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Review Article

Nourishing Yin traditional Chinese medicine: potential role in the prevention and treatment of type 2 diabetes

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Abstract: Type 2 diabetes mellitus (T2DM), a common and frequently occurring disease in contemporary society, has become a global health threat. However, current mainstream methods of prevention and treatment, mainly including oral hypoglycemic drugs and insulin injections, do not fundamentally block the progression of T2DM. Therefore, it is imperative to find new ways to prevent and treat diabetes. Traditional Chinese medicine is characterized by multiple components, pathways, and targets with mild and long-lasting effects. Pharmacological studies have shown that nourishing yin traditional Chinese medicine (NYTCM) can play a positive role in the treatment of T2DM by regulating pathways such as the phosphatidylinositol 3-kinase/serine-threonine kinase, mitogen-activated protein kinase, nuclear factor-kappa B, and other pathways to stimulate insulin secretion, protect and repair pancreatic β cells, alleviate insulin resistance, ameliorate disordered glucose and lipid metabolism, mitigate oxidative stress, inhibit inflammatory responses, and regulate the intestinal flora. The pharmacologic activity, mechanisms, safety, and toxicity of NYTCM in the treatment of T2DM are also reviewed in this manuscript.

Keywords: Type 2 diabetes, nourishing Yin traditional Chinese medicine, pharmacological mechanism, active ingredients, safety, toxicity

Introduction

The pathogenesis of diabetes mellitus (DM), which is a chronic metabolic disorder, is closely correlated to the interaction of genetic and environmental factors, leading to a disturbance of insulin (INS) secretion or different degrees of insulin resistance (IR) [1]. DM is a medical condition characterized by hyperglycemia and typical clinical manifestations, including polydipsia, polyuria, polyphagia, and weight loss. This disease often affects large and small blood vessels as well as peripheral nerves, resulting in long-term damage, functional impairments, and failure of different organs including the eyes, kidneys, nerves, and blood vessels [2, 3]. These effects result in conditions such as retinopathy, renal failure [4], diabetic foot [5], diabetic neuropathy [6], and diabetic osteopathy [7], which significantly impact an individual's health and quality of life. According to the 2021 Global Diabetes Map data released by the International Diabetes Federation, the global prevalence rate of DM among the 20-79-year-old age group was approximately 10.5% (536.6 million people) in 2021, and it is estimated that the rate will increase to approximately 12.2% (783.2 million people) by 2045 [8]. Therefore, DM has become a critical global public health issue that poses a serious threat to human health [9], and its prevention and control are becoming increasingly challenging.

Currently, there are two main drug treatment methods for DM in clinical practice: injection of INS and oral hypoglycemic agents. Although oral administration of INS is performed, absorption barriers, such as enzyme and chemical barriers, result in low bioavailability (<0.5%) [10]; therefore, INS has mainly been subcutaneously injected since its discovery by Banting in 1921 [11]. Although various types of oral hypoglycemic agents exist, including biguanides, thiazolidinediones, sulfonylureas, alpha-glucosidase

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inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists [12], taking these drugs can easily lead to side effects such as hypoglycemia, gastrointestinal reactions, and rash. Because DM is incurable, the focus of treatment is optimal glycemic control and prevention of complications, thus enhancing an individual's quality of life [13].

According to the basic theoretical views of traditional Chinese medicine (TCM), maintaining the balance between Yin and Yang is crucial for optimal health [14]. However, this equilibrium is disrupted in pathological states. DM is considered as "Xiaoke" in TCM, primarily involving Yin deficiency and body fluid depletion [15]. Guided by the theory of "treating deficiency with tonic", nourishing yin traditional Chinese medicine (NYTCM) has a rich history of replenishing Yin and body fluids of the five viscera for the prevention and treatment of DM [16]. Modern pharmacologic studies have revealed that NYTCM plays an active role by protecting and repairing pancreatic β cells, stimulating INS secretion, alleviating IR, ameliorating disordered glucolipid metabolism, mitigating oxidative stress, inhibiting inflammatory responses, and regulating intestinal flora [17]. This manuscript conducts a brief analysis of the pathogenesis of DM, summarizes the pharmacological activities and mechanisms of common NYTCMs for the prevention and treatment of DM, and examines their safety and toxicity. The findings will not only inform the rational development and application of NYTCM but also provide a foundation to elucidate the scientific mechanisms of TCMs in the prevention and treatment of DM.

In this review, relevant literature was searched using keywords, such as diabetes mellitus, hyperglycemia, and insulin, in the PubMed, Medline, Web of Science, Science Direct, CNKI, and VIP databases from 2003 to 2023. Relevant data were collected from Chinese traditional books, the Chinese Pharmacopoeia, and TCM formulas to identify the anti-diabetes effects and potential mechanisms of NYTCM. Finally, the possibility of NYTCM as an alternative therapeutic option for diabetes is discussed proactively, and further research on NYTCM is analyzed and surveyed.

The modern interpretation of diabetes

Definition and classification

The World Health Organization defines DM as a metabolic disease characterized by chronic hyperglycemia that results from disturbances of substances such as sugars, fats, and proteins, which is caused by defects in INS secretion and/or action due to multiple etiologies [18]. The diagnostic criteria include a fasting plasma glucose (FPG) level ≥126 mg/dl (7.0 mmol/L), 2-h postprandial plasma glucose level ≥200 mg/dl (11.1 mmol/L) in a 75-g oral glucose tolerance test, random plasma glucose level ≥200 mg/dl (11.1 mmol/L) [19], or glycated hemoglobin (HbA1c) level ≥6.5% [20]. In addition, the typical clinical symptoms of polydipsia, polyuria, and weight loss are also important for the clinical diagnosis of DM [21]. DM is a prevalent, chronic, non-communicable disease worldwide and primarily falls into four broad categories: type 1 DM, type 2 diabetes mellitus (T2DM), special type DM, and gestational DM [22]. Because T2DM is much more prevalent than other types and accounts for 90% of DM incidence [23], so this review mainly focuses on T2DM.

Pathogenesis

Plasma glucose refers to the concentration of glucose in the bloodstream, which is the major transport form of sugar and the dominant energy supply of the body. It is well known that plasma glucose levels are not constant, and fluctuations within a certain range are influenced by a variety of factors, such as food intake, exercise, and psychological factors [24]. INS, secreted by β cells located in the pancreatic islets, is a hypoglycemic protein hormone in the body that accelerates the uptake and utilization of glucose by cells. The insulin receptor (INSR) is a ubiquitous protein found on the cell membrane of various cell types that binds to INS, promoting the reduction of plasma glucose levels [25]. When the sensitivity of INSRs to INS decreases, gradual progression to a state of IR will occur [26]. When plasma glucose increases, β cells release INS into the bloodstream, which can cause cells (mainly muscle cells and adipose tissue) to absorb glucose from the bloodstream and convert it into

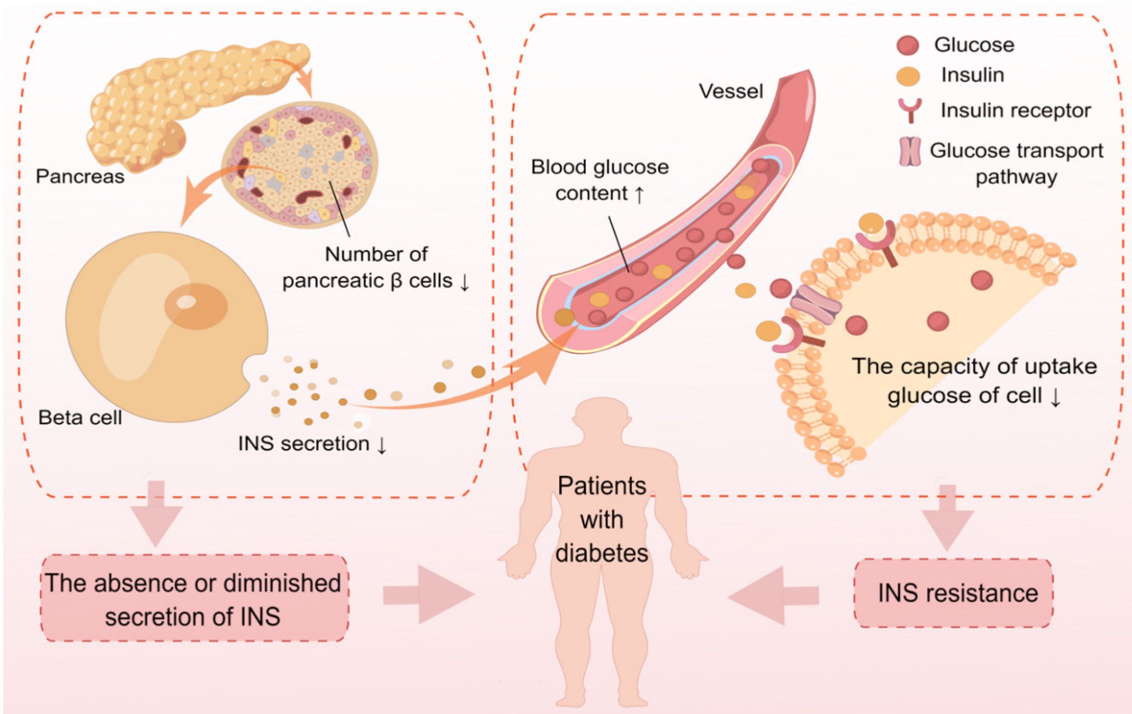

Figure 1. Pathogenesis of diabetes. INS means insulin, upward arrows indicate an increase, downward arrows indicate a decrease, orange arrows represent the direction of disease progression, pink arrows represent the consequences of the disease, and dashed square boxes represent the pathologic processes.

energy or store it. If secretion of INS is decreased or lacking or if IRs are increased due to the environment, genes, or their interactions, glucose in the blood becomes difficult to utilize and remains at high levels. This ultimately leads to metabolic disorders involving glucose, fat, and proteins [27], which is the main mechanism of T2DM (**Figure 1**).

The occurrence of T2DM results from complicated interactions among genetic, environmental, dietary, and obesity-related factors [28, 29]. Current studies indicate that multiple factors, such as lipid metabolism disturbances, oxidative stress, inflammatory responses, and intestinal flora disorders, can induce or aggravate T2DM development. Lipid metabolism disorders can inhibit INS secretion and signaling, leading to disorders of glucose metabolism characterized by increased total cholesterol (TC), triglycerides (TG), and low-density lipoprotein (LDL-C) and reduced high-density lipoprotein (HDL-C) [30]. Oxidative stress weakens the body's antioxidant capacity, ultimately causing damage to β cells, IR, and DM complications [31]. Inflammatory responses involve high levels of inflammatory mediators, including interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α), in tissue cells and blood-derived inflammatory cells, which can affect glucose transport and INS secretion. Intestinal flora disorders affect energy metabolism, and imbalances in metabolism can cause receptors to trigger inflammatory responses, ultimately leading to the attenuation of pancreatic secretory function and low sensitivity of short-chain fatty acid and other types of metabolism to INS [32].

Recognition of T2DM in TCM theory

TCM is a classical type of medicine and is a time-honored medical practice in China, boasting a unique, comprehensive, and well-established theoretical system of herbal prescriptions. because of the clinical features of "excessive thirst, hunger, and urination" in T2DM resemble those of "Xiaoke disease" [33], T2DM can be classified within the scope of Xiaoke disease in TCM. T2DM has been recorded in "*Huang Di Nei Jing*" and "*Wai Tai Mi Yao*", which demonstrates that T2DM has been recognized for a very long time in TCM. TCM theory posits that the occurrence of Xiaoke disease is mainly due to various factors such as a weak constitution, overconsumption of rich and sweet food, and emotional imbalances, which lead to a deficiency of Yin and fluids. The disease is centered in the five viscera, predominantly involving the spleen (stomach), liver, and kidneys [34]. TCM also classifies Xiaoke disease into various syndrome patterns, such as Yin deficiency with internal heat, Qi and Yin dual deficiency, liver and kidney dual deficiency, and mixed syndrome patterns [35].

The flavor and nature theory of Chinese herbs is one of the core components of TCM's herbal property theory and serves as an essential basis for TCM prescription formulation. The four natures, also known as the four Qi, are cold, hot, warm, and cool. The theory represents the thermodynamic properties of herbs and reflects their tendencies toward the balance of Yin and Yang in the human body [36]. Herbs with cold and cool properties typically have the effects of clearing heat or nourishing Yin, while those with hot and warm properties often possess the functions of dispelling cold or invigorating Yang. Consequently, traditional Chinese herbal medicine can be used to regulate the balance of Yin and Yang in the body to prevent and treat diseases.

It is clear that T2DM has the characteristics of "Yin deficiency and fluid depletion". Based on the fundamental TCM principle of "nourishing deficiency", NYTCM can be employed to achieve the goals of balancing the body's Yin-Yang and strengthening the constitution. Thus, since ancient times, TCM has adopted the "Yin-nourishing method" as a fundamental treatment, using NYTCM to prevent and treat Xiaoke disease. NYTCM has various advantages, including a long history, abundant resources, diverse categories, definite therapeutic effects, and no significant adverse reactions. Therefore, these herbs can serve as an excellent entry point for the prevention and treatment of T2DM, providing a broader development space for the clinical prevention, treatment, and symptom reduction of T2DM.

NYTCMs and their active ingredients in the prevention and treatment of T2DM

NYTCMs can stimulate INS secretion, protect and repair β cells, alleviate IR, ameliorate disordered glucolipid metabolism, mitigate oxidative stress, inhibit inflammatory responses, and regulate intestinal flora for the prevention and treatment of T2DM. In this review, we summarize the active ingredients and mechanisms of action of NYTCMs commonly used to prevent and treat T2DM, as shown in **Table 1**, and focus on the glucose-lowering mechanisms of seven different NYTCMs.

Ophiopogon japonicus (L.f) Ker-Gawl. [Liliaceae; Ophiopogonis Radix]

Ophiopogonis Radix, with the functions of nourishing Yin, promoting fluid production, moistening the lungs, and clearing heartburn, is used as a health food and a therapeutic agent for the prevention and treatment of diseases [56]. Ophiopogonis Radix is historically an essential medicine for the treatment of T2DM that acts through various mechanisms. It can prevent and treat DM by increasing the serum INS content and the sensitivity of tissues and organs to INS, regulating glucose and lipid metabolism, and enhancing antioxidant effects. The main effective components of Ophiopogonis Radix in preventing and treating DM are polysaccharide compounds. Studies have found that oligosaccharides from the herb have a regulatory effect on the phosphatidylinositol 3-kinase (PI3K)/serine-threonine kinase (Akt) signaling pathway by regulating the mRNA expression levels of related factors including insulin receptor substrate 1 (IRS1), INSR, PI3K, Akt, and glucose transporter 2 (GLUT2) to play a vital role in the regulation of glucolipid metabolism and IR disorders [57]. Li et al. found that oligosaccharides of *Ophiopogon japonicus* can enhance INS activity, decrease FPG levels, increase glycogen content in the liver and skeletal muscle, and alleviate pathological changes in the pancreas and kidneys in DM rats. These compounds regulate the GLP-1 level and glucokinase and phosphoenolpyruvate carboxykinase (PEPCK) enzyme activity to improve the symptoms of DM and alleviate complications [58]. Xiao et al. found that the total polysaccharides of *Ophiopogon japonicus* can alleviate damage in liver and pancreatic tissue, increase glucokinase and glycogen synthase activity, and inhibit glucose-6-phosphatase (G6Pase) and glycogen phosphorylase activity to improve glucose metabolism and INS signal transduction [59]. In addition, Ophiopogonis Radix can reduce the serum levels of FPG, TC, TG, and LDL-C by regu-

Table 1. Chemical constituents and curative mechanisms of representative NYTCM

Herb	Chemical constituents	Anti-diabetic effect	Curative mechanism	Ref.
Ophiopogonis Radix	Ophiopogonin polysaccharide, steroidal saponins, homoisoflavonoids	Improving INS sensitivity and glucose consumption, regulating glycolipid metabolism, and inhibiting oxidative stress	Ophiopogonin polysaccharide exert hypoglycemic effects not only by inhibiting NF-κB pathway, but also by regulating expression of PI3K, Akt, INSR, PPARγ and PTP1B in IR HepG2 cells	[37, 38]
Dendrobii Caulis	Dendrobium polysaccharides, alkaloids	Regulating β cells function and glucose metabolism, inhibiting oxidative and inflammatory response	Dendrobium polysaccharides can inhibit the expression of cAMP-PKA and G6Pase/PEPCK to regulate glucose metabolism, modulate INSR to alleviate IR, and exert anti-diabetic activity by upregulating IRS1-PI3K-Akt phosphorylation, INS-2mRNA and IGF-1mRNA expression	[39]
Anemarrhenae Rhizoma	Anemarrhenae Rhizoma polysaccharide, saponins, bisbenzophenones	Repairing islet cells, increasing INS sensitivity, regulating liver metabolism and oxidative stress, protecting target organs	Saponins can activate the PI3K/Akt, Nrf2 and AMPK-mTOR pathway to regulate Akt phosphorylation, IL-6, TNF-α, ROS, MDA, GSH-Px	[40, 41]
Polygonati Rhizoma	Polygonatum polysaccharides, saponins, flavonoids	Promoting glucose uptake, glycogen synthesis and β cells survival rate, reducing oxidative stress and inflammatory response, regulating lipid metabolism and IR	Polygonatum polysaccharides can activate the Nrf2/HO-1 pathway, increase the expression of IRS-2, Nrf2 and HO-1, and decrease the expression of IL-1β, IL-6 and TNF-α. It can also adjust the p38MAPK, and AMPK pathways to play a role in treating DM	[42]
Mori Fructus	Flavonoid, anthocyanins, polysaccharides	Regulatiing glycolipid metabolism and hepatic glycogen levels, preventing hepatic gluconeogenesis	Anthocyanin extracts can accelerate glycogen synthesis and inhibit gluconeogenesis by modulating the PI3K/Akt/GSK-3β and PI3K/Akt/FOXO1 pathways to regulate glucose homeostasis	[43]
Lycii Fructus	Lycium barbarum polysaccharides, flavonoids, carotenoids	Improving INS secretion and sensitivity, reducing oxidative stress and sugar absorption, regulating energy metabolism	Lycium barbarum polysaccharides can alleviate IR by regulating IRS-1, TNF-α and Nrf2 expression, inhibiting JNK and p38MAKP phosphorylation, and exhibiting anti-inflammatory and anti-oxidant properties by enhancing the levels of SOD, CAT, GSH-Px, MDA and NO	[44]
Puerariae lobatae Radix	Isoflavones, polysaccharides, Saponins	Alleviating IR, oxidative stress and inflammatory, protecting target organs	Puerarin can accelerate the transport of glucose sugar by enhancing PKB, exhibite anti-inflammatory and anti-oxidant by reducing TNF-α levels; and protect of DM retina by inhibiting retinal AGEs formation, reducing RAGE, VEGF and NF-κB activation	[45]
Polygonati odorati Rhizoma	Polygonatum odoratum, saponins, flavonoid	Protecting β cells, improving INS secretion and sensitivity, inhibiting oxidative stress, accelerating glucose absorption	Polygonatum odoratum can regulate PI3K-Akt and PPARγ pathways to regulate cellular metabolism and ameliorate IR, and decrease the concentration of inflammatory factors, including IL-6 and TNF-α, to improve islet function	[46]
Trichosanthis Radix	Variola polysaccharides, variola agglutinin	Regulating glycolipid metabolism, elevating anti-oxidant stress and immune competence, improving intestinal flora balance	Variola protein regulates autoimmunity by increases the levels of $CD4^+$ T and $CD8^+$ T lymphocytes in the spleen and promoting the secretion of the cytokine IL-4, and increase expression of AMPK, GLUT1, GLUT4 gene and decreased PEPCK and G6Pase gene	[47, 48]
Schisandrae chinensis Fructus	Polysaccharides, schisandrae chinensis lignin	Stimulating INS secretion, suppressing β cells apoptosis and oxidative stress, regulating glycolipid metabolism, protecting target organs	Polysaccharides can regulate the protein expression of GLUT4, IRS1 and AKT to improve glucose consumption, and increase Bcl-2 and inhibit JNK and cleaved caspase-3 protein expression	[49, 50]
Dioscoreae Rhizoma	Chinese yam polysaccharides, steroidal saponins, allantoin, protein	Protecting β cells, increasing INS secretion and sensitivity, mitigating oxidative stress, balancing intestinal flora	Allantoin can improve insulin sensitivity and improve glucose utilization by promoting adrenal β-Endophilin secretion. Chinese yam polysaccharides can improve HK and SDH activities	[51]
Ligustri lucidi Fructus	Polysaccharides, triterpenoids, iridoid, flavonoids	Facilitating INS sensitivity, protecting β cells, regulating glycolipid metabolism, reducing inflammatory response and oxidative stress, adjusting immune competence	Ligustrum extract can regulate glycolipid metabolism by modulating PPAR-α receptors, activating AMPK, PI3K/AKT, PTP1B pathways, and through the NF-κB pathway to regulate IRS1-GLUT4 protein expression, thereby improving glucose transport	[52]

Lilii Bulbus	Polysaccharides, steroidal saponins, flavonoids	Enhancing β cells secretion and proliferation, glucose uptake and utilization, anti-oxidant stress and anti-inflammatory	Lily polysaccharides can regulate CAT, SOD and GSH-Px contents for anti-oxidation, and inhibit NO, PGE2, TNF-α, IL-6, and the NF-κB pathway for anti-inflammation	[53]
Rehmanniae Radix	Catalpol, rehmannia glutinosa oligosaccharide, rehmannia polysaccharides	Protecting β cellular functions, inhibiting gluconeogenesis, IR, inflammatory response and oxidant stress	Catalpol can alleviate IR and inflammatory responses via AMPK/PI3K/Akt, JNK and NF-κB signaling pathways. Total digitonin can prevent and treat DN by inhibiting TGF-β Wnt1 and Wnt/β-Catenin pathways	[54]
Ecliptae Herba	Thiophenes, flavonoids, coumarinyl ethers, triterpenoid saponins	Alleviating oxidative stress and inflammatory, regulating glycolipid metabolism	Flavonoids can exert anti oxidative stress by regulating SOD, GSH-Px and MDA levels, and reduce the lipogenic process by inhibiting the Akt/mTOR pathway	[55]

INS: insulin, NF-κB: nuclear factor-k-gene binding, PI3K: phosphatidylinositol 3-kinase, Akt: protein kinase B, INSR: Insulin receptor, PPARγ: peroxisome proliferator-activated receptor γ, PTP1B: protein tyrosine phosphotase 1B, IR: insulin resistance, cAMP: cyclic-AMP, PKA: protein kinase A, G6Pase: glucose-6-phosphatase, PEPCK: phosphoenolpyruvate carboxykinase, IRS1: insulin receptor substrate 1, IGF-1: insulin-like growth factor 1, Nrf2: nuclear factor erythroid-2 related factor 2, AMPK: activated protein kinase, mTOR: mechanistic target of rapamycin, IL-6: interleukin-6, TNF-α: tumor necrosis factor-α, ROS: reactive oxygenspecies, MDA: malondialdehyde, GSH-Px: glutathione peroxidase, HO-1: heme oxygenase-1, IRS-2: insulin receptor substrate 2, p38MAPK: p38 mitogen-activated protein kinase, GSK-3β: glycogen synthase kinase 3β, FOXO1: forkhead box protein O1, JNK: c-Jun N-terminal kinase, SOD: superoxide dismutase, CAT: catalase, NO: nitric oxide, PKB: protein kinase B, AGEs: advanced glycation end products, RAGE: receptor for advanced glycation end products, VEGF: vascular endothelial growth factors, GLUT1 and GLUT4: glucose transporter 1 and 4, HK means hexokinase, SDH: succinate dehydrogenase, PGE2: prostaglandin E2, TGF-β: transforming growth factor-β.

lating the biosynthesis pathway of ubiquinone and other terpenoid quinones, thus promoting glycerol oxidation to reduce pancreatic lipid peroxidation and improve glucolipid metabolism disturbances in T2DM mice [60].

Dendrobium officinale Kimura et Migo. [Orchidaceae; Dendrobii Caulis]

There are many uses for Dendrobii Caulis, such as improving stomach health, promoting fluid production, nourishing Yin, and clearing heat. The main hypoglycemic active components of the herb are Dendrobium polysaccharides, which can promote the function of pancreatic islet β cells and liver glycogen synthesis, alleviate IR, increase the INS level, inhibit liver glycogen degradation and heterogenesis, enhance antioxidant stress capacity, alleviate inflammatory responses, and regulate intestinal enzyme activity. These compounds act by regulating signaling proteins and pathways such as the cyclic AMP-protein kinase A, nuclear factor-kappa B (NF-κB)-inducible nitric oxide synthase (iNOS)-nitric oxide, PI3K/Akt, mitogen-activated protein kinase (MAPK), and Akt/forkhead box protein O1 (FoxO1) pathways, thereby exerting their hypoglycemic effects [61]. Dendrobium can reduce the content of related lipids in the serum of rats, alleviate the deposition of lipid plaques in the aorta, reduce the LDL-C/HDL-C ratio in the serum, inhibit the expression of TNF-α and IL-6 in the serum and aorta, and reduce the occurrence of inflammatory reactions in mice induced by high-fat and high-cholesterol diets [62]. In addition, the herb can significantly protect target organs from damage caused by DM. For example, Chen et al. found that a *Dendrobium officinale* mixture may inhibit the phosphorylation of PI3K, Akt, and mechanistic target of rapamycin (mTOR) in kidney tissue of rats with diabetic nephropathy (DN) by inhibiting the PI3K/Akt/mTOR signaling pathway, upregulating the expression of light chain 3 and Beclin-1 mRNA to improve renal function and reduce renal damage, and playing a protective role in kidneys of DN rats [63]. In the past, the stem of Dendrobii Caulis was often used, but its flowers and leaves also have medicinal value. Studies have shown that a polysaccharide from *Dendrobium officinale* leaves, LDOP-A, can increase the levels of short-chain fatty acids (SCFAs) in the colon and regulate the microstructure of the intestinal microbiota. The mechanism may be related to promoting an increase in SCFA levels [64].

Anemarrhena asphodeloides Bge. [Liliaceae; Anemarrhenae Rhizoma]

In addition to clearing heat and purging fire, Anemarrhenae Rhizoma also nourishes Yin and moistens dryness. Polysaccharides from Anemarrhenae Rhizoma can reduce FPG, IL-6, and TNF-α levels and hepatic malondialdehyde (MDA) content in model rats and regulate fasting insulin (FINS) levels and the enzyme activities of catalase (CAT) and superoxide dismutase (SOD). Additionally, these compounds can modulate the expression of Phospho-IRS1 and Glut4 in the INS signaling pathway, inhibit pyruvate carboxylase activity to reduce gluconeogenesis, and promote glycogen synthesis and glucose utilization [65]. Han et al. researched the potential mechanism of the hypoglycemic and INS-sensitizing effects of Rhizoma Anemarrhenae extract (TFA) in DM rodents. The results demonstrated that TFA mediated the activation of adenosine 5'-monophosphate-activated protein kinase (AMPK) and phosphorylation of its downstream target acetyl-CoA carboxylase, thereby significantly reducing FPG and serum INS levels, increasing the size and the number of β cells, and improving the glucolipid metabolism of model mice. This highlights the possible use of TFA for the management of T2DM [66]. Additionally, unabsorbed components of *Anemarrhena asphodeloides* extract can regulate the diversity and composition of intestinal flora, enrich potentially beneficial bacteria, and inhibit the growth of potentially harmful bacteria. Absorption of a small proportion of these components could reduce blood lipid and inflammation levels, restore endoplasmic reticulum, ribosome, and antioxidant stress protein levels, promote the regeneration of pancreatic cells, and improve their function via PRDX4 overexpression [67].

Polygonatum kingianum Coll. et Hemsl. [Liliaceae; Polygonati Rhizoma]

Polygonati Rhizoma can tonify Qi, promote fluid production, nourish Yin, moisten the lungs, and strengthen the spleen and kidney. Modern pharmacologic research has found the herb has hypoglycemic, hypolipidemic, and anti-inflammatory effects, and its main bioactive component is *Polygonatum sibiricum* polysaccharides (PSPs) [68]. One study provided evidence that PSPs can upregulate the expression of Akt, PI3K, IRS1, phosphate inositol-dependent protein kinase-1 (PDK1), GLUT2, phosphatidylinositol 1,2,3,4,5-pentaphosphate (PIP5K), and glycogen synthase mRNA in the liver tissue of streptozotocin (STZ)-induced DM mice, downregulate the expression of glycogen synthase kinase 3β (GSK-3β) mRNA, activate the IRS1-PI3K-PDK1-Akt, PI3K-Akt-GSK-3β-GYS, and PI3K-Akt-PIP5K-GLUT2 signaling pathways to improve INS secretion and INSR activity, facilitate glycogen synthesis in the liver, and enhance glucose conversion and utilization. These effects ultimately reduce SOD, glutathione peroxidase, and MDA activity and alleviate glucose metabolism disorders caused by oxidative stress, thereby regulating the plasma glucose level and playing a role in preventing and treating diabetes [69]. In addition, PSPs can increase the relative abundance of bacteria produced by SCFAs to regulate the abundance and diversity of intestinal microbiota, promote the recovery of the intestinal permeability barrier, restrain endotoxin entry into the circulation, alleviate inflammation, and prevent glucose and fat metabolism disorders [70]. Wang et al. established a DM mouse model to investigate the protective effect of PSPs on retinal damage caused by DM and its possible mechanism. The western blot results showed that PSPs upregulated the expression of B-cell lymphoma-2 factor and downregulated the expression of the epidermal growth factor, p38 mitogen-activated protein kinases, vascular endothelial growth factor, and transforming growth factor-β (TGF-β) proteins. Thus, these results indicate that PSPs show a protective effect on plasma glucose homeostasis and retinal microvascular complications in a dose-dependent manner [71].

Morus alba L. [Moreaceac; Mori Fructus]

Mori Fructus nourishes Yin, promotes fluid production, nourishes the blood, and moistens dryness. Its main active components are flavonoids, anthocyanins, and polysaccharides. Mori Fructus polysaccharides (MFPs) can significantly increase INS secretion and promote β cell proliferation, as well as decrease the level of MDA and increase SOD and CAT activity in STZ-induced DM mice. Therefore, MFPs can effectively alleviate damage to pancreatic, liver, and kidney tissue and have significant INS-sensitizing, antioxidant, and hypoglycemic activity [72]. Long et al. found that the herb could significantly improve glucose tolerance, markedly increase SOD activity and the glutathione (GSH) concentration, reduce the concentrations of free fatty acids, prevent histopathological changes, increase alanine transaminase and aspartate transaminase activity, and significantly increase the richness of the intestinal microbial community [73]. Research has shown that Mulberry anthocyanin extract (MAE) can, through activation of the PI3K/AKT pathway, recover phosphorylation of AKT and GSK-3β in HepG2 cells induced by high glucose and palmitic acid levels, alleviate IR in HepG2 cells, and improve glucose consumption and uptake and glycogen content. Additionally, in vivo animal experiments showed that MAE supplementation (50 and 125 mg/kg body weight per day) clearly decreased FPG, serum INS, leptin, TG, and TC levels and increased the level of adiponectin in model mice, which indicates that MAE has potential benefits in improving dysfunction in diabetic mice and mitigating IR in HepG2 cells [74].

Lycium barbarum L. [Solanaceae; Lycii Fructus]

Lycii Fructus possesses a range of medicinal values, such as tonifying the liver and kidneys, nourishing Yin, and regulating deficiency. It is rich in polysaccharides, carotenoids, phenolic acids, flavonoids, and betaine [75]. *Lycium barbarum* polysaccharide (LBP) is the primary active ingredient for diabetes treatment and can decrease the FPG level, enhance oral glucose tolerance, regulate dyslipidemia, and mitigate oxidative stress. Researchers have established a diabetic model using a high-fat diet (HFD) and STZ to investigate how LBP regulates intestinal flora in the prevention and treatment of T2DM. LBP increased CAT, SOD, and GSH activities, decreased inflammation, regulated the intestinal flora composition, promoted SCFA production in DM mice, and regulated glycolipid metabolism through the IRS/PI3K/Akt pathway, which demonstrated that LBP notably alleviated hyperglycemia, hyperlipidemia, and IR in T2DM mice [76]. Liu et al. explored the impact of LBP on diabetic peripheral neuropathy (DPN) and its possible mechanism. They found that LBP mildly decreased the plasma glucose level, partially mitigated hyperalgesia and allodynia in diabetic rats, reduced nerve fiber myelin sheath damage, restored expression of the myelin-related proteins myelin protein zero and myelin basic protein in the sciatic nerve of DM rats, and induced protective autophagy by inhibiting activation of the mTOR/ribosomal protein S6 kinase beta-1 (p70S6K) pathway in DPN [77].

Pueraria lobata (Willd.) Ohwi. [Leguminosae; Puerariae lobatae Radix]

Puerariae lobatae Radix can be used to facilitate fluid production, quench thirst, reduce fever and diarrhea, and unblock meridians. Puerarin polysaccharides and puerarin are the main effective ingredients and can alleviate IR, protect the kidney and liver, and have anti-inflammatory and antioxidant effects [78]. *Pueraria lobata* polysaccharides have shown potential anti-diabetic effects by activating the PI3K/AKT pathway to regulate the expression of the PI3K, AKT, and FoxO1 enzymes, thereby mitigating IR and regulating glucolipid metabolism in mice [79]. In addition, this effect can also be achieved by regulating the expression of the AMPK, peroxisome proliferator-activated receptor γ (PPARγ), and mTOR proteins and the structure of intestinal microbiota to regulate the PPAR pathway and alleviate IR [80]. Puerarin has the ability to help manage diabetes and its complications by activating the GLP-1 receptor and PI3K/Akt pathways, inhibiting reactive oxygen species (ROS) production in the pancreas, enhancing GLUT4 and PPAR expression, increasing fatty acid oxidation in skeletal muscle and adipose tissue, activating PI3K/Akt in the liver for β cell regeneration, enhancing the INSR signaling pathway, promoting glucose transport and uptake, and inhibiting gluconeogenesis to improve INS secretion, alleviate IR, and reduce plasma glucose levels [81].

In summary, some indispensable NYTCMs, such as Ophiopogonis Radix, Dendrobii Caulis, and Anemarrhenae Rhizoma, contain various pharmacologic components, including polysaccharides, flavonoids, saponins, and alkaloids. In contrast to western medicine, NYTCMs act through synergistic effects of multiple compositions, channels, and targets to play an efficacious role in the prevention and treatment of T2DM and its complications.

Classic NYTCM formulas for the prevention and treatment of T2DM

Formulas, also called compound prescriptions, are the main forms of TCM in clinical application, and their frequency of application far exceeds that of a single herb for preventing and treating diseases because the formula can reduce toxicity and/or increase curative efficacy through compatibility rationality [82]. For example, Gastrodiae Rhizoma and Puerariae lobatae Radix are traditional Chinese herbal medicines that are frequently used in combination in the clinical treatment of cardio-cerebral vascular diseases. Their use in combination can significantly increase the systemic exposure of bioactive ingredients, including puerarin, genistein, and gastrodin, and improve the blood drug concentrations in model animals. Unidirectional intestinal perfusion experiments have shown that Gastrodiae Rhizoma can promote the absorption of the ingredients of Puerariae lobatae Radix to exert synergistic effects [83]. *Tripterygium wilfordii* and its active ingredient triptolide have positive therapeutic effects on autoimmune diseases, but their use is limited because of their unavoidable hepatotoxicity and nephrotoxicity. The toxicity of *Tripterygium wilfordii* can be mitigated by combinational application of *Panax notoginseng* and *Rehmannia glutinosa* [84]. Therefore, after identifying the active ingredients in TCM formulas and determining their synergistic mechanism of action, rational compatibility may enable herbs to exert greater therapeutic effects and alleviate adverse and toxic side effects.

Compared with chemical hypoglycemic drugs, NYTCM formulas focus on holistic regulation and individual therapy, which allows them to exert their unique advantages in the treatment of T2DM and its complications through multiple targets and mechanisms. Therefore NYTCM formulas and their preparations are potential alternatives for the prevention and treatment of T2DM. Many classical, well-known formulas for preventing and treating T2DM and its complications, along with their exact curative effects, are recorded in ancient medical classic texts, such as Yuye Decoction, Yuquan Granules, Yangyin Jiangtang Tablet, and others, and the Pharmacopoeia of the People's Republic of China. Additionally, clinicians can flexibly adjust the composition or dosage of the formula to prescribe it according to the different constitutions and facultative of patients to achieve improved efficacy. We summarize some relevant, frequently used NYTCM formulas and herbal compositions and their clinical efficacy and provenance in the prevention and treatment of T2DM in **Table 2**.

Anti-diabetic mechanisms of NYTCMs

A great deal of research has been conducted on the active components and the mechanism of action of NYTCMs in the treatment of T2DM, and remarkable progress has been achieved. NYTCMs can exert their preventive and therapeutic effects through multiple pathways to repair pancreatic islet β cells, stimulate INS secretion, alleviate IR, ameliorate oxidative stress, suppress inflammatory responses, regulate glycolipid metabolism and intestinal flora, and decelerate the development of complications. NYTCMs affect similar or different signaling pathways, such as their action on INSRs to enhance IRS1 and IRS2 activity, as well as their action on PPAR-α. Both of these actions can increase PI3K and Akt activity to regulate the expression of GSK-3β, Glut2, FoxO1, PEPCK, and G6Pase, thereby achieving various anti-diabetic effects (**Figure 2**).

Repair of β cells and stimulation of INS secretion

Pancreatic islet β cells are the only endocrine cells capable of INS secretion. INS is the only hormone with plasma glucose-lowering effects. Reduction of the β cell count or impairment of their function results in decreased INS secretion, thus weakening plasma glucose regulation and leading to elevated glucose levels, which triggers T2DM. INS, V-maf musculoaponeurotic fibrosarcoma oncogene homolog A (MafA), and pancreatic and duodenal homeobox factor-1 (PDX-1) are maturation markers of pancreatic β cells that can be used to evaluate their development and function [95]. Zhao found that *Dendrobium nobile* polysaccharides can significantly increase INS-1 cell proliferation under high-glucose conditions and elevate the expression of INS, PDX-1, and MafA mRNA, indicating that *Dendrobium officinale* polysaccharides can repair β cell function and stimulate INS secretion [96]. The PI3K/Akt/FoxO1 pathway is crucial for INS signaling and influences glucose reduction, INS secretion, and the proliferation of β cells, among which Akt and FoxO1 are the key proteins in the pathway. The Astragali Radix-Puerariae lobatae Radix herb pair can significantly elevate PI3K and Akt expression, reduce FoxO1, G6Pase, and PEPCK expression, and hinder gluconeogenesis by regulating the PI3K/Akt/FoxO1 pathway, thereby repairing liver injury, stimulating INS secretion, and playing a role in the prevention and treatment of DM [97].

Alleviation of IR

The glucose-lowering effect of INS relies on its receptor, and IR occurs when target organs or tissues containing the INSR exhibit reduced sensitivity and responsiveness to INS [98]. IR and the disturbances of its associated signaling pathways are important mechanisms of DM. FPG, FINS, and the homeostatic model of insulin resistance (HOMA-IR) index are well-established diagnostic indicators of IR that can suggest the degree of sensitivity to INS, and their main regulatory pathways include IRS1/PI3K/Akt, MAPK, and Smad3 [99]. TFA significantly decreased FPG and FINS levels as well as the HOMA-IR index and increased the size and the number of β cells in mice to exert glucose-lowering effects and ameliorate IR. Additionally, a hyperinsulinemic-euglycemic clamping study showed that TFA is an INS sensitizer and can improve overall glucose and lipid metabolism in diabetic rodents, thus TFA may help in the treatment of D2TM [66]. Researchers have discovered that low-molecular-weight polysaccharides of *Ophiopogon japonicus* may alleviate IR and glycolipid metabolism disorders by upregulating the mRNA expression levels of IRS1, INSR, PI3K, Akt, and GLUT2 while downregulating the mRNA expression level of GSK-3β in the IRS1/PI3K/Akt signaling pathway [57].

Amelioration of glucose metabolism

The body regulates glucose storage and maintains plasma glucose homeostasis through multiple mechanisms such as glycogen synthesis, glycogen decomposition, and gluconeogenesis. When glucose metabolism is disrupted, a hyperglycemic state and diabetes can occur. α-Glucosidase is a crucial enzyme that controls glucose derived from food sources, and inhibiting its activity leads to reductions of INS and

Table 2. Composition and efficacy of classic compound formulas for the prevention and treatment of DM

Compound formula	Recorded books	Constituent herbs	Clinical efficacy	Ref.
Yuquan Granules	Pharmacopoeia of the People's Republic of China	Trichosanthis radix, Puerariae lobatae radix, Ophiopogonis radix, Ginseng radix et rhizoma, Poria, Mume fructus, Astragali radix, Glycyrrhizae radix et rhizoma, Rehmanniae radix, Schisandrae chinensis fructus	Yuquan Granules combined with metformin can decrease the level of TG, TC, LDL-C, FPG, 2hPG and HbA1c and increase INS sensitivity	[85]
Qizhi Jiangtang Capsule	Pharmacopoeia of the People's Republic of China	Astragali radix, Rehmanniae radix, Polygonati rhizoma, Hirudo	Qizhi Jiangtang Capsule can reduce Glu, HbA1c, SCR, BUN, mAlb, and protect renal function in patients with DN	[86]
Jinqi Jiangtang Tablet	Pharmacopoeia of the People's Republic of China	Coptidis rhizoma, Astragali radix, Lonicerae japonicae flos	Jinqi Jiangtang Tablet can reduce the level of FPG, 2hPG, HbA1c, and alleviate IR	[87]
Shenqi Jiangtang Capsule	Pharmacopoeia of the People's Republic of China	Total ginsenoside of ginseng stems and leaves, Astragali radix, Rehmanniae radix, Dioscoreae rhizoma, Trichosanthis radix, Rubi fructus, Ophiopogonis radix, Schisandrae chinensis fructus, Lycii fructus, Alismatis rhizoma, Poria	Shenqi Jiangtang Capsule combined with metformin can improve the function of pancreatic islets β cell and decrease the level of FBG, 2hPG, HbA1c	[88]
Yangyin Jiangtang Tablet	Pharmacopoeia of the People's Republic of China	Astragali radix, Codonopsis radix, Puerariae lobatae radix, Lycii fructus, Scrophulariae radix, Polygonati odorati rhizoma, Rehmanniae radix, Anemarrhenae rhizoma, Moutan cortex, Chuanxiong rhizoma, Polyconi cuspidati rhizoma et radix, Schisandrae chinensis fructus	Yangyin Jiangtang Tablet combined with glimepiride tablet can regulate glucose metabolism and alleviate IR	[89]
Tangniaole Capsule	Pharmacopoeia of the People's Republic of China	Trichosanthis radix, Dioscoreae rhizoma, Astragali radix, Ginseng radix et rhizoma rubra, Rehmanniae radix, Lycii fructus, Anemarrhenae rhizoma, Asparagi radix, Poria, Corni fructus, Schisandrae chinensis fructus, Puerariae lobatae radix, Galli gigerii endothelium corneum	Tangniaole Capsule combined with insulin injection can effectively control Glu, reduce FPG, HbA1c, 2hPG and FINS, and alleviate oxidative stress in T2DM	[90]
Tangmaikang Granules	Pharmacopoeia of the People's Republic of China	Astragali radix, Rehmanniae radix, Paeoniae radix rubra, Salviae miltiorrhizae radix et rhizoma, Achyranthis bidentatae radix, Ophiopogonis radix, Puerariae lobatae radix, Mori folium, Coptidis rhizoma, Polygonati rhizoma, Epimedii folium	Tangmaikang Granules can alleviate IR, inflammatory responses and peripheral nerve symptoms, regulate glycolipid metabolism, and reduce Glu	[91]
Yuye Decoction	Yi Xue Zhong Zhong Can Xi LU	Dioscoreae rhizoma, Astragali radix, Schisandrae chinensis fructus, Galli gigerii endothelium corneum, Anemarrhenae rhizoma, Trichosanthis radix, Puerariae lobatae radix	Yuye Decoction can regulate glycolipid metabolism, promote INS secretion, alleviate IR, and prevent the development of complications such as DN, retinopathy, and peripheral neuropathy	[92]
Qiweibaizhu Powder	Tai Ping Sheng Hui Fang	Atractylodis macrocephalae rhizoma, Ginseng radix et rhizoma, Rehmanniae radix praeparata, Schisandrae chinensis fructus, Oxhide gelatin, Poria, Asteris radix et rhizoma, Zingiberis rhizoma praeparatum, Glycyrrhizae radix et rhizoma praeparata cum melle, Cinnamomum	Qiweibaizhu Powder combined with intradermal needle therapy can effectively reduce the Glu level of patients	[93]
Yunv Decoction	Jing Yue Quan Shu	Gypsum fibrosum, Rehmanniae radix praeparata, Anemarrhenae rhizoma, Ophiopogonis radix, Achyranthis bidentatae radix	Yunv Decoction can regulate INS, lower blood sugar, alleviate IR, inhibit oxidative stress and inflammatory responses, and its hypoglycemic effect is clear	[94]

TG: triglycerides, TC: total cholesterol, LDL-C: low-density lipoprotein, FPG: fasting plasma glucose, 2hPG: 2 h postprandial plasma glucose, HbA1c: glycated hemoglobin, INS: insulin, Glu: plasma glucose, SCR: serum creatinine, BUN: serum creatinine, mAlb: microalbumin, DN: diabetic nephropathy, IR: insulin resistance, FINS: fasting insulin.

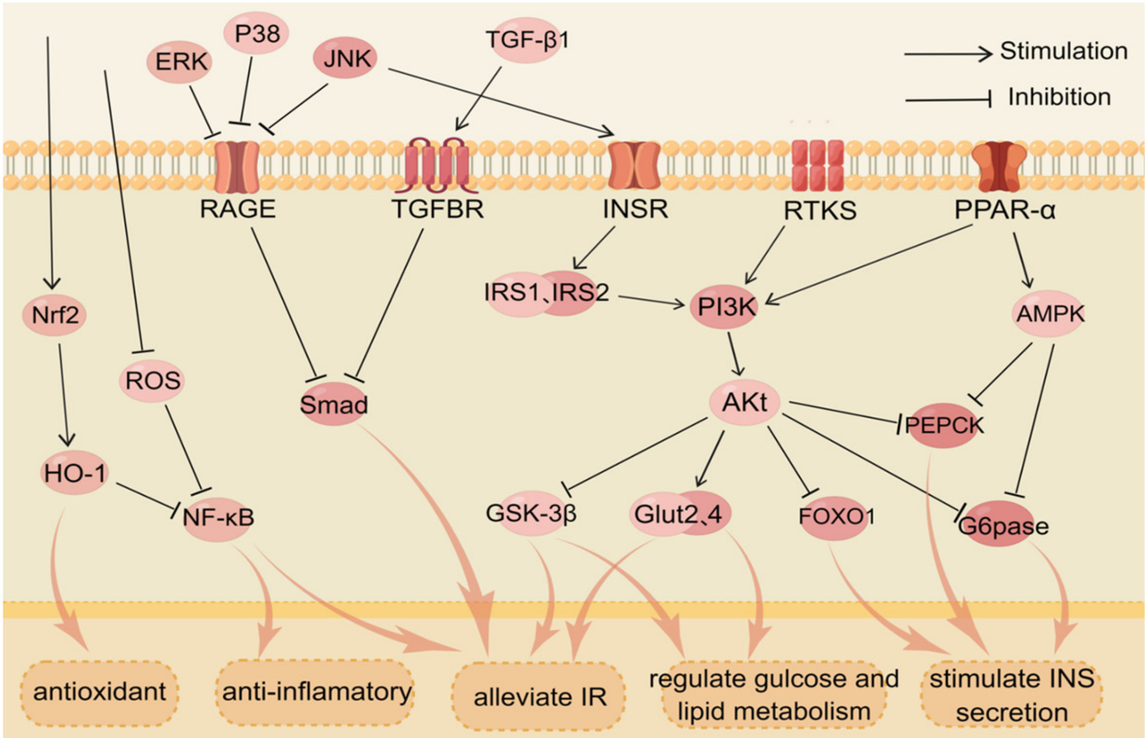

Figure 2. Mechanism of NYTCM in treating DM. INS: insulin, IR: insulin resistance, ERK: extracellular regulated protein kinases, P38: p38 mitogen-activated protein kinase, JNK: c-Jun N-terminal kinase, TGF-β1: transforming growth factor-β1, RAGE: receptor for advanced glycation end products, TGFBR: transforming growth factor beta receptor, INSR: Insulin receptor, RTKS: receptor tyrosine kinase, PPAR-α: peroxisome proliferator-activated receptor α, Nrf2: nuclear factor erythroid-2 related factor 2, HO-1: heme oxygenase-1, ROS: reactive oxygenspecies, NF-κB: nuclear factor-κ-gene binding, IRS1 and IRS2: insulin receptor substrate 1 and 2, PI3K: phosphatidylinositol 3-kinase, Akt: protein kinase B, AMPK: activated protein kinase, PEPCK: phosphoenolpyruvate carboxykinase, GSK-3β: glycogen synthase kinase 3β, Glut2 and Glut4: glucose transporter 2 and 4, FOXO1: forkhead box protein O1, G6pase: glucose-6-phosphatase, orange curved arrows represent the direction of development, pink ellipses represent the signal molecules influenced by NYTCM, and the orange dashed square boxes represent the outcomes after NYTCM intervention.

postprandial plasma glucose levels [100]. Lu et al. found that Polygonati Rhizoma and its different extract pairs can inhibit α-glycosidase, and the inhibition of total saponins is more pronounced, with a dose-effect relationship. These results suggest that total saponins from the herb have hypoglycemic effects by participating in the inhibition of α-glycosidase in the small intestine [101]. G6Pase and PEPCK are the main rate-limiting enzymes of hepatic gluconeogenesis, and inhibition of their expression will repress the glucose production pathway and plasma glucose content [102]. Trichosanthis Radix can downregulate the gene expression of PEPCK and G6Pase in STZ-induced T2DM mice and regulate liver function and glucose metabolism [48].

Regulation of lipid metabolism

Lipid metabolism disorder is one of the major mechanisms in the occurrence of DM, and it can inhibit INS secretion and signal transmission. Its detection indexes mainly include TC, TG, LDL-C, and HDL-C levels [103]. Some scholars have found that polygonatum polysaccharide can upregulate cellular lipid metabolism through the PI3K/Akt pathway, thus significantly reducing TC, TG, LDL-C, and HbA1c levels, increasing HDL-C, C-peptide, and INS levels, and improving the pathological degree of hepatocytes in rats to play a positive role in the treatment of T2DM [104]. The IRS1/Akt/Glut4 signaling pathway is closely associated with glycolipid metabolism in T2DM. Elevated glucose levels inhibit the binding of IRS-1 to INS receptors, reduce the expression of Akt and Glut4, and inhibit the activation of this pathway, leading to disturbances in glucose and lipid metabolism [105]. LBPs can upregulate IRS1, PI3K, and protein kinase B expression, promote Glut4 expression, improve glucose uptake and utilization, and alleviate glycolipid metabolism disorders in high-glucose states [106, 107].

Mitigation of oxidative stress

Oxidative stress is a pathologic condition characterized by an imbalance of oxidants and antioxidants in the body. It results in disruptions of redox signaling and control, molecular damage [108], and a decreased ability to scavenge excess harmful free radicals, ultimately causing cellular or tissue damage and dysfunction. Recent evidence has indicated that oxidative stress has a close relationship with the occurrence and progression of diabetes and its complications through modulation of multiple signaling pathways associated with β cell dysfunction and IR [109]. Various biomarkers of oxidative stress exist in DM, including lipids, proteins, DNA damage, GSH, CAT, and SOD [110]. LBP can significantly increase CAT, SOD, and GSH activity in model mice and exert antioxidative stress and anti-inflammatory effects, thus participating in the prevention and treatment of DM [76]. The ethyl acetate fraction of the ethanolic extract of mulberry fruit (MFE) reduced lipid peroxidation and improved the activity and levels of SOD and GSH in tissues. These results indicate that the potential mechanism of MFE in its anti-diabetic and neuroprotective effects is closely related to its upregulation of antioxidant enzyme activity [111].

Inhibition of the inflammatory response

Some investigators consider T2DM a chronic inflammatory disease, and IR can be alleviated and damage to pancreatic β cells can be reduced by inhibiting the inflammatory response [112]. Multiple signaling pathways such as NF-κB, MAPK, PI3K/Akt, protein kinase C, AMPK, and TGF-β play a significant role in the pathogenesis of chronic inflammation in obesity, DM, and other metabolic diseases. For example, after activation of the NF-κB signaling pathway, IL-1β, IL-6, TNF-α, and other inflammatory factors are produced by adipocytes, hepatocytes, and macrophages, which are regulated by the increase in NF-κB, thus inducing IR and facilitating the development of T2DM [113]. In recent years, the use of TCM monomers and TCM formulas to mediate inflammatory signaling pathways for the prevention and treatment of DM has been increasing. PSPs can play an anti-inflammatory and lipid-lowering role by activating the AMPK signaling pathway. PSPs can also effectively reduce the body weight, blood lipids, plasma glucose, INS, resistin, adiponectin, liver weight, and abdominal fat pad weight of HFD-induced obese mice, reverse the abnormal expression of TNF-α, IL-6, IL-1β, and iNOS in the NF-κB signaling pathway, reduce the expression of other inflammatory factors and lipid metabolism genes, and inhibit the inflammatory response [114].

Regulation of the intestinal flora

The interaction between the gut microbiota and T2DM is receiving increasing attention [115]. This interaction can lead to impaired β cell function and reduced INS sensitivity through several mechanisms, including affecting the metabolism of SCFAs and bile acids (BAs) and the endotoxin response [116]. SCFAs can directly activate the G-protein-coupled receptors GPR43 and GPR41, which can enhance the secretion of GLP-1 and peptide YY (PYY) by intestinal L cells, thereby promoting INS secretion, mitigating IR, and inhibiting gluconeogenesis [117]. LBP can increase the production of SCFAs, significantly increase the expression of GPR41, GPR43, GLP-1, and PYY, stimulate INS secretion, alleviate IR, and significantly regulate the intestinal flora composition in diabetic mice [76]. BAs are pivotal signaling molecules that control glucolipid and energy metabolism by binding to the nuclear hormone farnesoid X receptor (FXR) and exert effects on intestinal incretin secretion, hepatic gluconeogenesis, glycogen synthesis, energy expenditure, inflammation, and the gut microbiome configuration [118]. Zhang et al. found that a *Dendrobium officinale* mixture could ameliorate disorders of glucose and lipid metabolism in model mice by increasing hepatic FXR protein expression and reducing BA production [119].

Protection of target organs and reduction of complications

T2DM can easily cause various complications involving multiple organs and tissues, even leading to blindness, kidney failure, death, and other serious consequences [120]. The rhizome extract of *Anemarrhenae asphodeloides* can decrease the levels of MDA and advanced glycation end products in serum and the sorbitol concentration in the lens, reduce the endothelium/pericyte ratio, and alleviate the pathological changes of the lens and retina to prevent progression of eye complications [121]. Its total saponins may ameliorate glucose levels in DM rats by regulating the PI3K/AKT/hypoxia-inducible factor-1 pathway, thereby correcting glycolytic metabolism and playing a role in the treatment of DM [122]. LBP can markedly regulate the levels of light chain 3II, Beclin1, and P62, inhibit activation of the mTOR/p70S6K pathway in the sciatic nerve, and improve autophagy in DM rats to exert protective effects against DPN [123].

Safety and toxicity of NYTCMs

Chinese herbal medicines, an indispensable component of TCMs, have received increasing attention and use as alternative and adjuvant medicines in international therapy [124]. However, the frequent adverse reactions/incidents of TCMs have seriously hindered their further development and internationalization. For example, TCMs have a remarkable effect on the treatment of COVID-19, but their use is still questioned by the international community due to problems with the safety of TCM therapy [125]. NYTCMs play an important role in the prevention and treatment of T2DM through various mechanisms that exert excellent hypoglycemic effects, but their safety and toxicity are unavoidable problems in clinical application. According to a toxicity study, most NYTCMs have no obvious toxicity. However, there are only a few reports regarding this problem, and only a few studies have documented the cardiotoxicity and hepatotoxicity of TCMs. Overall, the harm of traditional herbs can be effectively avoided, and the balance of efficacy, safety, and toxicity can be kept as long as scientific and reasonable compatibility and usage methods are used within the limited dosage specified in the Chinese Pharmacopoeia [126].

Cardiotoxicity

Cardiotoxicity refers to the cardiac dysfunction and myocardial damage caused by the use of drugs, which is one of the major safety concerns for their clinical application [127]. In recent years, extensive studies on the evaluation of cardiac safety and prevention of cardiotoxicity by TCMs have been conducted, particularly for traditional herbs and their components with cardiotoxicity [128]. For example, Opogonin D' (OPD'), a main effective component of *Ophiopogon japonicus*, was found to significantly reduce the viability and increase the apoptosis rate of cardiomyocytes at a dose of 5 $\mu mol \cdot L^{-1}$. The toxic mechanism may involve the initiation of an intracellular endoplasmic reticulum stress reaction due to intracellular Ca^{2+} overload, which triggers apoptosis pathway-related factors and induces apoptosis, suggesting that the major saponin component, OPD', in *Ophiopogon japonicus* may have cardiotoxicity [129].

Hepatotoxicity

The hepatotoxicity of drugs refers to the liver damage caused by drugs or their metabolites, which is a relatively common clinical toxic effect [130]. Timosaponin A3 (TA3) is one of the major steroidal saponin components isolated from Anemarrhenae Rhizoma, but it can induce hepatotoxicity by inhibiting the activity of BA transporters [131]. Wu et al. found that TA3 treatment reduced the expression of BA transporters in hepatocytes in a dose-dependent manner while increasing ROS generation and heme oxygenase-1 expression and decreasing the adenosine triphosphate level and mitochondrial membrane potential. These results indicate that TA3 triggered liver injury by inducing ROS generation and inhibiting BA transporter expression, whereas mangiferin (10-200 μg/ml), another active component of Anemarrhenae Rhizoma, mostly blocked the ROS generation induced by TA3, suggesting that mangiferin could protect hepatocytes from TA3-induced hepatotoxicity [132].

Conclusion

T2DM, as the third most common chronic, noncommunicable disease worldwide, is characterized by a complex pathogenesis, long disease course, and lack of a cure. T2DM often damages multiple target organs such as the brain, heart, and kidneys due to hyperglycemia [133] and poses a serious threat to human health. Its prevention and treatment have become a global public health problem, as well as an urgent problem to be solved in international healthcare systems. Contemporary medicine has made significant progress in studying the mechanism of NYTCMs, such as Ophiopogonis Radix, Dendrobii Caulis, Anemarrhenae Rhizoma, and Polygonati Rhizoma, in the prevention and treatment of T2DM. The value and status of traditional Chinese herbs in clinical practice have also gradually gained recognition, and TCM treatments have been added to the 2017 edition of the *Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes*. Numerous studies have shown that NYTCMs can regulate various factors related to DM, such as FBG, FINS, IRS, GLUT4, ROS, IL-6, and TNF-α, by affecting the PI3K/Akt, MAPK, NF-κB, and other signaling pathways to repair pancreatic islet β cells, promote INS secretion, alleviate IR, regulate glucose and lipid metabolism, mitigate oxidative stress, inhibit inflammatory responses, and regulate intestinal flora to prevent and treat T2DM. TCM has the advantages of mild efficacy, long-lasting effects, minimal toxicity and adverse effects, and significant curative effects.

NYTCMs for the prevention and treatment of T2DM hold great potential for further development, but there are still key issues that need to be addressed to facilitate their broader application. First, most current studies of anti-diabetic effects are based on the effects of extracts or single components of NYTCMs on animal or cell models, and a single component cannot fully reflect the holistic and synergistic effects of TCMs. It is advisable to combine the principles of TCM compatibility and conduct an in-depth analysis of the chemical components of these herbs to comprehensively elucidate the relationships and interaction mechanisms among the effective components. Second, TCMs often contain both effective and potentially toxic components, making the precise dosage crucial for treatment. However, there is insufficient research on the “dose-effect-toxicity” relationship between the effective components of NYTCMs and their hypoglycemic effects. Ensuring safety and efficacy requires studying the metabolic processes of these herbs using omics techniques and investigating the relationships between drug dosage, efficacy, and toxicity. Finally, compared to modern medicine, there is a lack of science-based evidence and insufficient clinical research data on the prevention and treatment of diabetes with NYTCMs. To address this issue, large-scale clinical trials guided by the principles of TCM holism and dialectical thinking should be conducted to obtain higher-level clinical evidence. Therefore, conducting systematic studies on the chemistry and pharmacological mechanisms, elucidating the chemical structures of individual components, and adopting multi-disciplinary and multi-technical strategies to elucidate the material basis and mechanisms of action of NYTCMs in the prevention and treatment of DM will be a future research directions for the majority of TCM researchers. These studies will provide additional evidence for the mechanisms of TCMs and NYTCMs in preventing and treating T2DM, enabling deeper exploration of the scientific essence of TCMs and accelerating their modernization.

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None.

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