turicibacter. Additionally, it improves liver metabolism in NASH mice by modulating the metabolic pathways of histidine and tryptophan [18]. The study of the therapeutic mechanism of Zanthoxyli bungeanum Maxim. in NAFLD reveals that it downregulates Actinobacteriota while upregulating the relative abundance of Bacteroidota in the gut microbiota of NAFLD mice, thereby affecting the activities of pathways such as PPARα and promoting fatty acid oxidation [6].

Dendrobii officinalis Kimura et Migo can enhance intestinal barrier function by elevating the relative abundance of gut microbiota including Lactobacillus acidophilus, Prevotella, and Akkatales while decreasing the relative abundance of Gram-negative bacteria such as Sutterella and Escherichia-Shigella. This results in the inhibition of lipopolysaccharide from enterotoxigenic bacteria, the liver through portal vein circulation, reducing toll-like receptor 4 (TLR4) and NF-κB-mediated inflammatory responses, thereby exerting a therapeutic effect on NAFLD [19].

Chinese herbal compound. Triphala, a traditional Tibetan medicine formula in China, is composed of three herbal plants: Terminalia chebula, Terminalia bellirica, and Phyllanthus emblica. Experimental results have demonstrated that Triphala can protect liver cells by increasing the relative abundance of Lactobacillus in the intestines of HFD rats, promoting the secretion of short-chain fatty acids, and reshaping the intestinal microbiota environment [7]. The Xie Zhuo Tiao Zhi decoction, derived from “Zexie Decoction” in “The Essentials of the Golden Chamber”, comprises Chinese herbal such as Alismatis Rhizoma and Atractylodis Rhizoma. Xie Zhuo Tiao Zhi decoction primarily improves cell pyroptosis, lipid accumulation, and other injuries by increasing the relative abundance of Lactobacillus valens and intervening in purine metabolism and related pathways [20]. Xiao-Ke-Yin is a medicine-food homology formula comprising Polygonati Rhizoma and Dioscoreae Rhizoma. Xiao-Ke-Yin downregulates cholesterol synthesis-related genes such as Hmgcr and Mvkb, inhibits the DCA/LCA-FXR-FGF15 signalling pathway, increases the relative abundance of Bacilli, and reduces the relative abundance of Clostridia, Parabacteroides, and Bacteroides, thereby improving glucose and lipid metabolism [8]. Zhishi Dazhao decoction, composed of eight Chinese herbs, including Aurantii Fructus Immaturus (Zhishi) and Rhei Radix et Rhizoma (Dahuang), has the effect of clearing heat and dissolving blood stasis (removes harmful substances deposited in the body). Zhishi Dazhao decoction can reduce the F/B ratio in the intestine, increase the expression of tight junction proteins such as occludin and ZO-1, decrease LPS permeability, and improve NAFLD symptoms [21]. Lingguizhugan decoction, which consists of Chinese herbs such as Peria (Fuling) and Cinamomoni Ramulus (Guizhi), ameliorates hepatic lipid metabolism and inflammation by modulating 11 genera of intestinal bacteria and related metabolites, including downregulating the relative abundance of Ruminococcus_t, Odoribacter, and Butyrivimonas [22].

Inhibition of ferroptosis
Ferroptosis, a unique form of programmed cell death, is primarily characterised by iron overload and lipid peroxidation. Clinical and experimental studies have identified varying degrees of iron metabolism disorders and lipid peroxide accumulation, which are characteristic of ferroptosis in multiple liver diseases. For example, ferroptosis in hepatocytes and intrahepatic macrophages promotes progression from simple steatosis to steatohepatitis. Therefore, inhibition of ferroptosis may be a novel therapeutic strategy for NAFLD [23]. Chinese herbal extracts protect hepatocytes by regulating multiple pathways related to ferroptosis. Many key proteins in these pathways, such as SIRT1 and PPARα, are also involved in regulating lipid metabolism and energy metabolism, thus exerting multiple effects in alleviating NAFLD.

Chinese herbal extract. Citri Grandis Exocarpium (Huaajuhang) can inhibit the TF/TIR signalling pathway, increase the expression of Ferroportin 1 (Fpn1), and improve intracellular iron deposition [24], Puerarin, isolated from Pueraria lobata (Willd.) Ohwi, activates the SIRT1/Nrf2 signalling pathway to inhibit ferroptosis, thus improving NAFLD [25]. Verbenalin, the main component of Verbena officinalis L., inhibits ferroptosis and improves liver injury by modulating the MDMX/PPARα signalling pathway [26]. Researchers found that Arbutin can bind to fat mass and obesity-associated protein to inhibit its function while promoting m6A methylation in the 3’-UTR region of solute carrier family 11 member 11 (SLC7A11) (a member of the solute carrier family, mainly involved in the transport of amino acids across the plasma membrane), and inhibiting ferroptosis in hepatocytes of high-fat diet mice [27]. Epigallocatechin gallate, an active component of tea polyphenols, can scavenge mitochondrial reactive oxygen species in hepatocytes and inhibit activation of the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, thereby inhibiting ferroptosis and exerting a therapeutic effect on NAFLD [28].

Chinese herbal compound. Erchen decoction removes dampness and eliminates phlegm, and it is composed of Chinese herbs such as Pinelliae Rhizoma and Citri Reticulatae Pericarpium. Research has shown that this prescription can upregulate the expression of Caveolin-1 (Cav-1), thereby inhibiting the protein levels of fatty acid synthase (FASN), sterol regulatory element-binding protein 1 (SREBP1), and other proteins, and inhibiting ferroptosis to achieve therapeutic effects [29].

T2DM and its complications
T2DM is a clinical syndrome primarily characterised by chronic hyperglycaemia, which stems from a combination of genetic and environmental factors. It is often associated with long disease duration and numerous complications, frequently affecting vital organs such as the heart, brain, and kidneys, which can be life-threatening in severe cases [30]. In TCM, T2DM treatment emphasises holistic regulation, syndrome differentiation, and comprehensive adjustment to restore balance in yin and yang, and coordinate the functions of the visceral organs. TCM-based therapies offer unique advantages, including gradual and sustained therapeutic effects as well as minimal side effects and toxicities.

Diabetes complications involve multiple organs and systems and represent the leading cause of diabetes-related morbidity and mortality. They are also significant contributors to new cases of blindness, renal failure, and nontraumatic lower limb amputations among adults. Diabetes-related complications can be broadly classified into vascular and non-vascular categories, with further subdivisions into microvascular complications (including nephropathy, retinopathy, and neuropathy) and macrovascular complications (coronary heart disease, peripheral arterial disease, and cerebrovascular disease). Microvascular complications are unique to diabetes. Non-vascular complications include gastroparesis and male erectile dysfunction (ED) [31, 32]. Extensive clinical research has indicated that chronic hyperglycaemia is a crucial contributing factor to diabetes-related complications. However, the mechanisms underlying functional abnormalities in various cells and organs vary, resulting in different effects of Chinese herbal monomers, extracts, and compound prescriptions for the treatment of diabetes complications (Table 2) [33–38].

T2DM
The early stages of T2DM, pancreatic β-cell dysfunction emerges, which progresses to cellular damage or even cell death over the course of the disease [39]. Chinese herbal medicine (CHM) has distinct characteristics in the prevention and treatment of diabetes and adopts a holistic approach tailored to individual patients based on their syndromes, symptoms, constitution, disease duration, and age. Leveraging modern techniques such as network pharmacology, molecular pharmacology, and molecular pathology, a comprehensive analysis was conducted on the components of CHM, their targets, and disease targets. This analysis established a common target network that clarified the key pathways or targets of the multicomponent active ingredients in CHM, including the PI3K/Akt signalling
pathway. Consequently, the patterns of CHM and its compounds prescribed for preventing IR and ameliorating insulin secretion disorders have been elucidated.

**Improvement of defects in pancreatic islet β-cell function and IR.** Schisandin B, extracted from *Schisandra chinensis* (Wuweizhi), binds to glucagon-like peptide-1 receptors (GLP-1R). GLP-1 is a gut hormone secreted by the ileum and colon that promotes insulin release. After binding to GLP-1R, Schisandin B activates the cAMP/PKA signalling pathway, thereby promoting insulin secretion at the cellular level [40]. Mung bean exosome-like nanoparticles, derived from mung bean sprouts, enhance protein phosphorylation levels, inhibit the activity of the PI3K/Akt signalling pathway, and downregulate its downstream protein glycogen synthase kinase-3β (GSK-3β). This promotes the expression of antioxidant-related proteins nuclear factor erythroid-derived 2-like 2 (Nrf2) and heme oxygenase-1 (HO-1), enhancing the antioxidant stress capability of the cell. Simultaneously, mung bean exosome-like nanoparticles upregulated the expression of glucose transporter 4 (GLUT4), optimising the ability of cells to uptake glucose and improving the symptoms of T2DM mice through multiple pathways [41].

*Rosa roxburghii* Tratt. (silk-spinning rose) possesses potential anti-diabetic activity and contains over 20 active ingredients, such as ellagic acid and quercetin, among which 13 are related to the treatment of T2DM. These active ingredients can exert therapeutic effects through multiple signalling pathways such as PI3K/ATK and RAS [42]. Mulberry extract (*Morus alba* L.), has good hypoglycaemic effects. Experiments have shown that Mulberry extract can exert its effects by activating the AMPK/GLUT4 and AMPK/ACC signalling pathways [43]. Lycopene, derived from tomatoes and other fruits, has been found to reduce the inflammatory level of pancreatic β-cells by inhibiting the TLR4/MyD88/NF-κB signalling pathway, which helps improve their function [44]. Sinomine, an active compound extracted from *Sinomenium acutum*, can activate the EGF/Nrf2/HO-1 axis to inhibit ferroptosis, and improve the inflammatory state and oxidative stress of pancreatic β-cells, thus treating T2DM [33]. *Hippophae Pructus*, a TCM with spleen-invigorating effects, contains total flavonoids of *Hippophae rhamnoides* as its main component. Total flavonoids of *Hippophae rhamnoides* inhibits inflammatory responses and

| Table 2 Study on the mechanism of action of the main single TCM in the treatment of T2DM its complications |
|---------------------------------------------------|------------------------------|-----------------|-----------------|------------------|-----------------|
| Single Chinese medicine/prescription | Main components of Chinese herbal extracts/active ingredients/prescriptions | Type of study | Main findings | References |
| **Stephanie Tetrandrae Radix** | Stolon | Sinomenine | In vivo experiments (rats) | Can activate Nrf2/HO-1 axis to inhibit iron death and treat T2DM. | [33] |
| **Yu-Ye decoction** | / | Dioscorea oppositifolia L., Astragalus mongholicus Bunge | In vivo experiments (rat), biochemical markers, metabolomics | Modulation increases the number of Lactobacillus and Candidatus_Saccharimonas genera and decreases the number of Allobaculum and Desulfovibrio in the intestinal flora of rats via the tryptophan and triglyceride metabolism pathway. | [34] |
| **San-Huang-Yi-Shen capsule** | / | Astragalus mongholicus Bunge, Cuscuta chinensis Lam., Salvia miltiorrhiza Bunge | In vivo experiments (mice), transmission electron microscopy | Inhibition of iron death and amelioration of mitochondrial damage and cellular iron overload status by up-regulation of cystine/GSH/GPX4 axis expression for the treatment of diabetic nephropathy (DN). | [35] |
| **Lychee seed** | Mature seed | Lychee seed polyphenol (LSP) | In vivo (mice), in vitro (hREC), flow cytometry | Expression of VEGF and NLRP3 inflammatory vesicles was significantly reduced in mouse retinal tissues, effectively inhibiting neoangiogenesis and inflammatory response, and improving blood-retinal barrier damage. | [36] |
| **Catharanthus roseus (L.) G. Don** | Flower | Vincamine | In vivo experiments (mice) | Alleviation of inflammatory response through inhibition of β-Arrestin2/1xβa/NF-κB axis, activation of CaMKII/AMPK/SIRT1/PGC-1α axis to regulate mitochondrial function, and amelioration of nerve injury. | [37] |
| **Shaofu Zhuyu decoction** | / | Isorhamnetin, quercetin, chrysophanic acid | In vivo experiments (rat), transcriptomics, network pharmacology, molecular docking, cellular thermal displacement assay experiments | Significantly improved erectile function and alleviated inflammation in the corpus cavernosum of DM rats through multi-targets such as CYP1B1, LCN2, SLC6A4 and the PI3K-AKT signalling pathway. | [38] |

T2DM, type 2 diabetes mellitus; VEGF, vascular endothelial growth factor; NLRP3, NOD-like receptor family pyrin domain containing 3; DN, diabetic nephropathy; LSP, Lychee seed polyphenol; CYP1B1, cytochrome P450 family 1 subfamily B member 1; LCN2, Lipocalin-2; SLC6A4, solute carrier family 6 member 4.
alleviates T2DM symptoms by suppressing the protein levels of protein kinase C, alpha (PRKCA), mitogen-activated protein kinase 10 (MAPK10), and p65 TNF-α [45]. The Zibu Piyun recipe is an effective prescription composed of Talinum paniculatum, Dioscorea Rhizoma, and other ingredients for treating cognitive dysfunction. Diabetes-associated cognitive decline is brain damage caused by diabetes. Zibu Piyun recipe can increase the expression of peroxisome proliferator-activated receptor γ coactivator 1-alpha (PGC-1α) and Mitofusin 2 (Mfn2), protecting mitochondria by improving mitochondrial biogenesis, and regulating insulin sensitivity to alleviate IR [46]. Plantaginis Semen-Coptidis Rhizoma is a traditional compound formula with good hypoglycemic effects, primarily treating T2DM by inhibiting the AGE/RAGE signalling pathway and reducing pro-inflammatory cytokines, reactive oxygen species, and reactive nitrogen intermediates [47]. Huayuwendan decoction clears heat, eliminates phlegm, and dissipates blood stasis. It consists 292 chemical components and may exert anti-inflammatory effects and improve metabolic disorders in T2DM by inhibiting the IL-17/NF-κB signalling pathway [48].

Regulation of gut microbiota. Similar to NALFD, gut microbiota dysbiosis is closely associated with the development of T2DM, causing pathological processes such as hyperglycaemia and IR. This is an important factor that influences the onset and progression of T2DM. C1H6 monomers or extracts, compounds, and dietary therapy based on TCM can improve gut microbiota distribution, regulate amino acid metabolism, and exert anti-inflammatory and antioxidant effects, leading to the improvement of pancreatic islet β-cell dysfunction and IR, exerting hypoglycaemic actions, and alleviating clinical symptoms of T2DM. Polygonatum sibiricum polysaccharide, extracted from Polygonatum sibiricum Red., possesses hypoglycemic and anti-inflammatory effects. Polygonatum sibiricum polysaccharide can influence the serum metabolic pathways of arginine, proline, tryptophan, and glutathione by reducing the F/B ratio, increasing the relative abundance of Blautia, Akkermansia, and Parabacteroides; and decreasing the relative abundance of Megamonas funiformis and Escherichia, thereby treating T2DM [49]. Bear bile powder, extracted from the bile of black bears, can further reduce blood glucose and lipid levels by improving tryptophan, sugar, and triglyceride metabolism pathways and increasing the relative abundance of Romboutia while decreasing the relative abundance of Dubosia and Anaerostipes, ultimately improving T2DM [50]. Infusion or intake of amino acids can induce IR, and the addition of elevated levels of circulating branched-chain amino acids to a HFD can severely exacerbate IR. Mortus alba L. water extracts can improve IR by improving the distribution of multiple microbiota, such as Anaerovorax, Bilophila, Blautia, and Clostridium, and inhibiting branched-chain amino acids levels in the body [51]. Total Astragalus saponins, extracted from Astragalus membranaceus, can delay the progression of T2DM by increasing the relative abundance of Bildobacterium and Ruminococcaceae UCG-014 while decreasing the relative abundance of Lactobacillus and Turicibacter, and inhibiting the PI3K/Akt/GSK-3β signalling pathway [52].

When insulin deficiency and IR occur, they can independently or simultaneously cause metabolic disorders of carbohydrates, fats, proteins, water, and electrolytes, in addition to abnormal glucose metabolism. The Jiang-Tang-San-Huang pill, a classical prescription used clinically in the long-term treatment of T2DM, consists of Persicae Semen and Rhe Rhiz. et Rhizoma. It regulates bile acid (BA) metabolism and improves the pathological state of T2DM by reducing the F/B ratio and increasing the relative abundances of Romboutia, Turicibacter, and Bildobacterium [53]. Yu-ye decoction, another classical prescription for T2DM treatment composed of Chinese herbs such as Dioscoreae Rhizoma and Astragali membranaceus, alleviates T2DM by increasing the abundance of Lactobacillus and Candidatus Saccharimonas and decreasing the number of Allobaculum and Desalfovibrio in the gut microbiota of rats, thereby regulating tryptophan and triglyceride metabolic pathways [34]. Jiaoai pill, a compound commonly used clinically for T2DM treatment, is composed of Coptidis Rhizoma and Cinnamomi Cortex and exerts its therapeutic effect on T2DM by reducing the relative abundance of Actinobacteria and affecting the metabolism of multiple amino acids such as valine [54]. “Maccog”, a TCM tea made from Ophiopogonis Radix, Gynostemma pentaphyllum, and other herbs, can regulate intestinal microbial imbalance, effectively lower blood sugar and lipids, and offer advantages of convenience and simplicity in brewing [55].

Diabetic nephropathy (DN) DN is a microvascular complication of the kidneys caused by chronic hyperglycaemia that leads to metabolic imbalances such as dyslipidaemia. It is characterised by a complex pathogenesis, challenging treatment, and poor prognosis. Clinically, it mainly manifests as an elevated urinary albumin-to-creatinine ratio and a continuous decrease in glomerular filtration rate [56]. Early detection, early intervention, and effective treatment can delay irreversible kidney damage and progression to end-stage renal failure, which has significant medical and social value. Chinese herbal monomers, extracts, and compounds primarily regulate programmed cell death, inflammation, fibrosis, and oxidative stress.

Chinese herbal extract. To explore the therapeutic mechanism of Rosa laevigata Michx. polysaccharide in treating DN by alleviating renal inflammation and oxidative stress, experimental results show that Rosa laevigata Michx. polysaccharide improves DN by modulating riboflavin and tryptophan metabolism, increasing the levels of tryptophan metabolites such as 3-hydroxybenzoic acid and N-acetylserotonin, and inhibiting ferroptosis [57]. Lupone, extracted from “Dajiaojifen”, can inhibit the NF-κB pathway to alleviate inflammation, while also delaying the progression of renal fibrosis by inhibiting the TGF-β/Smad/CTGF pathway, thereby delaying the progression of DN [58]. Hirudin improves cell pyroptosis and inhibits kidney injury in DN mice by downregulating the expression of interferon regulatory factor 2 (Irf2) and inhibiting the regulation of Gasdermin D (Gsdmd) [59]. Rutin, a polyphenolic flavonoid found in Sophora flavescens, restores autophagy to alleviate DN by inhibiting the phosphorylation of the PI3K/AKT/mTOR axis, a metabolic process that maintains intracellular homeostasis and is closely associated with kidney diseases [60].

Chinese herbal compound. The san-Huang-Yi-Shen capsule is composed of TCM herbs, such as Astragalus Radix (Huangqi) and Cascatae Semen (Tusizi). It improves mitochondrial damage and cellular iron overload by upregulating cytochrome/GSH/GPX4 axis expression, inhibiting ferroptosis, and alleviating DN [35]. The QiZhu TangShen Formula consists primarily of eight traditional Chinese herbs including Astragali Radix and Ligustri Lucidi Fructus. It replenishes qi, dissolves blood stasis. QiZhu TangShen Formula improves glycolipid metabolism and stabilises renal function by regulating pathways such as PI3K/AKT and MAPK/ERK [61]. Gan-song Yin is an ancient formula for the treatment of diabetes utilising “spices” such as pinewood, agarwood, and clove. It contains active ingredients like hypericin and gallic acid, which interfere with adipocyte secretion of miR-21-5p, regulate the TGF-β1/SMAD signalling pathway, and inhibit the proliferation of renal tubular epithelial cells [62]. Shen-Qi-Jiang-Tan granule originates from the prescription “Huangqi decoction” and is composed of Schisandrae Chinensis Fructus and Astragali Radix. It acts on the NFκB signalling pathway, downregulates the expression levels of downstream p-p65, p-JNK, and caspase-3, inhibits apoptosis, and improves DN through multiple pathways [63]. Yi-Shen-Hua-Shi granules are an effective formula for the clinical treatment of DN, composed of Poria and Alismatis Rhizoma. It increases the abundance of Lactobacillus and Lactobacillus murinus in the intestine and regulates glycerophospholipid metabolism and related pathways to exert its effects [64]. ShenKang injection replenishes Qi and and removes harmful substances. Extracts from Chinese herbs, such as Rhus palmatum, can inhibit Kclh-like ECH-associated protein 1 (Keap1), promote the expression of Nrf2, Ho-1, and glutathione peroxidase 4 (Gpx4), improve cellular oxidative stress, and delay disease.
progression [65]. Numerous experiments conducted over the past year have confirmed that TCMs can treat DN by modulating the gut microbiota; however, the underlying mechanisms remain unclear. Specifically, most experiments focusing on the gut microbiota have only observed changes in the abundance of beneficial and pathogenic bacteria without conducting in-depth investigations into the targets whereby pathogenic bacteria and their metabolites damage the kidneys.

### Diabetic retinopathy (DR)

The prevalence of DR among global diabetic patients stands at 22.27%, which can lead to blindness in severe cases [66]. TCM treatment has been shown to improve clinical symptoms, vision, and fundus function in patients with DR. Currently, most studies have small sample sizes and short observation periods. In future, by increasing the sample size and extending the observation period, further exploration of its long-term efficacy and underlying mechanisms could be conducted, providing a strong basis and reference for its clinical application.

#### Chinese herbal extract.

*Cucurma wenyujin* Y. H. Chen and C. Ling (Wenjyujin) promote blood circulation and remove blood stasis. Elema-1,3,7(11),8-tetraaza-8,12-lactam, one of its active ingredients, can improve vitreous microvascular leakage by inhibiting the expression of tumor necrosis factor-α (TNF-α) and intercellular adhesion molecule-1 (ICAM-1), as well as vascular endothelial growth factor (VEGF) phosphorylation [67]. LSP, isolated from lychee seeds, significantly reduces the expression of VEGF and NLRP3 inflammasomes in the retinal tissue of db/db mice after LSP treatment. Both in vitro and in vivo experiments have demonstrated that LSP can effectively inhibit neovascularization and inflammatory response, thereby improving blood-retinal barrier damage [36].

#### Chinese herbal compound.

Bushen Huoxue prescription consists of *Rehmanniae Radix* (Dihuang) and *Salviae Miltiorrhizae Radix et Rhizoma* (Danshen) among other herbal ingredients. It can be used to prevent and treat ocular diseases caused by an ascending fire deficiency. Pharmacogenomic research has shown that Bushen Huoxue prescription contains active ingredients such as ajugol and protocatechuic acid, which improve retinopathy in diabetic rats through various metabolic pathways involving glycine and sucrase [68]. The Qiming granules are formulated with *Astragali Radix* (Huangqi) and *Cassiae Semen* (Juemingzi) among other TCMs. They contain active ingredients like quercetin and kaempferol, which treat DR by regulating the activities of hypoxia inducible factor 1-α (HIF1α), VEGF, and the PI3K/AKT signalling pathway [69].

### Diabetic peripheral neuropathy (DPN)

DPN is characterised by distal symmetry and multiple nerve dysfunction in the limbs, which can lead to disability and deformities in severe cases [70]. The pathogenesis of DPN is not fully understood, and its prevention and treatment remain challenging. The mechanisms of action of herbal extracts and compound prescriptions in treating DPN include inhibition of inflammatory responses, suppression of oxidative stress, correction of metabolic disorders, and improvement of microcirculation.

#### Chinese herbal extract.

Vinacine, derived from the *Catharanthus roseus* (L.) G. Don, can alleviate inflammatory responses by inhibiting the β-Arrestin2/3/B/A/NF-NF axis, activating the CaMKKβ/AMPK/SIRT1/GC-1u axis to regulate mitochondrial function, and improve nerve damage [37]. Honokiol, extracted from *Magnolia officinalis* Rehd. et Wils. (Houpo), upregulates the expression of SLC7A11 and GPX4, increases Nrf2 protein in the nucleus, and inhibits ferroptosis. It also activates the AMPK/SIRT1 pathway to alleviate oxidative stress. Furthermore, honokiol can increase the sensitivity of T2DM rats to heat and mechanical stimuli, thereby improving DPN [71].

#### Chinese herbal compound.

Compound Qiyun granules, a TCM compound, mainly consists of *Astragali Radix* (Huangqi), *Cicadae Periostracum* (Chantui), and other ingredients. Compound Qiyun granules treats DPN by inhibiting the PI3K-Akt and MAPK axes, lowering the threshold of T2DM rats to heat and mechanical stimuli, and improving pathological conditions such as sciatic nerve myelin sheath separation [72].

### DED

ED is a common sexual dysfunction defined as the inability of men to achieve or maintain an erection sufficient for sexual intercourse, which significantly affects their quality of sexual life [73]. Epidemiological data indicate that over 100 million people worldwide suffer from ED, and this number is expected to exceed 300 million by 2025 [74]. The prevalence of diabetes mellitus (DM) in China is as high as 10.9%, and age is an independent risk factor for ED that is positively correlated with the severity of DED [75]. Owing to its complex neurovascular aetiology, DED is difficult to treat, and the current first-line treatments for ED, oral phosphodiesterease-5 inhibitors, show limited efficacy [76]. In the context of an ageing society, there is an increasing trend in patients with DED [77]. TCM which focuses on improving the physical and psychological states of the elderly population, has been successful in the prevention and treatment of DED. However, there are few reports on its underlying mechanisms, deserving attention and further research.

#### Chinese herbal extract.

NO/cGMP is an essential signalling pathway for penile erection, and cGMP can influence the activity of contractile proteins in the corpus cavernosum smooth muscle cells by regulating calcium channels, thereby improving male erectile function. *Ailbisia syggia* leaves contain various compounds that improve sexual functions, such as tryptophan and glutamine. Studies have found that NO levels increase with *Ailbisia syggia* leaves intake, leading to the alleviation of ED [78]. Icarin and Iciscaride II are active components of the *Epimedium brevicornu* Maxim. (*Yinxyanghuo*), which can improve cavernosal endothelial cell dysfunction and neuropathy, treating DED by inhibiting the AgSα-RAGE-OS axis and enhancing the expression of sproftry-related EHV1 domain-containing protein 1 (SPRED1) [79]. *Gynochthodes officinalis* (F.C. How) Razafim. & B BREMER is a traditional medicine used to treat ED. Studies have shown that after fermentation, *Gynochthodes officinalis* (F.C. How) Razafim. & B BREMER alleviates inflammation in rats with DED by activating the PI3K/Akt/eNOS pathway, promoting angiogenesis in the corpus cavernosum, and assisting in normal erection [80].

#### Chinese herbal compound.

Shaofu Zhuyu decoction is commonly used for the treatment of DED. Its main component, isorhamnetin, can reduce inflammation in the corpus cavernosum by regulating multiple targets, such as *CYP1B1*, *LCN2*, *SLEC6A4*, and the PI3K/AKT signalling pathway, significantly improving erectile function in rats with DM [38].

### DGP

The primary symptoms of DGP include early satiety, postprandial fullness, nausea, vomiting, abdominal distension, and upper abdominal pain [81]. Currently, Western medicine treats DGP primarily through the administration of gastric emptying-promoting drugs, antiemetic drugs, acid-suppressing drugs, antibiotics, or the surgical implantation of electrical stimulators to stimulate the gastric muscles, aimed at alleviating symptoms and improving patients’ quality of life [82]. On the contrary, TCM relies on the principles of syndrome differentiation and treatment, providing individualised therapy based on the different stages, developmental phases, and syndrome types of DGP. It addresses this problem from a holistic perspective, thereby benefiting more patients with DGP. However, its mechanism of action remains unclear. *Alpinia officinarum* Hance, which is a traditional Chinese herb used to treat gastrointestinal diseases, can improve delayed gastric emptying symptoms in mice by upregulating the expression of Phospholipase C β 3 (PLCβ3) and increasing intracellular Ca2+ concentration when used in combination [83].

### Obesity

Obesity is a chronic metabolic disorder that is caused by multiple
factors. When the body consumes more calories than it expends, the excess calories are stored in the body as fat, leading to conditions such as cardiovascular disease, diabetes, and certain cancers. Extracts, compounds, and TCM-based teas primarily treat obesity by regulating lipid metabolism, IR, and antioxidant activities (Table 2) [84–88].

### Chinese herbal extract

Black tea is obtained through the post-fermentation of tea leaves (*Camellia sinensis*), of which theabrownin is the primary component. In vivo studies have shown that theabrownin can regulate the serotonin-related pathways eNOS/HSIs and SERT/MAO-A and upregulate the relative abundance of serotonin-related gut microbiota such as *Akkermansia*, *Bacteroides*, and *Parabacteroides*. Obesity can be prevented and treated by promoting fatty acid oxidation, fat decomposition, and oxidative stress, it prevents and treats obesity [84]. Liupao tea, a type of black tea, has been found that Liupao tea water extract can inhibit the expression of Peroxisome proliferator-activated receptor γ (PPARγ), CCAAT/Enhancer Binding Protein α (C/EBPα), and Fas cell surface death receptor (FAS) genes, all of which are related to lipid metabolism, lipid synthesis, and IR. Liupao tea water extract also activate the IRS-1/P3K/AKT/GLUT4 signalling pathway, enhances cellular antioxidant capacity, optimises glucose uptake, improves IR and fat production, and inhibits obesity [89]. It has been reported that red ginseng extracts improve glucose and lipid metabolism. Red ginseng extracts can activate TGR5 (BA receptor 5, regulating BA metabolism as well as host glucose, lipid, and immune metabolism), induce GLP-1 (which stimulates insulin secretion, inhibits glucagon secretion, and delays gastric emptying), increase circulating BAs and improve HFD-induced obesity and IR in mice [90]. Berberine, one of the main active components of *Coptidis Rhizoma*, can activate PPARγ (a member of the PPAR family closely related to lipid metabolic activities). This activation inhibits the activity of CCAAT/enhancer-binding protein α (Cebpα), Pparγ promoters, and Ho-1 promoters, thereby corrects lipid metabolism, reducing inflammation, and combating oxidative stress [91].

### Chinese herbal compound

Wen-Shen-Jian-Pi-Hua-Tan decoction, commonly used to treat obesity with decreased or deficient function of the spleen and kidney is composed of *Cinnamomum Cortex*, *Poria*, and other ingredients. Obesity can damage the kidneys and lead to obesity-related glomerulopathy (ORG). Wen-Shen-Jian-Pi-Hua-Tan decoction improves adipogenesis and renal BA metabolism in mice with ORG by upregulating FXR expression and activating the SIK1/SREBP-1c axis [85]. Si-Ni-San, a decoction composed of *Bupleuri Radix* and *Paoniae Radix* Alba, soothes the liver and relieves depression. It improves obesity by promoting fat decomposition via activation of the Akt/AMPK/HSL signalling pathway, specifically targeting the gut microbiota [92].

### Table 3 Action mechanism of main TCMs and prescriptions in the treatment of hyperuricemia, obesity and thyroid diseases

<table>
<thead>
<tr>
<th>Single Chinese medicine/ prescription</th>
<th>Main components of Chinese herbal extracts/active ingredients/ prescriptions</th>
<th>Type of study</th>
<th>Main findings</th>
<th>References</th>
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<tr>
<td>Camellia sinensis (L.) Kuntze</td>
<td>Theabrownin</td>
<td>In vivo experiments (mouse), untargeted metabolomics, faecal microbial transplantation, nuclear magnetic resonance</td>
<td>Up-regulation of the relative abundance of <em>Akkermansia</em>, <em>Bacteroides</em> and <em>Parabacteroides</em> against obesity and NAFLD through activation of eNOS/HSIs and inhibition of the SERT-MAO-A signalling pathway.</td>
<td>[84]</td>
</tr>
<tr>
<td>Wen-Shen-Jian-Pi-Hua-Tan decoction</td>
<td>Icarin, cinnamaldehyde, hesperidin, atracylodin, nobiletin and pachymic acid</td>
<td>In vivo experiments (rat), transmission electron microscopy, metabolomics</td>
<td>Improvement of adipogenesis and abnormal BA metabolism in ORG mice by up-regulation of farnesoid X receptor (FXR) expression and activation of SIK1/SREBP-1c axis.</td>
<td>[85]</td>
</tr>
<tr>
<td>Astragalus Radix</td>
<td>Bacillus subtilis-fermented <em>Astragalus membranaceus</em> (BFA)</td>
<td>In vivo experiments (mouse), metabolomics</td>
<td>Regulating the metabolism of histidine and purine and increasing the relative abundance of <em>Butyricimonas</em>, <em>Odoribacter</em> and <em>Collinsella</em> to increase fatty acid synthesis can effectively reduce uric acid.</td>
<td>[86]</td>
</tr>
<tr>
<td>DaiTongXiao</td>
<td>Elsholtzia rugulosa Hemsl., <em>Pinus tabuliformis</em> Carr.</td>
<td>In vivo experiments (rat), in vitro experiments (J774A.1 cells)</td>
<td>Modulation of intrinsic immune classical pathways to delay Graves’ ophthalmopathy (GO) progression by inhibiting NLRP3, NF-κB proteins intestinal microbial environment.</td>
<td>[87]</td>
</tr>
<tr>
<td>Yijung decoction</td>
<td><em>Zingiber officinale</em> Rosc. (Family: Zingiberaceae) rhizome</td>
<td>In vivo experiments (rat)</td>
<td>Inhibition of intestinal TLR4 and Nod2/Pgllp1 expression attenuates the inflammatory response and regulates <em>Prevotellaceae</em>, <em>Ruminococcaceae</em> and <em>Porabacteriodes</em> genera back to normal levels.</td>
<td>[88]</td>
</tr>
</tbody>
</table>

NAFLD, nonalcoholic fatty liver disease; BA, bile acid; ORG, obesity-related glomerulopathy; FXR, farnesoid X receptor; BFA, Bacillus subtilis-fermented *Astragalus membranaceus*; GO, Graves’ ophthalmopathy; NLRP3, NOD-like receptor family pyrin domain containing 3; NF-κB, nuclear factor kappa-B; TLR4, toll-like receptor 4.
**Hyperuricemia (HUA)**

HUA is a disease caused by the excessive accumulation of uric acid in the body. Deposition of uric acid monohydrate crystals in the joints, leading to local inflammation, is an important factor in the development of gouty arthritis [93]. Additionally, HUA is associated with various conditions, such as hypertension, diabetes, and kidney diseases. TCM treatment of HUA primarily aims to reduce the production of uric acid in the body, promote its excretion, alleviate inflammation, and prevent and treat diseases by regulating the gut microbiota.

**Chinese herbal extract**

Agapinin 7-O-glucoside extracted from *Paonia suffruticosa* Andrews reduces uric acid production in the body by inhibiting the activity of xanthine oxidase (XOD). It also alleviates symptoms in hyperuricaemic mice by inhibiting uric acid transporter 1 (URAT1) and glucose transporter 9 (GLUT9), enhancing the expression of (ATP)-binding cassette efflux transporter 2 (ABCG2) and organic anion transporter 1 (OAT1), and promoting uric acid excretion [94]. By utilizing *Bacillus subtilis* to ferment the Chinese herbal *Astragalus membranaceus*, BFA was obtained. BFA can effectively lower uric acid levels by regulating metabolites such as histidine and purine, increasing the relative abundance of *Butyricimonas*, *Odoribacter*, and *Collinsella*, thus promoting fatty acid synthesis [95].

**Chinese herbal compound**

DaTongXiao, a classic prescription by the Dai ethnic group in China for the treatment of GO, is primarily composed of *Elsholtzia rugosa* Hemsl. and *Pinus tabuliformis* Carr. Research has shown that DaTongXiao can delay the progression of GO by inhibiting NLRP3 and NF-kB proteins, thus regulating the classical pathway of innate immunity [87]. Qingre Huazhuo Jiangsu Decoction, composed of Chinese herbs, such as *Portia* (Fuling) and *Perilla frutescens* (Zisu), clears heat and reduces inflammation. It targets GO by inhibiting the PI3K/AKT/mTOR pathway and upregulating the expression of intracellular autophagy proteins [95]. Renal herb formula, a self-designed prescription consisting of *Astragalus Radix*, *Lonicerae Japonicae Caulis*, and other herbs, contains effective ingredients such as chlorogenic acid. Chlorogenic acid can increase B-cell lymphoma-2 (Bcl2) levels, decrease Bcl-2 associated X protein (Bax) levels to inhibit renal cell apoptosis, and simultaneously inhibit NF-kB-mediated inflammatory responses, thereby improving the symptoms of hyperuricaemia nephropathy [96].

**Thyroid diseases**

Thyroid diseases primarily include hyperthyroidism, hypothyroidism, thyroid nodules, and benign and malignant thyroid tumours. Their occurrence and development are closely associated with abnormalities in glycolipid metabolism, which can affect the hypothalamus-pituitary-thyroid axis, further influencing thyroid hormone levels and autoimmune status, ultimately leading to thyroid nodules, enlargement, or atrophy. Additionally, disturbances in the gut microbiota can contribute to the development of these diseases by participating in thyroid hormone metabolism, immune regulation, and cross-immune reactions.

**Chinese herbal extract**

Graves’ disease is characterised by thyroid enlargement and hyperthyroidism. HaiZao-KunBu, a TCM formula that can soften hard masses and dissipate nodules, contains active ingredients such as *Fucus vesiculosus*. These ingredients exert therapeutic effects by activating multiple classical signalling pathways, including PI3K-AKT and MAPK [97]. Parthenolide, isolated from *Tanacetum parthenium*, is effective in treating papillary thyroid carcinoma. It exerts an antitumour effect by regulating two key target proteins, PLAG2GA and PLAG2GA (which belong to the phospholipase A2 family and catalyse the hydrolysis of the second acyl group on phospholipid glycerol molecules. The resulting lipids play a role in inflammation, tissue damage, and the regulation of cellular metabolism) [98].

**Chinese herbal compound**

Yijing decoction, a classical prescription created by Zhang Zhongjing, consists of TCMs such as *Zingiberis Rhizoma Recens* and *Atractylodis Rhizoma*. It also warms and tonifies the body. Yijing decoction can inhibit the expression of TLR4 and Nod2/Pglyrp1 in the intestine, thereby reducing inflammatory reactions, regulating the distribution of gut microbiota, such as *Prevotellaceae*, *Parabacteroides*, and *Ruminococcaceae*, and improving the hypothemic state of hypothyroid rats [88].

**Discussion**

Recently, the boundaries between endocrine and metabolic diseases have become increasingly unclear. With further research, metabolic mechanisms have been found to play crucial roles in the pathogenesis of various endocrine diseases, thereby altering the traditional understanding of some diseases. The scope of endocrine metabolic diseases is expanding and metabolic interventions have become a common clinical treatment method. Interventions in metabolic processes can fully utilise the multi-target advantages of TCM. Research on the mechanisms of Chinese herbal monomers, extracts, and compounds in the treatment of endocrine metabolic diseases has focused on signalling pathways and network regulation mechanisms. Although a substantial body of literature has confirmed the efficacy of TCM in the treatment of T2DM, obesity, and other diseases, the underlying mechanisms remain unclear [99].

In recent years, the rapid development of various omics technologies has led to breakthroughs in the study of pathogenic and therapeutic mechanisms of endocrine metabolic diseases. These advanced technologies have not only revealed multiple pathways and modes of hormone signal transduction but also have greatly enriched our understanding of endocrine metabolic diseases and their prevention and treatment methods. Metabolomics is an emerging interdisciplinary field that provides new approaches to studying complex biological problems. Metabolomics has established a modern technological bridge between endocrine metabolic diseases, such as NAFLD, T2DM, DN, and TCM. By analysing differences in small molecule metabolites, this technology not only facilitates the early diagnosis of these diseases but also holds the potential to identify the active substances responsible for the primary efficacy of TCM compounds. This, in turn, aids the identification of targeted drugs for the treatment of endocrine metabolic diseases [100, 101].

However, the study of metabolomics also faces several challenges and limitations. First, metabolomics integrates knowledge and methods from multiple disciplines, including biology, physics, chemistry, and computational statistics, enabling a comprehensive and in-depth study of metabolic processes. However, because of its highly interdisciplinary nature, metabolomics research requires cross-disciplinary collaboration and communication, which places high demands on research teams. Second, in terms of qualitative analysis, although current technologies can detect a large number of metabolites, the proportion of identified and annotated substances remains low compared to the total number of detected substances. Thus, our understanding of the structure and function of many metabolites remains insufficient, limiting our comprehensive understanding of metabolic processes. In quantitative analyses, the results obtained from metabolomics are often static and integrative, making it difficult to capture the dynamic changes and subtle differences in metabolic processes. In addition, because of the complexity of metabolic processes in biological systems, a single quantitative result often fails to accurately reflect the true metabolic status of the body.

Endocrine metabolic diseases are a typical class of dynamic diseases involving complex interactions among multiple metabolic pathways and mechanisms throughout their course. Currently, there is a tendency towards overly static research approaches for these diseases.
For example, in cases of gut microbiota dysbiosis and ferroptosis abnormalities, existing research methods often fail to fully capture the patterns of change and interactions. The integration of multi-omics technologies offers a new perspective on research. By combining information from genomics, transcriptomics, proteomics, and metabolomics, we can gain a more comprehensive understanding of the full picture of disease development and the molecular mechanisms involved in the treatment process with TCM. The integrated research approach helps us to elucidate the multi-target, multi-pathway mechanisms of TCM, providing more precise and effective solutions for clinical treatment.

During research involving experimental animal models, the application of transgenic animals, gene targeting, gene knockout, and tissue-specific gene expression technologies allows for precise research methods targeting specific hormones or hormone receptor genes. This enables the accurate replication of animal models with overexpression (simulating endocrine gland hyperfunction), low expression (simulating hypofunction), or no expression of a single hormone or its receptor gene. This lays a solid experimental foundation for studying pathogenic genes, hormone genes (including hormone-binding-related proteins), receptor genes (receptor-regulating-related proteins), and candidate risk factor genes for these diseases.

However, the clinical treatment of TCM emphasizes syndrome differentiation and treatment. For example, in T2DM, TCM syndromes include the four states of “stagnation (poor body circulation), heat (excessive body heat or inflammation), deficiency (lack of energy), and damage (damage to tissue or function)”. The pre-diabetes stage corresponds to the “stagnation” state, the later stages commonly involve “heat” and “deficiency”, and the complication stage corresponds to the “damage” state. Preparing animal models that meet the requirements of TCM syndromes has always been a key challenge in experimental TCM research. This is mainly owing to the complexity and dynamic nature of TCM syndromes, which makes it difficult to fully simulate them using simple experimental methods.

At the same time, TCM theories such as the holistic concept, the theory of the Yin-Yang balance, the unique theories of Chinese herb properties have significant implications for guiding research at the cellular and molecular levels. These theories emphasize overall regulation and balance, which differs from the single-target treatment approach of Western medicine. Therefore, we need to consider how to integrate these unique TCM theories into modern biological research methods to comprehensively reveal the therapeutic mechanisms of Chinese medicine.

In reviewing the latest progress in TCM for treating endocrine and metabolic diseases, we also recognized the unique and significant clinical value of TCM complex prescriptions and single-herb formulations in their respective fields. TCM complex prescriptions, which contain multiple herbs, can target complex endocrine diseases through multiple-target and multi-pathway treatments. This comprehensive treatment approach can better regulate patients’ endocrine systems and enhance the treatment effects. Different herbs in complex prescriptions can act synergistically to enhance efficacy, reduce side effects, and improve patient tolerance and quality of life. In contrast, TCM single-herb formulations contain only one herb with a single component and a clear mechanism of action, which enables them to target a specific endocrine disease more directly. In clinical practice, TCM single-herb formulations may be a more suitable choice for patients with a single symptom, mild conditions, or those who need rapid symptom relief. Furthermore, because of their relatively few side effects, they are a better option for patients who are sensitive to medications or have other health issues. Based on the specific conditions and needs of the patients, an appropriate TCM complex prescription or single-herb formulation should be selected for treatment. Therefore, both have an important clinical value in the treatment of endocrine diseases.

With its profound theoretical system, rich practical experience, and unique complex prescriptions and active substances, TCM provides effective ways to treat endocrine and metabolic diseases, such as diabetes and thyroid diseases. TCM can assist in alleviating symptoms and improving patients’ quality of life by regulating Qi, blood, and organ functions; adjusting endocrine system functions with acupuncture therapy; and employing physical and psychological treatments such as massage and emotional regulation. With technological advancements, modern pharmacological research and the application of new acupuncture techniques have offered more possibilities for TCM in the treatment of endocrine and metabolic diseases. Further research and exploration are needed to fully exploit the unique advantages of TCM in this field and provide more effective and safer treatment options for clinical practice.

Summary and outlook

In summary, TCM has a vast potential for the prevention and treatment of endocrine and metabolic diseases. However, this approach has numerous challenges. With technological advancements, deepening research, and continuous refinement of researchers’ thinking, the standardisation and regularisation of TCM are bound to improve. This will not only propel further development of TCM theory but also promise to usher in new avenues and unprecedented breakthroughs in the treatment of endocrine and metabolic diseases. We believe that the integration of TCM and modern medicine will lead to broader horizons in the treatment of these diseases.

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