

The Therapeutic Effect and Mechanism of Traditional Chinese Medicine in Type 2 Diabetes Mellitus and Its Complications

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Abstract: Traditional Chinese Medicine (TCM) has recently emerged as a beacon for the treatment of diabetes and its complications. Many TCMs that are commonly used, have the potentially demonstrated significant anti-diabetic effects. The mechanisms of these effects have been extensively discussed using modern techniques, such as genomics, mass spectrometry, and network pharmacology. Studies have demonstrated that TCM can influence glucose metabolism and pancreatic function via a diverse array of mechanisms including PI3K/AKT and AMPK pathways. TCM not only exhibits potential in the treatment of diabetes but also reduces the risk of diabetic complications. It is effective in the treatment of diabetic nephropathy (DN), diabetic retinopathy (DR), diabetic neuropathy (DPN), diabetic cardiomyopathy, and peripheral angiopathy. Research has demonstrated that prescriptions, Chinese herbal medicines, and their extracts play a role in a variety of molecular mechanisms such as antioxidation, apoptosis regulation, hypoxia improvement, autophagy, and promotion of glucose and lipid metabolism. The antioxidant properties of TCM have received considerable attention. Recent studies have demonstrated that they are capable of effectively eliminating free radicals from the body and reducing damage to cells caused by oxidative stress. Consequently, they are crucial in the treatment of diabetes and its associated complications. This review summarizes the ever-expanding scope of TCM applicability in the field of diabetes, providing crucial support and innovative ideas for modern healthcare. TCMs could help seek more effective pharmacological targets in basic study and as well serve as the complement to the strategy of diabetic prevention and treatment benefiting the patients. More and more large series of RCT and clinical investigations will eventually examine the efficacy of specific TCM formulas on the therapeutic effect of DM and its complication where currently treatments could not be satisfied.

Keywords: T2DM, TCM, pharmaceutical, diabetic complications

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease that affects the health and quality of life of individuals at an unprecedented rate in the context of increasingly complex global health challenges. Endocrine doctors must cope with significant medical issues, including the requirement to control patients' blood glucose levels more effectively, prevent complications, and improve the overall health of patients.¹ The medical community is continuously investigating new treatment strategies as the limitations of traditional oral medicine, insulin therapy, and lifestyle adjustments have become increasingly significant. Consequently, the basic framework for diabetes management has been reevaluated.²

Traditional Chinese Medicine (TCM), which is deeply entrenched in the Chinese nation's rich history and culture of China, offers a novel perspective and approach for the comprehensive treatment of diabetes. A specific chapter on "diabetes disease" was established by the renowned physician Zhang Zhongjing from the Han Dynasty in "Synopsis of the Golden Chamber" (Jin Gui Yao Lue). Zhang Zhongjing listed two formulas for DM in this chapter: "Baihu Jia

Renshen Decoction” for excess heat in the lung and stomach, and “Shenqi pills” for kidney qi deficiency syndrome.³ Owing to its comprehensive nature, TCM treatment methods can be expanded to encompass individualized care, which encompasses the prevention of complications, enhancement of quality of life, reduction of adverse drug effects, and flexibility and precision of blood glucose control.⁴ Simultaneously, TCM’s distinctive capacity to enhance the functionality of islets and modulate the neuroendocrine system is another factor that attracts the attention of diabetes researchers.^{5,6} This study aimed to provide an in-depth review of the application of Traditional Chinese Medicine (TCM) in the treatment of diabetes, with a particular focus on the mechanism of action of TCM. It also introduces a few classical prescriptions and the practicality of TCM for the treatment of diabetes.

Methods

We searched public database including PubMed and Science Direct, etc. Used the Mesh and other terms including “Traditional Chinese Medicine” or “TCM” or “TCM herbs”, “diabetes mellitus” or “diabetic complication” or “Diabetic retinopathy” or “Diabetic neuropathy” or “diabetic nephropathy” or “diabetic cardiomyopathy”, then combined the Mesh terms with the Boolean logic, in searching the related contents associated with the current topics. The searched literature encompasses the review, meta-analysis, original studies, etc. The purpose of this current study is a narrative review of current progress in TCM on diabetes and its complications, especially on the therapeutic mechanism.

Drugs, Prescriptions, and Mechanisms for Improving Blood Glucose in Type 2 Diabetes Mellitus

A meta-analysis summarized and analyzed the commonly cited TCMs for the treatment of diabetes “dissipating thirst syndrome”, including *Rehmannia glutinosa* Libosch (Di Huang), *Ophiopogon japonicus* (Mai Dong), *Poria cocos* (Fu Ling), *Panax ginseng* (Ren Shen), *Astragalus membranaceus* (Huang Qi), *Glycyrrhiza uralensis* Fisch (Gan Cao), *Dioscorea opposita* (Shan Yao), *Schisandra chinensis* (Wu weizi), *Cornus officinalis* (Shan Zhuyu), *Alisma orientale* (Ze Xie), *Trichosanthes kirilowii* (Gua Lou), *Anemarrhena asphodeloides* (Zhi Mu), *Scrophularia ningpoensis* (Xuan Shen), *Pueraria lobata* (Ge Gen), *Lycium barbarum* (Gou Qi), *Paeonia lactiflora* (Bai Shao), *Angelica sinensis* (Dang Gui), *Coptis chinensis* (Huang Lian), *Salvia miltiorrhiza* (Dan Shen), *Codonopsis pilosula* (Dang Shen), *Atractylodes macrocephala* (Bai Zhu), *Atractylodes lancea* (Cang Zhu).⁷

Among the effective proprietary Chinese medicines in literature research,⁷ the commonly used Chinese medicines included *Astragalus membranaceus* (Huang Qi), *Rehmannia glutinosa* Libosch (Di Huang), *Trichosanthes Kirilowii* Maxim (Gua Lou), *Schisandra chinensis* (Wu Weizi), *Dioscorea opposita* Thunb. (Shan Yao), *Ophiopogon japonicus* (Mai Dong), *Panax ginseng* (Ren Shen), *Pueraria* (Ge gen), *Poria cocos* (Fu Ling), *Anemarrhena asphodeloides* Bge (Zhi Mu), *Lycium barbarum* L (Gou Qi), *Glycyrrhiza uralensis* Fisch. (Gan Cao), *Salvia miltiorrhiza* (Dan Shen), and *Scrophularia ningpoensis* (Hemsl. (Xuan Shen), and *Cornus officinalis* Sieb. et Zucc. (Shan Zhuyu), and *A. officinalis* (Sam). Juzep. (Ze Xie), *Polygonatum sibiricum* red (Huang Jing), *Coptis chinensis* Franch. (Huang Lian), and *Pseudostellaria heterophylla* (Miq). Pax et Hoffm (Taizi Shen), *Paeonia suffruticosa* Andr. cortex, dried (Shao Yao), and *Polygonatum odoratum* (Mill). Druce (Yu Zhu), *Lonicera japonica* Thunb. (Jin Yin Hua), *Zea mays* (Yu mi Xu), and *Psidium guajava* L (Fan Shi Liu).

In another meta-analysis, the symptoms of diabetes were summarized,⁸ and obesity was found to be the most common symptom, followed by excessive eating, excessive drinking, excessive urination, fatigue, thirst and excessive eating, chest discomfort, pain, and weakness from the limbs to the trunk. The syndromes are characterized by moisture retention, spleen deficiency, Yin and Yang deficiency, Yin deficiency, liver qi stagnation, liver and kidney Yin deficiency, spleen and kidney Yang deficiency, kidney and Yin deficiency, liver qi stagnation, spleen deficiency, stomach heat incandescence syndrome, spleen deficiency syndrome, and spleen and kidney deficiency syndrome (Figure 1).

Classical formulas are a class of TCM prescriptions that have been historically tested and can effectively treat various diseases. A review summarized the famous classical formulas for treating DM including:⁹ *Coptis chinensis* Franch., *Rheum palmatum* L. (Da Huang); and *Bupleurum chinense* DC. (Chai Hu); *Astragalus mongholicus* Bunge (Huang Qi); The experimental analyses of the primary ingredients or bioactive substances from these classical formulas were

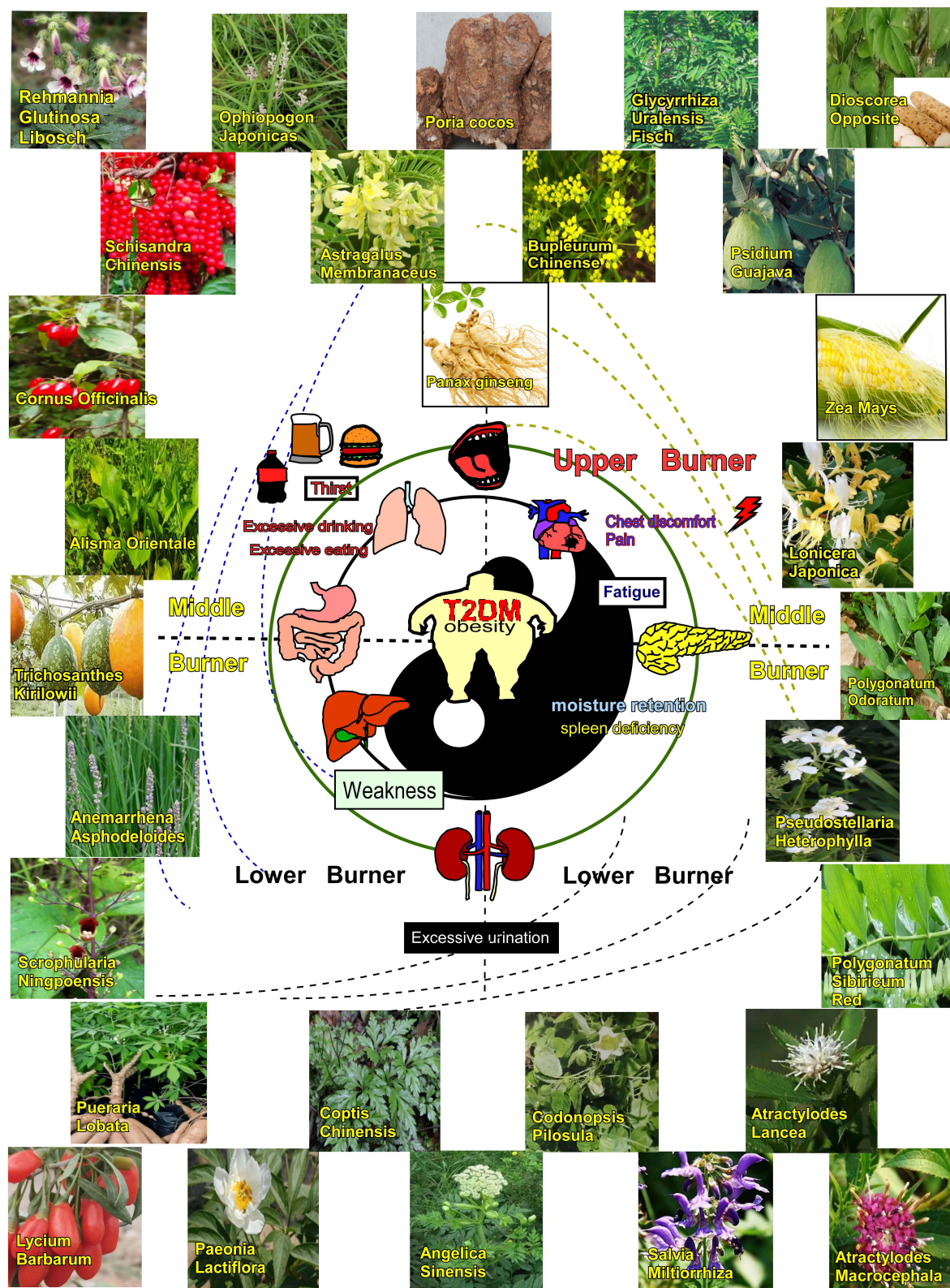


Figure 1 The most referenced TCM herbs to treat T2DM which were also known as the “XiaoKe” syndrome, classically characterized by the symptoms belongs to “Three Burns” - also termed as “Three Xiao” or “Three exhausting symptoms”. The “Upper Xiao”, which is comprised by the organs from “Upper Burner” of lung and heart, includes symptoms of “excessive drinking”; The “Middle Xiao” caused by the pathological changes within organs from “Middle Burner”, formally composed of digestive organs, such as liver, upper gastrointestinal tracts, pancreas or “Spleen” (a TCM concept), causes “excessive eating”, “weight loss”, “fatigue” and other numerous symptoms due to the moisture retention of “Middle Burner” and /or “spleen deficiency”; The “Lower Xiao” largely constitutes of kidney, bladder and other urinary organs, and lower gastrointestinal tracts from “Lower Burner”, the classical symptoms including the “excessive urination”, “weakness”, “diarrhea”, etc. These organs alteration can be inspected and analyzed through, the “Yin and Yang” transformation system and/or “Organ phase Theory” or “Zang Xiang Theory”.

summarized as:⁹ Flavonoids (which includes apigenin, baicalein, puerarin, quercetin, hesperidin, myricetin, kaempferol), Terpenoids (catalpol, loganin, oleanolic acid, crocin), Alkaloids (berberine, matrine, betaine), Curcumin, Cinnamaldehyde, Tan IIA (which is derived from *Salvia miltiorrhiza* Bunge).

Prescriptions for the treatment of diabetes were included in the review.⁸ Rehmannia pills, Xiaoke tablets, Yiqi Yangyin Huoxue Decoction, Jinlida granules, Yiqi Huoxue Decoction, berberine, Shenqi Jiangtang granules, mainly concentrated in tonifying spleen and nourishing qi Yin; Among them the most common herbs in order: Astragalus, Rehmannia, yam, Pueraria root, Coptis chinensis, Ophiopogon japonicus, salvia miltiorrhiza, Poria cocos, trichosanthin and rhizoma chinensis.

The following pathways could be involved in the established hypoglycemic effects of TCM drugs, which may affect both fasting and postprandial glucose regulation in T2DM patients in a different manner. Furthermore, employing contemporary metabolomics may facilitate the identification of additional molecules and metabolic mechanisms involved in blood glucose metabolism, thereby reducing complications (Figure 2).

TCMs Stimulate Insulin Release

Chinese medicines that stimulate insulin release include Coptis chinensis, *Urtica mairei* Levl (Dian Ci CAO), ginseng, Pueraria, *Anemarrhena asphodeloides* Bge, *Lycium barbarum* L, Rehmannia, *Terminalia chebula* Retz. (He Zi), Astragalus, *Cornus officinalis* Sieb. et Zucc, *Curcuma longa* L. (Jiang Huang) and *Momordica charantia* L. (Ku Gua).⁷ The signaling pathways related to islet function and liver glucose metabolism include PI3K/AKT, which regulates glucose uptake, glycogen synthesis, gluconeogenesis, and other metabolic pathways. A variety of TCM ingredients can regulate PI3K/AKT: 1) Flavonoids: baicalein (baicalein), flavone (chrysin), dihydroquercetin (diosmetin), small beige flavone (tricin), HM-chromeenone/hydrochalcone (HM-chromanone), puerarin (puerarin), α -Methyl artoflavanocoumarin (α -methyl artoflavanocoumarin), loureirin B (loureirin B), wild baicalein (fisetin), kaempferol (kaempferol), quercetin, apigenin, poncirin, naringenin; 2) Polyphenols: resveratrol, pterostilbene, curcumin and gallic acid; 3) Alkaloid: tetramethylpyrazine is derived from *ligusticum chuanensis*, hirsutine is derived from *Uncinus*, 1-Deoxynojirimycin is derived from mulberry branches and leaves; 4) Terpenoids: sweet glycosides: siamenside I, mogroside III, mogroside IV, mogroside V; Triterpenoids such as: catalpol, oleanolic acid, asiatic acid, glycyrrhetic acid, maslinic acid; 5) Quinones: aloin, embelin, emodin; 6) Saponins: Astragaloside IV (IV), ginsenoside Rb2 (ginsenoside Rb2), ginsenoside R (ginsenoside Rg5); 7) Other categories: β -sitosterol (Beta-sitosterol), Taurine (Taurine), diaromatic heptanene/diphenylheptanoid compounds (Diarylheptanoid) and artemisinin (Esculin), etc.^{9,10}

Pancreatic Protection by TCM

Shenqi compound (SQC) is composed of Panax Ginseng, Astragali Radix, yam (*Rhizoma Dioscoreae*), Corni Fructus, Rehmanniae Radix, *Salviae Miltiorrhizae Radix et Rhizoma*, Radix Trichosanthis, and Rhei Radix et Rhizoma, which significantly reduce blood glucose levels, improve insulin resistance and hyperinsulinemia, and inhibit pancreatic cell hypertrophy. This effect was achieved by relieving oxidative stress and inflammation and inhibiting apoptosis and senescence of pancreatic beta cells. The Fufang-zhenzhu-tiaozhi formula (FTZ) protects pancreatic beta cells by promoting the regeneration of pancreatic cells, preventing inflammatory cell infiltration, and preserving the pancreatic cell mass. It was found that the expression of newborn-related molecules increased, such as Pancreatic development factor-1 (PDX-1), Insulin transcriptional activator (MAFA), and Neurogenin 3 (NGN3). Other Chinese herbs include puerarin, which maintains glucose stability in high-fat-induced diabetes models and promotes beta-cell genesis and GLP-1 levels.

α -Glucosidase Inhibition

Chinese medicines that inhibit α -glucosidase include *Cornus officinale*, Galla Chinensis (Wubei Zi), *Morus alba* (Sang Ye), Schisandra, *Glycine max* (Da Dou), and *Rheum officinale* Baill. (Da Huang), *Morus alba* L., cortex (Sang Bai Pi), *Anemarrhena asphodeloides* Bge, *Paeonia lactiflora* Pall., *Sanguisorba officinalis* L. (Di Yu), *Polygonum cuspidatum* Sieb Zucc (Hu Zhang), *Terminalia chebula* (Shi Jun Zi), *Cucurbita moschata* (Nan Gua), *Polygonum multiflorum* Thunb (He Shouwu), *Lycium barbarum* L, *Glycyrrhiza uralensis* Fisch. *Lilium brownii* F. E. Br. ex Miellez var. *viridulum* Baker (Green Leaf Baihe), *Commelina communis* L. (Yazhi Cao) and *Polygonatum odoratum*.⁷

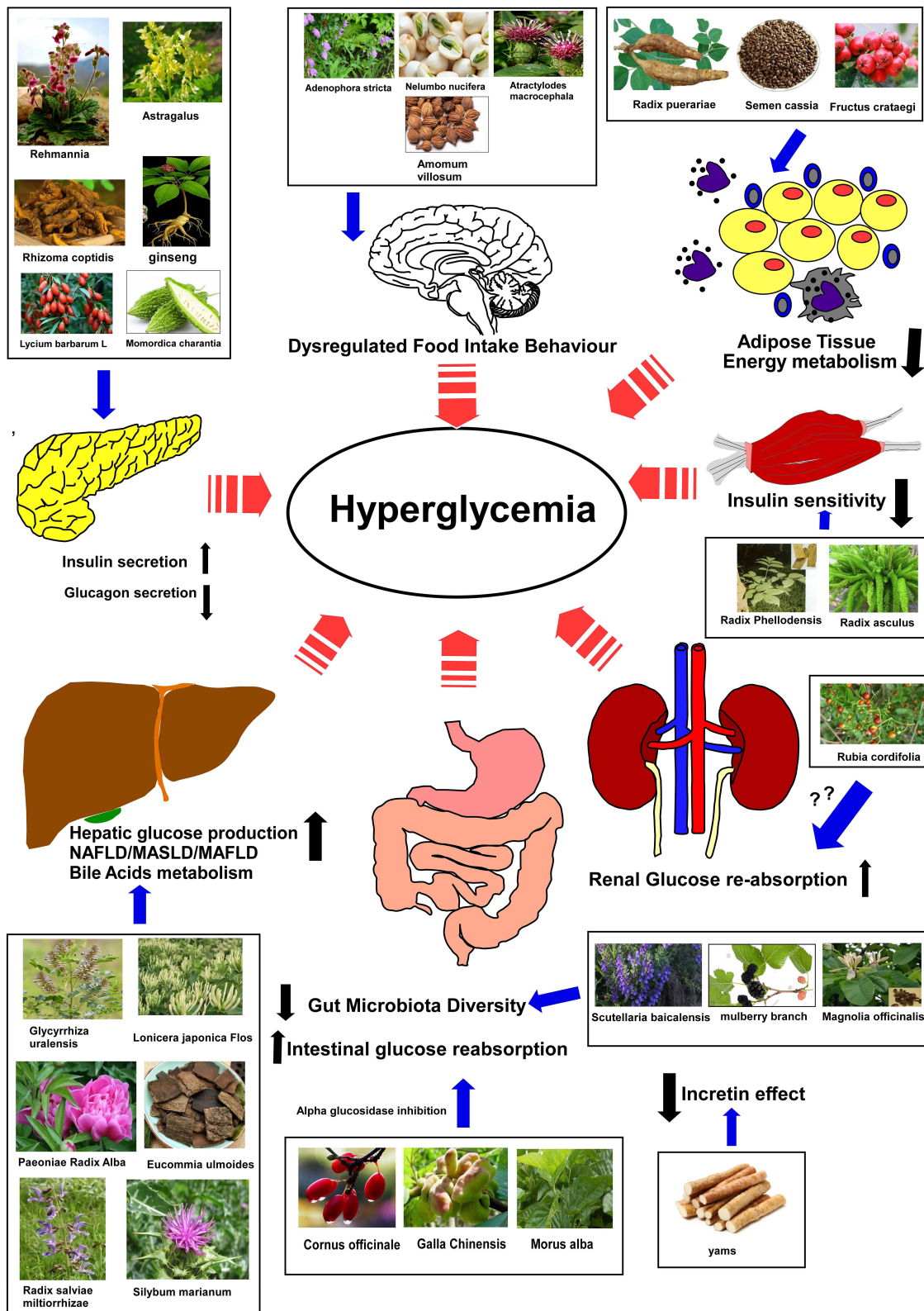


Figure 2 The therapeutic role of TCM herbs in the pathophysiology of T2DM represented as classical “ominous octet” theory proposed by the recipient of Banting Reward Prof. DeFronzo based on the major pathophysiology of T2DM and intervention or pharmacological targets: 1) the pathophysiology of pancreas: decreased islet β cell insulin secretion; 2) the increased islet α cell glucagon secretion; 3) the overproduction of hepatic glucose production; 4) the attenuated “incretin effect” such as glucagon-like peptide-1 (GLP-1) or glucose dependent insulinotropic polypeptide (GIP) secreted by the intestinal cells; 5) enhanced glucose re-absorption by the renal approximate tubular cells; 6) desensitized in the insulin-targeting organ including skeletal muscles; 7) the dysfunctional and metabolic alteration of adipose tissue; 8) disorganized neurotransmitters within central nervous system (CNS) associated with ingestion behavior and bodyweight regulation.

The Proposed TCM Herbs in Treating Obesity and Related Risk Factors for T2DM

Obesity and metabolic syndrome are closely related to T2DM and mutually metabolically influenced. For treating obesity or metabolic syndrome, TCM emphasizes comprehensive interventions, including lifestyle management, herbal medicine, acupuncture, Tuina, Taichi, and dietary therapy. TCM herbs have long been shown to have special advantages such as safety, lower side effects, and effectiveness, especially for maintaining the effects and benefits of body weight loss. Some investigators have proposed that TCM herbal prescriptions may be considered for the discontinuation of GLP-1 therapy and could further promote weight loss. The mechanism underlying this effect is related to the modulation of energy homeostasis of intake and expenditure, reduction of insulin resistance, and improvement of glucose and lipid metabolism. The commonly recommended herbs including ginseng, bitter melon, Cinnamon (Gui Pi), etc.¹¹ Rhizoma coptidis inhibits fat accumulation and improves insulin resistance; Semen cassia (Jue Ming Zi) can promote lipid metabolism and reduce its absorption; Fructus crataegi (Shan Zha) may reduce lipid accumulation and improve digestion; Radix puerariae can increase energy expenditure while concurrently reducing fat accumulation; Folium mori (Sang Ye) inhibits fat accumulation and regulates lipid metabolism; Rhizoma polygonati, Radix astragali, and Radix ginseng may affect energy balance and regulate lipid and glucose metabolism.¹¹

Metabolic-associated fatty liver diseases, including metabolic dysfunction-associated steatotic liver disease (MASLD) or metabolic-associated fatty liver disease (MAFLD), are markers of insulin resistance and etiological factors for T2DM. In addition to body weight and metabolic risk factor management, the intervention of liver metabolism malfunction is also critical to prevent complications and relieve the adverse consequences related to MAFLD or MASLD, such as T2DM and cardiovascular diseases.¹² For many decades, owing to complicated pathophysiological mechanisms, there have been numerous conceptualizations, but only a few medications have shown effective therapeutic results, except for recent reports of outcomes in clinical trials of incretin-based therapies, including Semaglutide, Dual agonists GLP-1/GIP RAs, GLP-1/GCGRs,^{13–15} and basic studies,¹⁶ which showed the endocrine paradigm for effective MAFLD or MASLD treatment.¹⁷ There have also been numerous basic and clinical studies on the therapeutic potential of TCM on MAFLD or MASLD.¹⁸ In addition to converged mechanisms with incretin-based therapies on metabolic-parameter modulation (glucose, lipid, body weight, insulin resistance, oxidative stress, etc.), gastrointestinal micro-environment modulation is also important, including effects on metabolites and patterns of gut microbiota regulation,¹⁹ thus influencing hormone adaption in the gut-brain axis, as well as immune and inflammation profiles, benefiting metabolic risks related to MASLD or MAFLD. A review presented an overview of the mechanism of TCM in MAFLD, especially in immune adjustment, targeting macrophages, neutrophils, T lymphocytes, nature killer cells (NK cells), and dendritic cells.²⁰

Improving the Role of Glucose Metabolic Factors in T2DM

Some studies have suggested that the Chinese herbal medicine *Murrayae Folium et Cacumen* (Jiulixiang) extracts flavonoids and other substances (including 5,6,7,3',4',5'- hexamethyl flavonoids (3), 5, 6, 7, 3',4'- five methoxy flavone (6), 5, 7, 3',4',5'- five methoxy flavone (8), 5, 7, 3',4'- 4 methoxy flavone (9), and 7-hydroxyl - 5, 3', 4'-trimethyl flavone (32)) that can improve the metabolism of patients with diabetes.²¹ Preclinical studies have shown that total flavones can improve kidney injury in diabetic rats, possibly by regulating blood glucose, lipid metabolism, oxidative stress, and inflammatory factors. At the same time, it can also reduce the incidence of diabetic cardiomyopathy in T2DM rats and inhibit oxidative stress, inflammation, and apoptosis by up-regulating the expression of NF-E2-related factor 2 and heme oxygenase-1 gene. It can also reduce blood glucose levels in alloxan-induced diabetic rats, improve complications, such as hypercholesterolemia and hypertriglyceridemia, and reduce related injuries. Studies have shown that its hypoglycemic effect is similar to that of metformin and glibenuride, affecting the opening and closing of ATP-sensitive potassium ion channels. One study revealed that flavonoids can significantly lower blood glucose, improve lipid metabolism disorders, increase plasma C-peptide and insulin levels, and improve β -cell secretion index and insulin resistance, malondialdehyde levels, and IL-1 β , IL-6, and tumor necrosis factor (TNF)- α expression.

Huai Yang is highly praised as “Chinese Yam” and its main ingredients include water, starch, non-starch polysaccharides, fiber, protein (90% dioxine), allantoin, dopamine, phytic acid, choline, ergosterol, trace elements, etc.,²² Its starch contains resistant starch (not digestible 2 hours after a meal), high amylose/amylopectin (type C starch), which

delays digestion and absorption, delays postprandial-blood glucose rise, reduces insulin levels 30 and 60 minutes after a meal, improves insulin resistance, and has the effect of preventing diabetes. In vitro studies have shown that resistant starch promotes the synthesis of short-chain fatty acids in the large intestine. Inhibits liver cholesterol synthesis and proliferation of colon cancer cells. Yam polysaccharides are biologically active carbonic water polymers. After purification, it exhibits antioxidative, hypoglycemic, antimicrobial, immunomodulatory, and antitumor effects. Yam/dioscorin was found to inhibit angiotensin-converting enzyme activity in vitro, have antihypertensive effects in vivo, have concentration- and pH-dependent antioxidant effects in vitro, and trap hydroxyl-free radicals. The composition of Batatasin II–V is similar to that of resveratrol, which can prevent and improve diabetes. Other small molecules, such as trans-N-p-coumaroyl tyramine (TCT), allantoin (allantoin), and CYP, have preventive effects on diabetes. Continuous injection of yam extract into streptomycin-induced diabetic rats improved fasting blood glucose levels and delayed kidney injury. Allantoin injection can improve insulin resistance, increase adrenal β -endorphin secretion, activate opioid μ -receptor to promote the expression of glucose transporter IV, and studies have found that allantoin can activate imidazoline I3 receptor to increase insulin secretion in rats. Batatasin I and other similar ingredients also inhibited α -glucosidase, delayed postprandial glucose increase, and significantly reduced the adverse reactions of the digestive tract and liver damage compared to acarbose, miglitol, and voglibose. High-purity CYP promoted glucose uptake and glucose transporter II expression, thereby improving insulin sensitivity in FL838 cells treated with TNF- α in vitro. Other medicinal benefits of yams include antioxidative stress, inflammation, immune regulation, blood pressure reduction, improvement of blood lipids, and antitumor effects. Yam is often combined with other TCM, such as Liuwei Dihuang pills. Modern medicine has found that yam (9–15 g), raw coix seed, and poria can effectively treat “puffiness.” The combination of Astragalus and Huai Yam (30 g) had an obvious therapeutic effect on diabetes, diarrhea, and asthma. Huai Yam combined with epimedium can be used to improve apnea, exercise ability, and quality of life in patients with stable, moderate, and severe COPD.

Panax Notoginsenoside R1 in *Panax notoginseng* activated the PI3K/AKT signaling pathway in rats,²³ inhibited the activity of phosphorylated p65, and reduced inflammation and apoptosis; In vitro, various cell models (RSC96, Min6, HK-2, Muller) were found to reduce caspase-3, miR-503, DNA repair enzyme PARP, and reactive oxygen species. Activation of the PI3K/AKT, Wnt/ β -catenin, and NRF2-HO-1 pathways increased miR-29a and GSK-3 β ; inhibited TGF β and collagen I expression; inhibited oxidative stress, inflammation, and apoptosis; reduced VEGF expression in retinopathy; and reduced p62/SQSTM1 expression. Increased PINK1, Parkin activation, and LC3-II/LC3-I ratio to reduce fine-grained damage. α 3 β 1 integrin deficiency induces adhesion to the glomerular basement membrane, resulting in diabetic nephropathy (DN), NG-R1 improving α 3 β 1 expression and protects podocytes from hyperglycemic damage and may be involved in increased PI3K/AKT activation and decreased p65 phosphorylation.

Primary Metabolic Pathways Related to Hypoglycemic Effects of TCM Prescriptions Revealed by Modern Methodologies

Multiple metabolomics methodologies have been used to assess the critical ingredients related to TCM prescriptions and their associated pathways.²⁴ The Ge-Gen-Jiao-Tai-Wan (GGJTW) Decoction, Qijian mixture, and Huanglian decoction (HLD) are well-known decoction decoctions used to treat T2DM. GGJTW comprises kudzu root, *Coptis chinensis*, and cinnamon, in which kudzu can improve insulin resistance and protect β -cells. According to metabolomics, GGJTW caused significant changes in 37 potential markers related to the regulation of bile acid biosynthesis and promoted the synthesis of taurine and cholic acid.

The “seven-element formula (Qijian Fang)” comprise Astragalus, Pueraria root, *Ramulus euonymus*, and Rhizome. Astragalus can reduce blood lipids and blood glucose, improve edema and oxidative stress, and have a wide range of pharmacological effects in T2DM, such as in mice. Hydrogen magnetic resonance spectroscopy (1H-NMR) has shown that seven components can improve the metabolic profile of liver cells, and seven components can reduce blood glucose by regulating branched-chain amino acids such as valine, leucine, and isoleucine.²⁵ The increase in plasma levels and the enhancement of catabolism are related to the enhancement of insulin sensitivity. In addition, the seven-element formula regulated the metabolic pathways of alanine, aspartic acid, and glutamic acid. 1H-NMR revealed significant changes in

other metabolites, such as phosphatidylcholine, citric acid, inositol, glycerin, anserine, trimethylamine, n-oxide, glutarate, lactate, alanine, acetate, inosine, 3-hydroxybutyric acid, glutathione, taurine, niacinamide, xanthine, adenine, and glycine.

Ultra-high-performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UHPLCQTOF/MS) revealed that the extract of *Scutellaria scutellaria* could regulate blood glucose metabolism through a pathway related to glycerophospholipid metabolism. Another high-performance liquid chromatography-mass spectrometry (HPLC-MS) study found that Huanglian Decoction interfered with a diabetic rat model through glycolic acid metabolism and phenylalanine and citric acid cycles.²⁶ Geogi root has anti-inflammatory and anti-oxidative stress effects, which may be related to its flavonoids, such as baicalin (Baicalin), wogonoside (baicalein), and wogonin (Baicalein), which can reduce insulin resistance and inhibit gluconeogenesis. *Coptidis Rhizoma* contains a variety of alkaloids, such as berberine, coptisine, palmatine, and especially berberine. Recent studies have shown that it reduces blood glucose levels and promotes insulin secretion. However, this is only part of improving blood glucose levels, and most of the effects of T2DM alleviation are still under study. Some studies have found that berberine can activate the AMPK, GLUT1, and AKT/GLUT4 signaling pathways, increase GLP-1 levels, upregulate insulin receptor (InsR) mRNA expression, and inhibit PEPCK and G6Pase expression. Inhibits inflammatory mediators (IL-1, IL-6, TNF- α , COX-2, and inducible Nitric Oxide Synthase (iNOS)) and regulates lipid metabolism; cholic, deoxycholic, and glycolic acids are associated with glucose metabolism. Glycinic acid can inhibit inflammation by activating and regulating the Takeda G protein-coupled receptor 5 (TGR5). Cholic and deoxycholic acids block the binding of glycyrrholic acid to TGR5. In addition, phosphatidylcholines, lysophosphatidylcholines, hemolytic phosphatidyl ethanolamine (lysophosphatidylethanolamines), and yellow purine nucleoside (xanthosine) participate in uric acid metabolism is T2DM a marker of inflammation, which can improve the metabolism of these inflammatory response-related substances, thereby improving and alleviating T2DM. Other herbs included ginger (*Rhizoma Zingiberis*), *Glycyrrhiza uralensis* Fisch, *Cinnamomum verum* J. Plesl, *Panax ginseng* C.A. Mey, and *Pinellia ternata* (Thunb). *Makino* and *Ziziphus jujube* mills are involved in the regulation of glycolipid metabolism. HPLC-MS identified markers related to the tricarboxylic acid cycle and lipid metabolism; cytosine, phenylalanine, glucose, L-carnitine, phenylpyruvate, betaine, citrate, and hippuric acid are regulatory products of *Coptis* decoction.

The Ge-Gen-Qin-Lian Decoction (GGQLD) contains *Pueraria*, *Scutellaria*, *Rhizoma* decoction, and *Glycyrrhiza* decoction, and it was found to have a hypoglycemic effect through analysis of the local pharmacologic method and network pharmacology.²⁷ In vitro studies have shown that 4-hydroxymephenytoin promotes insulin secretion in the RIN-5F cell model and improves insulin resistance in 3T3-L1 adipocytes, suggesting that the function and mechanism of Chinese herbal medicine prescriptions in treating diseases can be determined using a network pharmacological database. In addition, intestinal flora analysis revealed that it can regulate flora, restore intestinal permeability, and inhibit inflammation.

Similarly, 24 of these bioactive granules were predicted in Lian-Ge granules composed of *Coptis* and *Radix gerber*, *Salvia miltiorrhizae*, seaweed, resveratrol, and taurine, which have blood-sugar-lowering properties, including berberine, puerarin, danshinolic acid A, and sinigrin, and can affect nine targets and 111 metabolic-related pathways.²⁸ *Astragalus membranaceus* is a hypoglycemic herb commonly used in TCM. Some studies verified 13 important T2DM targets identified by network pharmacology through quantitative real-time PCR, demonstrating that *Astragalus membranaceus* improves the insulin signaling pathway by upregulating casein kinase activity, ensuring normal lipid metabolism, and increasing insulin sensitivity.²⁹

In addition, changes in intestinal flora are one of the mechanisms underlying TCM regulation. *Roseburia* and *Faecalibacterium prausnitzii* in Clostridiales can produce short-chain fatty acid (SCFA) butyrate,^{30,31} which can affect G protein-coupled receptors, promote the secretion of various hormones, and activate the vagus nerve, whereas gram-negative bacteria can cause insulin resistance due to the production of lipopolysaccharide (LPS).³² GGQLD and berberine significantly changed intestinal flora, promoted the abundance of butyrate-producing bacteria, and reduced intestinal inflammation and blood glucose levels;³³ Flavonoids in *Sophora flavescens* Aiton reduce blood glucose by regulating the metabolite axis of the host-gut microbiota.³⁴

Delaying the Pathophysiology of Cardiovascular Systems and Diabetic Osteoporosis

Aging of blood vessels and their cellular organs is a manifestation of senile diabetes patients.^{35–37} Studies have found that some Chinese herbal extracts³⁸ can delay the pathophysiology of endothelial cells caused by hyperglycemia and hyperlipidemia, such as extracts of ginseng, notoginseng, and *Ligusticum chuanxium*, which may increase intracellular autophagy activity, increase mitochondrial membrane potential, reduce DNA damage caused by reactive oxygen species (ROS) aggregation, improve cardiac aging and vascular calcification, and delay vascular aging by inhibiting the protein expression of AMPK/mTOR-related pathways. Other pathways include inhibition of Thioredoxin Interacting Protein (TXNIP) and NF- κ B signaling upstream of the NLRP3 inflammatory body and promoting of Nrf2 signaling related to antioxidant pathways.

TCM has also been shown to improve diabetic osteoporosis: *Epimedium brevicornum* -Bax/Bcl-2 signaling pathway,^{39,40} *Phedendron chinense* Schneid extracts Arabinoxylans-advanced glycation end-products (AGE)/receptors of AGE(RAGE),⁴¹ Asparagine root (*Anemarrhenae Rhizoma*),^{42,43} and *Phellodendri Chinensis* Cortex improved the osteoporosis phenotype, significantly enhanced the trabeculae -NLRP3, Asc, caspase, Gsdmd, IL-1 β , Nrf2-Keap1; Ligustroflavone in *forsythia* (*Ligustrum lucidum*) increases the level of parathyroid hormone PTH and regulates calcium homeostasis.⁴⁴ *Rehmand-igf-1* /PI3K/mTOR;⁴⁵ The meta-analysis summarized the therapeutic effects of 9 TCM prescriptions on osteoporosis in elderly patients with diabetes. Common Chinese medicines include *Epimedium*, *Angelica sinensis*, *Rehmannia*, and *Astragalus*.⁴⁶ The three proprietary Chinese medicines were Jintiange Capsules and Tangmaikang Granules. In the extract study, one clinical study suggested that the Qianggu Capsule could reduce pain caused by osteoporosis and improve bone mineral density and blood glucose. Essential extracts include total flavones, such as *Drynaria roosii* Nakaike [*Polypodiaceae*, *Drynariae rhizoma*], which can promote bone turnover through the BMP2/ Smad signaling pathway.

Prevent Muscle Loss/Preservation of Insulin Sensitivity

Astragalus and yams prevent muscle atrophy caused by diabetes by regulating mitochondrial dysfunction, including the Rab5a/mTOR pathway.⁴⁷ Another study using an animal model in rats showed that *Radix vasculus* and *Radix Phellodensis* can reverse muscle atrophy through the Akt/mTOR/FoxO3 signaling pathway.⁴⁸

Improving the Pattern of Intestinal Flora

Extracts of *S. baicalensis*, including baicalin, can improve SCFA secreted by the intestinal flora. A literature review examined the role of the microbiota in mediating the therapeutic effects of certain TCM medications.⁴⁹ The total alkaloids of the mulberry branch can not only improve blood glucose metabolism but also regulate the distribution of beneficial intestinal flora. *Magnolia officinalis* polyphenol has anti-inflammatory and antibacterial effects, magnolol can improve the intestinal flora spectrum, and Qingke has a high protein content and contains β -glucan to regulate blood glucose and improve intestinal flora. The Chinese herbs that affected SCFA also included resveratrol and poria. *Radix scutellariae* and *Coptis* were used in various formulas: Gegen Qinlian Decoction, Banxia Xiexin Decoction, *Coptis Jiedu* Decoction, ginger and ginseng decoction, and *Cinnamomi Cortex*. The extract also improved the intestinal flora by inhibiting the LPS-binding protein-monocyte chemoattractant protein-1 (MCP-1) -CD14-TLR14 pathway. Ginsenosides have anti-inflammatory effects that can repair the intestinal barrier, improve LPS-related inflammation and intestinal flora disorders, inhibit the LPS-TLR4 signaling pathway, and alleviate T2DM symptoms. Some studies have found that Gegenqinlian Decoction has a hypoglycemic effect and decreased LPS and inflammatory indices accompany changes in intestinal flora. In addition, changes in intestinal hormones are related to changes in flora. Studies have found that based on metformin treatment, Shenlingbaizhu powder can reduce motilin levels in obese T2DM patients (spleen deficiency and moisture block). In contrast, somatostatin levels were higher than those in the control group. Dahuang Glycyrrhizin decoction combined with acupuncture improved gastrointestinal hormone secretion in patients with gastroparesis, significantly decreased gastrin and motilin levels, increased somatostatin levels, and improved gastric emptying. Similar research has been conducted on the Houpu Qiqi Decoction.

TCM and Treatment of Diabetic Complications

TCM has unique advantages in the treatment of DM complications, such as the protection and treatment of vascular complications, delayed vascular impairment and kidney injury,⁵⁰ regulating autophagy pathway.³⁸ Multiple reviews have summarized the potential mechanisms of TCM herbal extracts or monomers in treating complications of DM, including saponin monomers,⁵¹ luteolin,⁵² and kaempferol.⁵³

TCM Treatment of Diabetic Nephropathy (DN)

TCM Prescription and Proprietary Chinese Medicine

A meta-analysis of 37 RCT studies analyzed the efficacy of TCM 13 kinds of DN patent Chinese medicines, including Bailing capsule, compound Danshen dropping pills, Shenyang Kangfu tablets, Yishenhuashi Granules, Jinshuibao capsules, Huangkui capsules, Cichongyishen granules, Jinlida granules, Uiduoqing granules, Qikui granules and Shenan capsules. Among them, *Cordyceps sinensis* (BerK.) Sacc., *Salviorrhiza miltiorrhiza*, *Alisma plantago-aquatica* subsp. *orientale* (Sam). Sam, ginseng, and *P. cocos* are commonly used.⁴⁶ A systematic review summarized the potential pathways related to inflammation in DN (TLR, NLRP3, Nuclear factor erythroid 2-related factor 2 (Nrf2), AMPK, Mitogen-Activated Protein Kinase (MAPK), JAK-STAT, and AGE/RAGE pathways and the therapeutic effects of TCM.⁵⁴

The treatment of diabetic nephropathy (DN) with TCM mainly includes promoting fluid, nourishing blood, supplementing qi, nourishing Yin, detoxifying and detumescence;⁵⁵ 1) “Zishen-wan” comes from “Orchid Room Secret”. In vivo experiments show that it can regulate p38 MAPK and PI3K-Akt signaling pathway in db/db mice, and significantly inhibit the expression of inflammatory cytokines such as IL-1 β , IL-6 and TNF- α ;⁵⁶ 2) “Xiexin Decoction” can reduce the expression of inflammatory cytokines in kidney, possibly by regulating the NF- κ B pathway, in addition, it can also protect the kidney of DN rats by reducing mesangial proliferation, improving the matrix and thickening the basement membrane;⁵⁷ 3) “Jiangtang decoction” can reduce inflammatory response by activating PI3K-Akt and inhibiting NF- κ B pathway, thereby reducing the aggregation of glycosylation end products and their receptors, reducing COX-2 expression and delaying the progression;^{58–60} 4) Danzhi Jiangtang capsule significantly reversed the high expression of COX-2 and iNOS, inhibited JAK2-(STAT)1/STAT3-SOCS3 signaling pathway, and enhanced renal metabolism;⁶¹ 5) Huangkui Capsule may down-regulate the expression of p38 MAPK and Akt pathway, TGF- β 1 and TNF- α factors, which can inhibit oxidative stress, reduce the production of free radicals and other oxidative substances, promote the production of SOD, and prevent vascular endothelial damage;⁶¹ 6) Danzhidujiangtang capsule can significantly reduce the expression of COX-2 and iNOS in kidney tissue, inhibit JAK2-STAT1/STAT3 pathway on SOCS3 pathway, so as to prevent kidney from receiving more oxidative stress damage; 7) Sanzi Guben granule may reduce the production of oxidative stress product malondialdehyde (MDA), increase the production of reducing glutathione (GSH) and catalase (CAT) through Nrf2 up-regulation, and reduce blood cholesterol and triglyceride at the same time.⁶² The upregulation of nuclear factor Nrf2 can delay the DN progression.⁶³ In human renal HK-2 cells, it can also inhibit the decrease in the expression of E-cadherin, N-cadherin and Vimentin induced by cyclosporine A and improve renal interstitium fibrosis.⁶²

The TGF- β 1/SGK1 signaling pathway is the main pathway involved in glomerular fibrosis. 1) Naoxintong Capsule can effectively improve blood glucose and lipid metabolism disorders, activate insulin pathway, reduce extracellular matrix (ECM) and AGE aggregation, and down-regulate TGF- β /SMAD signaling pathway;⁶⁴ 2) “Huangqi Decoction” can significantly improve insulin resistance to kidney injury by regulating insulin receptor substrate 1 (IRS1) -PI3K-glucose transporter (GLUT) signaling pathway, thereby improving DN;⁶⁵ 3) “Chai Huang Yishhen Granule” can significantly improve the glomerular sclerosis index and reduce extracellular matrix deposition by TGF- β /SMAD;⁶⁶ 4) “Tongxinluo” can regulate EMT, down-regulate TGF- β /SMAD-mediated miR-21 kidney injury, and inhibit TGF- β 1 transport from glomerular endothelial cells to mesangial cells through exosomes, thus inhibiting glomerular fibrosis;⁶⁷ 5) Xiaokeping granules can reduce renal tubulointerstitial fibrosis by down-regulating TGF- β 1 and up-regulating Smad7;⁶⁸ 6) Through this pathway, “Fuxin capsule” can affect the role of VEGF/VEGFR2 in protecting renal vessels;⁶⁹ 7) “Jixue Paidu Tang-1” can reduce podocyte injury and kidney injury and inhibit EMT activity by inhibiting TGF- β 1/SGK1-LOC498759 signaling pathway;⁷⁰

On the other hand, podocytes damage can lead to the damage of filtration membrane integrity, and: 1) Zhenwu decoction can protect podocytes by inhibiting the overexpression of RAS and regulating renin and podocin;⁷¹ 2) Yishen Capsule can promote podocyte autophagy and protect kidney by regulating SIRT1/NF- κ B;⁷² 3) “Bushen Huoxue Decoction” was found to reverse markers of podocyte damage;⁷³

Basal membrane injury promotes the release of inflammatory factors and reactive oxygen species (ROS) production, leading to kidney injury.⁷⁴ 1) Qidi Tangshen granules significantly improved the structure of the basement membrane, possibly by regulating intestinal flora and the bile acid axis.⁷⁵ 2) “Jowiseungki” can improve the diversity and structure of intestinal flora in mice, reduce PKC- α /PI3K/Akt and NF- κ B/ α -SMAD signaling pathways and reduce inflammation and fibrosis.⁷⁶ 3) “Gandhi capsules” improved tyrosine and bile acid metabolism in clinical experiments, thereby improving glucose metabolism abnormalities;⁷⁷

Treating DN by TCM Herbs or Extracts

In a meta-analysis of senile DN, 18 RCT studies (10 DNIII/IV stages) suggested that Astragalus, yam, Tuckaia, white rhizoma, *Cornus officinalis*, and *Salvia miltiorrhiza* were commonly used Chinese herbs for DN. The Huangqi Guizhi Wuwu and Yiqi Yangyin decoctions improved blood glucose levels and DN. In a study of DN Chinese herbal extract in the elderly, it was found that Fucoidan in Haikun Shenxi capsules can reduce inflammatory factors and delay renal function decline, which may involve the AMPK-ULK1 signaling pathway.⁴⁶

Ligusticum chuanxiong extract inhibited oxidative stress and inflammation through the Nrf2 and NF- κ B pathways.⁷⁸ Hyperglycemia leads to the activation of NADPH oxidase (Nox) and the increase of renal ROS levels, leading to kidney injury;⁷⁹ Ethanol extract from *Bombax ceiba* and mangiferin can reduce ROS production and oxidative stress by inhibiting NADPH oxidase 4 (Nox4). In vitro studies⁸⁰ and *Nepeta Angustifolia* (C.Y.W) were found to inhibit peroxisome-induced apoptosis, possibly by increasing the mitochondrial membrane potential and inhibiting the caspase-mediated pathway.⁸¹ *Salvia miltiorrhiza* can enhance the expression of Nrf2 and downstream heme oxygenase (HO-1) and NADPH quinone oxidoreductase (NQO1) and downregulate the antioxidant response of Kelch-like ECH-associated protein 1 (Keap1).⁸² In addition, it was found that the metabolism of phospholipids, arachidonic acid, and pyrimidine are also involved in omics study.⁸³ The Chinese medicine monomer Danshinone IIA mitigated renal impairment in db/db mice, possibly by modulating NLPR3 inflammasomes, thioredoxin-interacting proteins, and interacting proteins.⁸⁴ Txnip expression inhibits pro-death and delays DN progression. By upregulating the expression of Nrf2, *Nelumbo nucifera* leaf extract can activate the activation signal of Akt, which inhibits oxidative stress and apoptosis. AKT phosphorylation can inhibit the downstream apoptotic signals of Bcl-2 associated X (Bax) and active caspase-3, thus playing a protective role in the kidneys.^{85,86}

AGE-induced mesangial cell injury leads to glomerular dysfunction. *Coriandrum sativum* seed extract can promote antioxidant enzyme content and reduce kidney protection by AGE products.⁸⁷ *Euonymus alatus* can effectively regulate disorders of glucose and lipid metabolism, downregulate the levels of collagen IV, fibrin-binding protein, and laminin, and downregulate the expression of TGF- β 1.⁸⁸ Renal P2X7 receptor activation is associated with renal mesangial cell expansion, glomerular filtration disorders, and interstitial fibrosis in patients.⁸⁹ Activation of the NLPR3 inflammasome can lead to podocyte injury,⁹⁰ and *Ophiocordyceps sinensis* can activate the receptor to effectively inhibit high expression of P2X7 and activation of the NLPR3 inflammasome.⁹¹ The ethanol extract of *Polygoni avicularis* significantly inhibits TGF expression, nephritis, and fibrosis.⁹² *Lycopus lucidus* Turcz and *Taxus chinensis* also regulate TGF- β by inhibiting the TGF- β 1/Smad signaling pathway.⁹³ *Schisandra* fruit can improve pathological changes in the kidney by downregulating the AGE/RAGE signaling pathway and nearly half the regulation of inflammatory mediators.⁹⁴

Abnormal apoptosis of podocytes can lead to damage of the glomerular filtration membrane, and the hiatus membrane, the last filtration membrane, contains nephrin and podocin.⁹⁵ *Schisandra chinensis* fruit extract can maintain the integrity of podocytes and hiatus membranes by inhibiting EMT and playing a protective role in the kidneys.⁹⁴ *Pueraria tuberosa* significantly inhibits the expression of hypoxia-inducing-factor-1 α (HIF1- α) and VEGF, upregulates nephrin, and protects the hiatus diaphragm integrity.⁹⁶ The AMPK-mTOR signaling pathway is important for the regulation of podocyte autophagy. *Cyclocarya paliurus* regulates podocyte autophagy by activating AMPK and reducing mTOR expression.⁹⁷

Curcumin inhibits lipid aggregation and oxidative stress by activating AMPK and simultaneously inhibiting NLRP3 inflammasome activity, thus playing an antifibrotic role.^{98,99} Dihydroquercetin, also known as dihydroquercetin, can significantly inhibit ROS and NLRP3 inflammasomes, as well as cell proliferation and fibrosis-related protein expression.¹⁰⁰ Andrographolide can reduce Nox1 expression, ROS production, and proinflammatory cytokine production by inhibiting the Akt/NF- κ B signaling pathway, thereby improving mitochondrial dysfunction and NLRP3 inflammasome activation.¹⁰¹ Berberine can inhibit the Toll-like receptor 4 (TLR4)/NF- κ B pathway to reduce kidney injury and inflammatory response and activate AMPK to protect podocytes.¹⁰² Chlorogenic acid has emerged as a potential therapeutic agent for diabetic nephropathy with antioxidant stress and inflammation, the mechanism of which may involve the regulation of the Nrf2/HO-1 and NF- κ B pathways.¹⁰³ Geniposide inhibits NF- κ B-mediated inflammatory response in DN.¹⁰⁴ Salidroside is present in the sea and can reduce the oxidative stress induced by hyperglycemia and damage to renal tubule cells by inhibiting apoptosis, inflammation, and fibrosis through the SIRT/PGC-1 α axis, a conserved member of the NAD⁺-dependent deacetylase family sirtuins.¹⁰⁵ Resveratrol can inhibit goyang-induced renal tubular cell EMT, possibly by inhibiting the NOX/ROS/extracellular signal-regulated kinase 1/2 pathway.¹⁰⁶ In vitro and in vivo studies have found that resveratrol can increase SIRT1 deacetylase activity by acting on the SIRT1/FOXO3a pathway, where SOD is significantly increased, but MDA is decreased.¹⁰⁷ Puerarin can resist oxidative stress and inflammation by regulating the SIRT1/FOXO1 pathway.¹⁰⁸ Nrf2 is a major regulator of cellular immunity owing to its toxicity and oxidative status. Schisandrin B can significantly inhibit fibrosis and apoptosis in renal cells, which may be related to inhibition of Nrf2 expression.¹⁰⁹ Akt is related to oxidative stress, and Tetramethylpyrazine or Ligustrazine can activate the Akt signaling pathway to inhibit oxidative stress.¹¹⁰ Some studies have found that AS-IV inhibits the expression of integrin-linked kinase (ILK), an intracytoplasmic binding regulatory protein associated with cell adhesion and extracellular matrix deposition;¹¹¹ restores integrin α 3/ β 1, and inhibits the Wnt/ β -catenin pathway, thus lessening oxidative stress damage and inflammation, delaying the progression of EMT, inhibiting the TGF- β 1-ILK-Akt pathway, and reducing abnormal protein expression on the podocyte surface.¹¹² Emodin inhibits the protein kinase RNA-like endoplasmic reticulum kinase (PERK)-eukaryotic inhibitory factor 2 α (eIF2 α) signaling pathway during ER stress.¹¹³ Mangiferin can promote podocyte autophagy, and AMPK-mTOR-ULK1 can delay DN progression.¹¹⁴ Seasonal saponins (Timosaponin B-II) can inhibit the expression of thioredoxin-acting protein (TXNIP) and NF- κ B, a linking molecule in the inflammatory pathway mediated by ROS and the NLRP3 inflammasome and the apoptosis pathway mediated by mTOR and upregulate the expression of mTOR to protect the kidney. 3-phosphatidylinositol-dependent protein kinase 1 (PDK1) regulates cell proliferation in the Akt signaling pathway.¹¹⁵ Artemisinin can inhibit TGF- β 1 expression and inflammatory pathways.¹¹⁶ Bergenin can also reduce the production of TGF- β 1, down-regulate p-Smad2/3, and promote the expression of Smad7 to alleviate kidney injury;¹¹⁷ naringenin can inhibit TGF- β 1/Smad pathway by up-regulating let-7 α of miRNA-let-7 family.¹¹⁸ Quercetin can inhibit TGF- β 1 overexpression and connective tissue growth factor (CTGF), act on the HIPPO pathway, promote the deposition of ECM components collagen I and IV, and fibronectin FN, and promote the decomposition or hypertrophy of mesangial cells.¹¹⁹⁻¹²¹

The iridoid and secoiridoid glycosides are iridoid glycosides. Catalpol is a type of iridoid glycoside found in many Chinese herbs,¹²² including *Rehmannia glutinosa*, *Plantago asiatica*, *Citrus bergamia*, *Scrophularia ningpoensis*, and *Crocus sativus*,^{123,124} in DN, can act on lipid metabolism and regulate insulin signaling pathway, inhibit renal inflammation, inhibit oxidative stress, reduce apoptosis, delay renal fibrosis, and increase autophagy.^{121,125-130} It can also delay extracellular matrix (ECM) aggregation in high-fat diet or Streptozotocin (STZ) rat models by downregulating angiotensin II (Ang II), TGF- β 1, and CTGF levels.¹²¹ Simultaneously, the NF- κ B pathway was downregulated. In AGE-treated mouse glomerular endothelial cells (mGECs), catalpol inhibited the RAGE/NF- κ Bp65/inducible nitric oxide synthase (iNOS) pathway and activated the PI3K/AKT/eNOS pathway.¹³¹ At the same time, catalpol can inhibit apoptosis and inflammation in high glucose-treated podocytes by reducing transcription and NF- κ B activation, regulating p38 MAPK and TLR4/MyD88 signaling pathways.¹²⁸ Catalpol can also inhibit oxidative stress, inflammation, and pyroptosis through the AMPK/SIRT1/NF- κ B pathway¹²⁷ via the TGF- β 1/Smad pathway to reduce Ang II-induced kidney injury;¹³² Rho family small GTPase A (RhoA)/RHO-associated protein kinase to alleviate endothelial cell dysfunction and fibrosis,¹²⁹ inhibit the expression of growth factor receptor connection 10 (Grb 10) in STZ mouse models, and promote the IGF-1/IGF-1 receptor signaling pathway;¹²⁶ improve hypoglycemia and lipids, protect renal

function, and regulate the expression of genes related to renal lipid metabolism,¹²⁵ and upregulate LC3B expression to increase podocyte autophagy, downregulate p62 expression to inhibit mTOR activation, and promote the nuclear translocation of transcription factor EB (TFEB).¹³⁰ At the same time, catalpol stabilizes the cytoskeleton, regulates galectin-3, inhibits macrophage infiltration and delays fibrosis;¹³³ regulate SIRT1, NF- κ B, Nrf-2, mitochondrial oxidative-related pathways to prevent kidney injury.^{134–136}

Loganin is an iridoid glycoside derived from *Cornus officinalis*.¹³⁷ It can reduce mesangial cell proliferation,^{138,139} oxidative stress,^{140,141} and fibrosis, and inhibit CTGF expression.¹⁴² Combined with catalpol, it can regulate AGE-RAGE, p38 MAPK, and NADPH oxidase 4 (Nox4) to inhibit apoptosis,¹⁴³ acting on RAGE-MCP-1/CC chemokine receptor 2 (CCR2) to reduce inflammation and macrophage infiltration.¹⁴⁴ The effect of this on NLRP3/caspase-1/gasdermin D of the pyrogenic pathway delays diabetic renal injury,¹⁴⁵ and loganin exhibits a high concentration in the kidneys while maintaining minimal presence in the brain, as it cannot cross the blood–brain barrier. This characteristic enhances its effectiveness in kidney protection.¹⁴⁶ However, its clinical application remains limited due to the lack of comprehensive documentation of its toxicity profile and detailed molecular mechanisms.

Geniposide is derived from *Gardenia* or other Chinese herbs such as *Eucommia ulmoides*, *Rehmannia*, and *Scrophularia ningpoensis*. They have antioxidant and anti-inflammatory properties,¹⁴⁷ anti-apoptosis,¹⁴⁸ autophagy regulation,¹⁴⁹ fibrosis reduction, intestinal flora regulation,¹⁵⁰ and glucose and lipid metabolism improvement.¹⁵¹ Besides acting on AMPK/SIRT1/NF- κ B,^{104,152} other mechanisms include autophagy mediated by PKR1, PK2, AMPK/unc-51-like kinase 1 (ULK1), and AKT-mediated inflammation.^{153,154}

Swertiamarin is derived from the root of *P. bimaculatus*.¹⁵⁵ Combined with *E. littorale* in T1DM rat models, it can reverse kidney damage and clear free radicals, reduce AGE, reduce inflammatory factors, inhibit oxidative stress, block the association between AGE and RAGE, and promote epithelial mesial transition.^{156,157} At the same time, another study found that it improved obesity and insulin resistance.^{37,158,159}

Gentiopicroside, derived from *Gentiana scabra*, can inhibit NF- κ B, up-regulate TGR5, regulate the TGR5-B-arrestin2-NF- κ B pathway, inhibit ECM aggregation, and can also act on AT1R/CK2/NF- κ B, to delay glomerular and renal tubule fibrosis.^{160,161}

Oleuropein, derived from whole olive plant or crude gentian, can improve inflammation¹⁶² and injury by acting on the MAPK signaling pathway¹⁶³ and reducing the expression of apoptosis-related proteins, such as Bax, caspase-3, and Bcl-2. Other targets include the inhibition of glomerular hypertrophy and sclerosis, decreased inflammatory cell infiltration, decreased NO synthesis, myeloperoxidase (MPO) activity, activation of 26S protease activity, and inhibition of ER stress.¹⁶⁴ Its bioavailability in humans and rats is low, highlighting the need for further research on its absorption, distribution, metabolism, and excretion to better understand its therapeutic potential.

MOR was derived from *Cornus officinalis*. Studies have found that MOR can reduce blood glucose, urinary protein, and urea nitrogen levels; improve creatinine clearance; downregulate SREBP-1 and SREBP-2; inhibit ECM and Nox4 overexpression; and restore autophagy flow.^{165–167} Simultaneously, MOR can also improve kidney injury caused by lipid toxicity, and the underlying mechanism involves PGC-1 α , which eases intercellular cholesterol efflux.¹⁶⁸

TCM for Diabetic Retinopathy

Prescription or Proprietary Chinese Medicine for Treating Diabetic Retinopathy (DR)

A meta-analysis found that three clinical studies of elderly DR Decoction included Danhuang Mingmu Decoction and Zhenwu decoction, which included three studies: compound Xueshuantong capsule, compound Danshen dropping pills, and Qijudihuang tablets.⁴⁶

“Danhong Huayu Oral Liquid” can inhibit inflammation and oxidative stress to improve DR and may affect the expression of TNF- α .¹⁶⁹ Some studies have found that “Mimenghua Decoction” may downregulate the core genes of the TNF- α gene network.¹⁷⁰ In addition, “Dangica Buxue decoction” reduced the expression of TNF- α in the retina of GK rats, and the migration and proliferation of endothelial cells induced by high glucose were inhibited by decreasing the expression of IL-1 β , IL-6, NF- κ B, MCP-1, ICAM-1, and VCAM-1.¹⁷¹ “Tongluo tangning” may block retinal MMP-2/9/13 by acting on the MIP1 γ /CCR1 axis.¹⁷² “Tonifying kidney and Huoxue” can reduce ocular fundus oxidative stress injury in DR Rats.¹⁷³ “Jianxuangqingre prescription” can inhibit retinal neurodegeneration by blocking endoplasmic

reticulum and mitochondria from oxidative stress-dependent damage,¹⁷⁴ among which, upregulation of tight junction protein and inhibition of AGE and RAGE to inhibit inflammation and apoptosis is an important mechanism to protect endothelial cells.¹⁷⁵ Xueshuantong has a protective effect on DR by blocking the TGF- β /smad2/3 oxidative stress signaling pathway.¹⁷⁶ Fufang Xueshuantong can reduce the expression of retinal VEGF via a YAP-mediated effect.¹⁷⁷ “Fushiming capsule” can significantly restore retinal function and prevent the decrease in retinal thickness by inhibiting the expression of VEGF- α , GFAP, and VCAM-1.¹⁷⁸ “Liuwei Dihuang pill” and “Ginkgo leaf capsule” can reverse microvascular injury,¹⁷⁹ “Danhong Injection” and “Naoxintong Capsule” have been shown to block retinal atrophy and the formation of cell-free capillaries in DR Mice and are related to the inhibition of caspase-3, MMP-2/9, and the aggregation of carbohydrate-related macromolecules.^{180,181} “Huoxue Jiedu recipe” can inhibit hyperglycemia-induced apoptosis and SOCS3/Stat3-induced VEGF overexpression and inflammation and block TIMP1-A2M-induced apoptosis, which is related to the deactivation of MMP-2/9 and regulation of the TIMP/MMP ratio.¹⁸²

TCM Mechanism and Herb for DR Treatment

Multiple studies have explored the role of TCM extracts in the therapeutic effects of DR.¹⁸³ Lycium barbarum polysaccharides (LBP) regulate the Rho/ROCK inflammatory signaling pathway, protect the blood-eye barrier, increase Bcl-2, reduce Bax levels, and reduce apoptosis.¹⁸⁴ ω 3 in flaxseed oil alleviates DR and retinal electrical stimulation by inhibiting inflammation and upregulating GPR120 (a receptor for ω 3).¹⁸⁵ The ethanol extract of Sannai alleviates retinal inflammation by inhibiting extracellular signal-regulated kinase (ERK1/2) and nuclear transcription factor (NF- κ B) signaling pathways.¹⁸⁶ Similarly, Dendrobium chrysotoxum Lindl inhibits the NF- κ B signaling pathway and decreases tight junction proteins, such as occludin, and claudin-1 to increase anti-inflammatory effects.^{187,188} Scutellaria increases the expression of claudin-1 and 19 in tight junctions,¹⁷⁵ counteracting TJ inhibition of TNF- α , PKC, and NF- κ B, thereby improving vascular permeability. *P. cuspidatum* extract can inhibit the HMGB1-RAGE-NF- κ B signaling pathway in the highly active group, further aggravating inflammation and preventing the increase in vascular permeability associated with DR.¹⁸⁹ In addition to inflammatory cascades, retinal ischemia and hypoxia can initiate DR neovascularization,^{190,191} which can inhibit the regeneration of capillaries in the posterior optic region of DR Rats by activating tetrandrine expression.¹⁹² *Vaccinium myrtillus*, *Lonicera japonica* Flos, *hibiscus Abelmoschus Manihot*, and total lignans from *Fructus Arctii* have been shown to inhibit DR Angiogenesis by enhancing VEGF expression and can also reduce PKC β 2 expression and inhibit the PKC pathway.^{193,194} *Dendrobium* inhibits VEGF/VEGFR2 and several other proangiogenic factors, such as MMP2/9, PDGF A/B, bEGF, and IGF-1.¹⁸⁷ Similarly, *Typhae pollen* polysaccharides can improve abnormal hemodynamics and hemorheology to prevent further hypoxia-ischemia and injury.¹⁹⁵ The ethanol extract of plantaginous semen decreases the expression of ICAM-1 and VCAM-1 by downregulating NF- κ B.¹⁹⁶ Crude saponins from *P. notoginseng* and blueberry anthocyanins inhibit the excessive production of free radicals caused by diabetes by regulating the Nrf2/HO-1 pathway.¹⁴⁶ Saponin notoginax can also reduce apoptosis in RGC-5 cells by inhibiting the mitochondrial stress-related eIF2 α /ATF4/CHOP pathway.¹⁴⁶ *Panax notoginseng* saponins (PNS) play an antioxidant role by regulating SOD, glutathione, and NADPH oxidase 4. *Aralia elata* inhibits apoptosis of ganglion cells by blocking the interaction between ChREBP and OGT.¹⁹⁷ Aqueous fruit pericarp extracts of *Litchi chinensis* Sonn, andrographolide, and phenol can inhibit aldose;^{198–200} therefore, they may interfere with the polyol pathway in DR, induce early growth reaction-1 to reduce the release of inflammatory mediators, inhibit VEGF, reduce the secretion of phosphorylated NF- κ B p65, and inhibit angiogenesis. Ginsenoside Rb1 and *Pterocarpus marsupium* Roxb. Extracts can significantly increase glutathione levels via the niacinamide adenine dinucleotide (NAD) -poly ADP-ribose polymerase (PARP) -serine deacetylase (SIRT) axis.^{201,202} Ginsenoside Rb1 increases SIRT activity and decreases PARP levels.²⁰¹ Ginsenoside Rg3 can reduce VEGF and TNF- α levels and inhibit angiogenesis.²⁰³ Astragaloside IV and luteolin can downregulate Nox4 expression,^{204,205} whereas astragaloside polysaccharides can affect the mitochondrial damage and apoptosis of Bcl-2 by regulating miR-182 and miR-195.^{206,207} Various Chinese medicinal components can affect the expression of protein kinase C (PKC) in aqueous extracts of *Moringa oleifera* Lam. and *Trigonella foenum-graecum* extracts could inhibit PC β and VEGF to improve oxidative stress,^{208,209} and *Trigonella foenum-graecum* could reduce the expression of inflammatory mediators.²⁰⁸ Excessive ROS can activate PARP, but hyperglycemic-induced PARP does not improve oxidative damage but increases it in peri-blood-retinal barrier (BRB) cells. Berberine and notosaponin R1 can regulate PARP

levels, and berberine may activate the upstream AMPK signaling pathway.^{210,211} Hesperidin also improves mitochondrial damage by restoring membrane potential.^{206,212} Puerarin can inhibit iNOS, reduce free radicals, and decrease apoptosis in RPE cells.²¹³ Tanshinone IIA protects RPE from OS-induced hypermethylglyoxal.²¹⁴ Calycosin regulates the NLRP3 inflammasome.²¹⁵ Fangchinoline inhibits the RAGE/NF- κ B pathway, whereas curcumin interacts with ROS-Akt/mTOR to inhibit inflammatory expression.²¹⁶ Gastrodin, Asiatic acid, and paeoniflorin block the TLR4/NF- κ B pathway to reduce inflammation.^{217–219} Ginkgo biloba extract decreased HIF- α expression.²²⁰ Specnuezhen can improve HIF- α and delay retinal angiogenesis.²²¹ Similarly, Berberis extract also affected delta-like ligand 4 (DL-4) and Notch-1 signaling. Chlorogenic acid in honeysuckle can block VEGF/ VEGFR2-mediated retinal endothelial cell angiogenesis by inhibiting VEGF secretion by microglia.²²² In addition to the effect of VEGF, the extract of *D. chrysotoxum* inhibits angiogenesis by MMP2/9 and PDGF A/B.¹⁸⁷ Hesperidin decreases ICAM-1, VEGF, and malondialdehyde levels and increases SOD levels.²²³ Zingiber zerumbet (L. Roscoe Ex Sm. rhizomes), and *Momordica cochinchinensis* (Lour). Spreng (*Momordica cochinchinensis* (Lour). Spreng. can improve DR by upregulating the pigmentative epidermal growth factor (PEDF).²²⁴ Artesunate and berberine have been found to induce autophagy and regulate AMPK pathway,^{225,226} while other components such as rustin and notoginseng saponin R1 can affect autophagy and reduce retinal damage. In addition, *Astragalus polysaccharides* can regulate the activity of the miR-204/SIRT1 axis to reduce endoplasmic reticulum stress,²²⁷ and notoginseng saponins can also affect CCAAT-enhancer-binding protein (C/EBP) homologous proteins to restore Bcl-2 expression.¹⁴⁶

TCM Prescription, Herbs and Extracts for, and Clinical Effects of DPN Treatment

TCM formulations were studied in five DPN studies in older adults. Common herbs included *Astragalus Astragalus*, *Spatholobus suberectus* Dunn, *Achyknee*, *Angelica*, *Carthamus tinctorius* L., *Paeonia lactiflora* Pall. and peach kernel (*Rosaceae*, *Rosaceae*) *Persicae Semen*. In one RCT of 68 DPN patients, berberine simultaneously improved blood glucose and 24-hour urinary protein levels, increased motor MNCV and sensory SNCV nerve conduction velocity, and enhanced neural effects possibly through the PI3K/Akt/Bcl-2, Nrf2/HO-1, and MAPK pathways.⁴⁶

A previous systematic review has summarized the potential of TCM medications for DPN.²²⁸ Clinical trials have found that although aloe did not improve overall DPN symptoms, it had a better effect on the sensory and motor fiber conduction speeds of the fibular and median nerves. *Ciwujia* combined with vitamins B1 and B12 had a significant effect on improving overall DPN symptoms compared to vitamin injection alone. *Erigeron* can significantly improve DPN symptoms compared with vitamin B1. *Ginkgo biloba* (*Ginkgo biloba*) combined with vitamins B1 and B12 showed no significant advantage over vitamin B injection alone in improving overall DPN symptoms.

Regarding patent medicine,²²⁸ *Qiyin* granules showed no significant improvement in DPN symptoms compared to cobalamide granules. Injection of *Fufang Danshen* combined with mecobalamin was more effective in improving symptoms than mecobalamin alone. The *Furong Tongmai* capsule improved symptoms more significantly than mecobalamin injection alone and had significant effects on the nerve conduction velocity of the common peroneal nerve sensation and motor fibers. In another study, *Tangluoan* capsule significantly improved the sensory and motor nerve conduction velocity of the common peroneal and median nerves compared with placebo. However, compared with adenosylcobalamin, *Tangluoan* capsules did not show significant improvement in overall symptoms, but the improvement in common peroneal nerve conduction velocity was relatively superior to that of adenosylcobalamin. The *tangmaining* capsule showed no improvement in symptoms compared to adenosylcobalamin. *Tongxinluo* capsules combined with mecobalamin did not improve the symptoms better than mecobalamin alone. However, the combination of B1 and B12 was more effective in improving the symptoms than vitamin monotherapy. The effect of *Xuefu Zhuyu* capsules combined with mecobalamin did not increase significantly. *Xuesaitong* capsules or injections contained notoginseng saponins and flavonoids. Adding *Xuesaitong* capsules based on mecobalamin did not significantly improve the symptoms, but the injection of vitamins B1 and B12 significantly improved the overall symptoms. *Buying Huanwu Tang* combined with mecobalamin has apparent advantages over mecobalamin alone in improving symptoms and conduction velocity of the common peroneal nerve. The improved *Buyang Huanwu* decoction combined with vitamins B1, B6, and B12 had a more obvious effect on symptom improvement than the vitamin treatment. *Guizhi Gegen Tang* combined with vitamin B1 and B6 did not have a significant advantage in improving symptoms compared with vitamin alone; *Jianbi Yiqi*

Tongluo Tang (Jianbi Yiqi Tongluo Tang) than the single drug adenosylcobalamin symptoms improved obviously; similarly, modified Danggui Sini Tang improved symptoms more significantly than vitamin monotherapy. Improved Huangqi Guizhi Wuwu Tang combined with mecobalamine was superior to mecobalamine monotherapy in symptom improvement; however, another study found no significant advantages compared to vitamins B1 and B6. The improved Sishen Jian had an obvious improvement effect compared with vitamins B1 and B12; compared with mecobalamin, Tangmai Yin showed better symptom improvement than mecobalamin. However, in terms of nerve conduction velocity, Tangmai Yin only had a better effect on tibial nerve sensory conduction velocity. Taoren Honghua Jian combined with mecobalamine significantly improved the symptoms. Tongbi Tang was superior to mecobalamine and vitamin B1. Xiaoke Tongluo Tang was not superior to vitamins B1 and B6, Yiqi Bushen Huoxue Tang (Yiqi Bushen Huoxue Tang) combined with indomethacin and vitamin B was not superior to indomethacin and vitamin B in symptom improvement, and Yiyiren Tang combined with mecobalamine was better than a single drug in improving symptoms.

Diabetic Cardiomyopathy

Two clinical studies have explored the effects of TCM prescriptions in elderly patients with diabetic cardiomyopathy (DCM). The Yangyin Yiqi Huoxue Recipe (Yangyin Yiqi Huoxue Recipe) improved the cardiac function of patients with hyperglycemia and heart failure by affecting the expression of VEGF. Zhigancao decoction can significantly improve arrhythmia and autonomic nervous dysfunction and reduce inflammation.⁴⁶

Diabetic Peripheral Vascular Disease

Three RCT trials on the aged studied the modified Huangqi Guizhi Wuwu Decoction and Tangmai Tongluo Decoction decoction treatment of lower extremity vascular lesions, which could improve lower extremity blood flow. Yiqi Tongluo Qingre cream can improve arteriosclerosis of the common carotid, popliteal, and dorsal foot arteries, and improve the lipid metabolism index. The four old Chinese patent medicine studies included the Naoxintong capsule, Yixinshu capsule, Yangxinshi tablet, and the Shexiang Baoxin pill. Four RCTS involving 432 elderly patients studied extracts of notoginseng, *Salvia miltiorrhiza*, *Ginkgo biloba*, and *Tribulus terrestris* L. [*Zygophyllaceae*, *Tribuli fructus*].⁴⁶

Antioxidant Effect and Mechanism of TCM

In general, a group of natural polysaccharides are usually mixed and co-exist with protein polyphenols to exert the maximum antioxidant effect,²²⁹ such as Pu'erh tea polysaccharide,²³⁰ *Gastrodia elata* polysaccharide,²³¹ In addition, Litchi polysaccharide and *Ampelopsis grossedentata* polysaccharide contain uronic acid, which has antioxidant effect.^{232,233} However, some studies have found that the antioxidant effects of polysaccharides, such as edible mushroom polysaccharides,²³⁴ can be significantly reduced by the removal of polyphenols and proteins. The different contents of polyphenols and uridylate in the polysaccharides of *Tremella fuciformis* have different antioxidant activities, which may be related to their different molecular weights and monosaccharide proportions.²³⁵

In general, the nuclear factor-E2-related factor 2 (Nrf2) signaling pathway mediates the inhibition of ROS oxidation, and Nrf2 which bind to Kelch-like ECH-related protein-1 (Keap1) to inhibit it, and its content in the cytoplasm is low owing to rapid degradation.²³⁶ Polysaccharides can promote the release of Nrf2, enter the nucleus, act on antioxidant elements (ARE), and promote the expression of downstream antioxidant proteins and Phase II toxin-related enzymes. The polysaccharides of *Ostrea rivularis* can promote downstream expression of Nrf2 and ARE genes.²³⁷ sulfated *Cyclocarya paliurus* polysaccharide (CPP) significantly increased Nrf2 protein and decreased the antioxidant effect of Keap1 protein, while glycogen synthase kinase 3 β (GSK3 β) was an upstream regulatory molecule.²³⁸ In addition, the phosphorylation of PI3K and AKT can inhibit the expression of JNK and IRS1 and effectively improve oxidative stress damage.^{239,240} Polysaccharides from *Angelica sinensis* can inhibit the caspase pathway containing cysteine, increase the expression of Bcl-2 and Bcl-xL, and play an antioxidant role. *Schisandra chinensis* polysaccharide (SCP) regulates the mitogen-activated protein kinase (MAPK) pathway and mitochondria-dependent apoptotic signaling to play an antioxidant role. Antioxidant polysaccharides can down-regulate p-jnk1, p-ERK1/2, p-p38, Bax, caspase 3 and cytochrome C, and up-regulate the action of Bcl-2 protein.^{241,242}

In addition, polysaccharides can play an antioxidant role by regulating enzyme activity. Primary endogenous antioxidants in the human body include superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) as endogenous antioxidants.^{243,244} Natural polysaccharides can affect the activities of these enzymes by acting on Keap1/Nrf2/ARE.²⁴⁵ It can also inhibit oxidases, such as nitric oxide synthase (iNOS), to reduce the damaging effects of oxidative stress, such as Angelica polysaccharides (ASP). In addition, natural polysaccharides can remove free radicals and substrates, and the hydroxyl group and side chain glucoside bond in their polysaccharide structure can provide electron-binding ROS to reduce oxidative stress and other damages.²⁴⁶

Lycium barbarum polysaccharide (LBP) can clear mitochondrial superoxide anions, and LBP4 has the strongest antioxidant activity among all polysaccharides.^{247,248} Astragalus contains mannose, Arabinose, and Galactose, and has been found to significantly inhibit malondialdehyde (MDA) production and increase SOD in the blood and liver of rats. CAT and GSH-Px expression;²⁴⁹ Dendrobium officinale polysaccharide (DOP) has strong free radical scavenging ability in 1, 1-diphenyl-2-picrylhydrazine (DPPH) scavenging test. At the same time, it also has strong activity in 2,2'-azobis(3-ethylbenzothiazolin-6-sulfonic acid) (ABTS) and hydroxyl radical scavenging experiments, which may be due to its smaller molecular weight, and also related to the method of purification in the experiment, such as freeze-drying method, which has stronger antioxidant effect.^{250,251} The main monosaccharides in the purified DOP were mannose and glucose, which could protect RAW 264.7 macrophages by resisting oxidative stress induced by hydrogen peroxide. Angelica sinensis has good antioxidant and antitumor properties and ASP is an important active substance. Studies have shown that, in addition to chondrocytes, H9c2 heart-derived cells in mice can protect against hydrogen peroxide-induced apoptosis. The mechanism includes that ASP inhibits ROS production and lactate dehydrogenase release by activating the ATF6 pathway, thereby improving oxidative stress and ER stress. Its ability to remove hydroxyl free radicals depends on its concentration. When the concentration reaches 800 mg/mL, the scavenging ability is close to the antioxidant level of vitamin C.^{252,253} Gastrodia elata includes gastrodin (gastrodin), luteolin (luteolin), Gastrodia polysaccharide (GP) and other components that have structural improvement, neuroprotective effects, regulation of intestinal flora, and immune enhancement effects.^{254–257} GP also has an anti-aging effect by scavenging hydroxyl free radicals, and oral GP can increase the antioxidant activity of SOD and GSH-Px in D-galactose-induced aging mouse models.²⁵⁸ Purslane polysaccharide (PP) promotes the production of serum cytokines and enhances the immune response to N-methyl-N'-nitro-N-nitrosoguanidine (MNNG)-induced gastric cancer in rats. PP increased the activity of SOD, CAT, and GSH-Px in a dose-dependent manner. The glucose and galactose in PP can clear all kinds of free radicals: superoxide anion free radical, hydroxyl free radical, DPPH free radical and various NO;^{259,260} The role of Polygonatum sibiricum polysaccharides (PSP) in anti-diabetes mellitus, fatigue and improvement of depressive behavior could reduce the level of 5-HT in hippocampus and the oxidative stress induced by LPS.^{261,262} In addition, it can inhibit the overactivation of the ROS/HPA axis and inflammatory response, and in vitro studies have found that it has a strong free radical scavenging effect. Polygonatum odoratum polysaccharide (PPO) has been shown to ameliorate oxidative stress in fatigue tests, including the clearance of lipid peroxidation.²⁶³

The composition of monosaccharides and the proportion and molecular weight of polysaccharides, especially the sulfuric acid groups, are related to their biological activities. The polysaccharides of five types of algae, *Ulva perulva*, *Laminaria*, *Ulva pluviosa*, and laver, showed antioxidant activity in vitro and still had strong antioxidant effects at high temperatures.²⁶⁴ *Laminaria* polysaccharide (LJP) has the strongest antioxidant effect, possibly because it contains more sulfhydryl and fewer hydroxyl groups.²⁶⁵ Fucoidan extracted from brown seaweed is a sulfated polysaccharide. The fucoidan extract had the strongest DPPH free radical scavenging ability at 90 °C. *Ulva perulva* polysaccharides can improve the oxidative stress induced by hydrogen peroxide by increasing SOD and CAT levels in the same experiment and ABTS.²⁶⁶ Brown algae have stronger antioxidant effects than green and red algae do. Some studies have found that fucoidan, laminaran, and alginate polysaccharides extracted from brown seaweed in Malaysia and laminaran polysaccharide from *Sargassum polycystum* have strong peroxide-anion scavenging ability, while alginate has strong DPPH free radical scavenging ability. After fermentation by different fungi, the antioxidant capacity of Alginate and Fucoidan can be enhanced, and the molecular weights of alginate and fucoidan can be reduced by nearly half after treatment.^{267–269} The fucose and sulfate contents in fucoidan and the ratio of mannuronic acid (M) to guluronic acid (G) in alginate (M/G) increased, suggesting that molecular weight and monosaccharide components may be important components affecting

antioxidants. In addition, in other experiments, alginate was degraded by radiation, and it was found that the smaller the molecular weight of M/G, the stronger its inhibition ability. For the same molecular weight, the higher the M/G ratio, the stronger is the antioxidant capacity.^{270,271}

Fungal polysaccharides are mostly derived from fruiting bodies or mycelia of medicinal fungi. Mushroom polysaccharides include *Lentinus edodes* polysaccharide (LEP), *Flammulina velutipes* polysaccharide (FVP), *Pleurotus ostreatus* polysaccharide (POP), etc.²⁷² It was found that LEP has a dose-dependent scavenging capacity for hydroxyl radicals, superoxide radicals, and chelating antioxidant capacity of iron divalent ions (Fe²⁺), which is also related to different molecular weights and hydrophobic cavities and cracks formed by covalent bonds between polysaccharides and protein molecules.²⁷³ *Pleurotus eryngii*, *Flammulina velutipes*, *Pleurotus ostreatus*, white *Hypsizygus* contain polysaccharide, and it found POP of these extracts which are rich in acid groups, with small molecular weight, possess strong antioxidant capacity.²⁷⁴ In other studies, it was found that polysaccharides from white mushrooms (*Agaricus bisporus*), *Auricularia auricula*, enoki mushrooms, and *Lentinus edodes* have the strongest antioxidant capacity because of their low molecular weight.²⁷⁵ The polysaccharide (GFP) in maitake mushrooms (*Grifola frondosa*) and other extracts have antioxidant free radical scavenging capabilities, as well as improved memory and anti-aging effects.^{276,277} The polysaccharide (GLP) in *Ganoderma lucidum* has antioxidant properties and contains glucose and galactose;²⁷⁸ *Hericium erinaceus*, *Cordyceps sinensis* and *Ganoderma atrum* have good antioxidant capacity and can prevent mitochondria-dependent apoptosis by activating antioxidant-related enzymes.^{279–281} It exerts protective effects against intestinal immune disorders and hepatotoxicity.^{279–281}

Lactobacillus plantarum extracellular polysaccharides not only have no cytotoxicity but also have strong antioxidant capacity.²⁸² Extracellular polysaccharide BTS44 of *Brevibacterium otitidis* has been found to have strong antioxidant effect in vitro experiments; These ingredients include mannose, arabinose, glucose and mannouronic acid;²⁸³ LBP32 from *Bacillus* sp can relieve endotoxin-induced inflammation and reduce oxidative stress.²⁸⁴ *Streptomyces* polysaccharides isolated from soil contain high levels of mannose and glucose, which can effectively remove free radicals.²⁸⁵ Other fungi, including *Streptomyces violaceus* MM72, are derived from marine actinomycetes.²⁸⁶

Animal materials in the sea can also provide animal polysaccharides, especially sulfated polysaccharides, with a higher content than land animals, where polysaccharides exist in the form of covalent bonds and protein complexes, providing the basis for antioxidant capacity.^{287–289} Most animal polysaccharides are found in the mucus, cartilage, and skin. *Misgurnus anguillicaudatus* polysaccharide (MAP) is a natural neutral polysaccharide that exists in the mucus of eel catfish and has the ability to scavenge free radicals and reduce damage to the DNA chain by hydroxyl radicals.²⁹⁰ Studies have found that it has the ability of dose-dependent scavenging free radicals in the treatment of diabetes, alleviating the damage of glycosylation and oxidative stress. Chondroitin sulfate extracted from sea cucumbers has a dose-dependent free-radical scavenging effect. *Rana chensinensis* skin (RCSP), which consists of glucose, galactose, mannose, the primary gradient of which may be used as potent natural antioxidant;^{291,292} Chitosan is a natural polysaccharide, which can come from shellfish, shrimp, crabs and some microorganisms. It is an effective scavenger of the main N-group free radicals and can protect human serum proteins. Chitosan with low molecular weight can inhibit neutrophil activation, prevent albumin oxidation, and reduce uremia related oxidative stress damage.^{293,294}

Natural polysaccharide derivatives include Sulfated Polysaccharides, Phosphorylated Polysaccharides, Carboxymethylated Polysaccharides, etc.²²⁹ The modification methods for neutral polysaccharides by sulfation are different from those used for acidic polysaccharides. Neutral polysaccharides can be dissolved in an organic solvent, and sulfated polysaccharides can be obtained by sulfation esterification. Acidic polysaccharides have fewer hydroxyl groups and are difficult to dissolve in organic solvents; therefore, they need to be combined with acidic resins and then with sulfuric acid groups. Sulfated polysaccharides in *auricularia* polysaccharides (AAP) had stronger antioxidant capacity.²²⁹ Sulfated polysaccharides in *Flammulina velutipes* have strong antioxidant capacities, which can improve aging and inflammation.²⁹⁵ The group substitution of *Momordica charantia* in plants resulted in a stronger antioxidant capacity than that of natural polysaccharides.²⁹⁶ The difference in group angle replacement also affects the antioxidant capacity.²⁹⁷ It was also found that changes in the sulfated chitosan site, relative molecular weight, and sulfated content in animal polysaccharides also affect antioxidant capacity.²⁹⁸ Phosphorylation of pumpkin polysaccharides can enhance antioxidant and free radical scavenging ability, and experiments on ginseng polysaccharide and garlic polysaccharide also

verified this finding.^{299–301} The content of antioxidant enzymes in the serum, liver, and other tissues increases after the phosphorylation of *M. melon* polysaccharides.²⁹⁶ Experiments on oyster mushrooms or oyster mushrooms exposed to fungi have also confirmed this phenomenon.³⁰² Carboxyl modification can increase the free radical scavenging ability of pumpkin, *Sargassum fusiforme*, and *Enteromorpha prolifera* polysaccharides after carboxylation.^{303–305} Other methods include acetylation modification (acetylation modification), hydroxy-propylation modification (hydroxy), selenization modification, sulfonation modification, and ammonium modification, which can increase the water solubility of the component and its biological activity and antioxidant capacity.²⁹⁶

Summary and Future Perspective

Many investigations have unveiled the therapeutic potential and mechanism of action of TCM drugs in T2DM and its complications. With the development of omics, mass spectrometry, and network pharmacology, the effective components of TCM and their mechanisms of action have been extensively explored. Further research is warranted to focus on the standardization and clinical application of TCM formulas to verify their efficacy and mechanisms of action. In addition, integrating modern medical methods and exploring the combination of TCM and Western medicine will highlight important directions for future research and comprehensive treatment. Despite benefiting more T2DM patients, TCM will promote the pathological studies of T2DM and cooperate with the international medical community communications.³⁰⁶ Overall, TCM has shown far-reaching prospects in treatment, and may ultimately contribute significantly to the overall well-being of humanity.

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Disclosure

The authors declare that there is no conflicts of interest.

References

- Zhang H, Shapiro ZXD, Gyl L, et al. Global burden of metabolic diseases, 1990–2021. *Metabolism*. 2024;160:155999. doi:10.1016/j.metabol.2024.155999
- Drake T, Landsteiner A, Langsetmo L, et al. Newer Pharmacologic Treatments in Adults With Type 2 Diabetes: a Systematic Review and Network Meta-analysis for the American College of Physicians. *Ann Internal Med*. 2024;177(5):618–632. doi:10.7326/M23-1490
- Zhang Z, Luo X. *Synopsis of Prescriptions of the Golden Chamber*. New World Press; 1987.
- Qiao C, Gu C, Wen S, et al. The Integrated Bioinformatic Assay of Genetic Expression Features and Analyses of Traditional Chinese Medicine Specific Constitution Reveal Metabolic Characteristics and Targets in Steatosis of Nonalcoholic Fatty Liver Disease. *Hepatic Med*. 2023;15:165–183. doi:10.2147/HMER.S428161
- Zhou W, Cheng X, Zhang Y. Effect of Liuwei Dihuang decoction, a traditional Chinese medicinal prescription, on the neuroendocrine immunomodulation network. *Pharmacol Ther*. 2016;162:170–178. doi:10.1016/j.pharmthera.2016.02.004
- Lin QR, Jia LQ, Lei M, et al. Natural products as pharmacological modulators of mitochondrial dysfunctions for the treatment of diabetes and its complications: an update since 2010. *Pharmacol Res*. 2024;200:107054. doi:10.1016/j.phrs.2023.107054
- Wang H, Shi S, Wang S. Can highly cited herbs in ancient Traditional Chinese medicine formulas and modern publications predict therapeutic targets for diabetes mellitus? *J Ethnopharmacol*. 2018;213:101–110. doi:10.1016/j.jep.2017.10.032
- Dou Z, Xia Y, Zhang J, et al. Syndrome Differentiation and Treatment Regularity in Traditional Chinese Medicine for Type 2 Diabetes: a Text Mining Analysis. *Front Endocrinol*. 2021;12:728032. doi:10.3389/fendo.2021.728032
- Li X, Geng-Ji JJ, Quan YY, et al. Role of potential bioactive metabolites from traditional Chinese medicine for type 2 diabetes mellitus: an overview. *Front Pharmacol*. 2022;13:1023713. doi:10.3389/fphar.2022.1023713

10. Feng Y, Ren Y, Zhang X, et al. Metabolites of traditional Chinese medicine targeting PI3K/AKT signaling pathway for hypoglycemic effect in type 2 diabetes. *Front Pharmacol.* 2024;15:1373711. doi:10.3389/fphar.2024.1373711
11. Chen YK, Liu TT, Teia FKF, Xie MZ. Exploring the underlying mechanisms of obesity and diabetes and the potential of Traditional Chinese Medicine: an overview of the literature. *Front Endocrinol.* 2023;14:1218880. doi:10.3389/fendo.2023.1218880
12. Oh R, Kim G, Lee KN, et al. Metabolic dysfunction-associated steatotic liver disease in patients with type 2 diabetes: risk of heart failure. *Cardiovasc diabetol.* 2024;23(1):391. doi:10.1186/s12933-024-02489-4
13. Loomba R, Hartman ML, Lawitz EJ, et al. Tirzepatide for Metabolic Dysfunction-Associated Steatohepatitis with Liver Fibrosis. *New Engl J Med.* 2024;391(4):299–310. doi:10.1056/NEJMoa2401943
14. Mantovani A, Byrne CD, Targher G. Efficacy of peroxisome proliferator-activated receptor agonists, glucagon-like peptide-1 receptor agonists, or sodium-glucose cotransporter-2 inhibitors for treatment of non-alcoholic fatty liver disease: a systematic review. *Lancet Gastroenterol Hepatol.* 2022;7(4):367–378. doi:10.1016/S2468-1253(21)00261-2
15. Lawitz EJ, Fraessdorf M, Neff GW, et al. Efficacy, tolerability and pharmacokinetics of survodutide, a glucagon/glucagon-like peptide-1 receptor dual agonist, in cirrhosis. *J Hepatol.* 2024;81(5):837–846. doi:10.1016/j.jhep.2024.06.003
16. Boland ML, Laker RC, Mather K, et al. Resolution of NASH and hepatic fibrosis by the GLP-1R/GcgR dual-agonist Cotadutide via modulating mitochondrial function and lipogenesis. *Nat Metab.* 2020;2(5):413–431. doi:10.1038/s42255-020-0209-6
17. Chrysavgis LG, Kazanas S, Bafa K, Rozani S, Koloutsou ME, Cholongitas E. Glucagon-like Peptide 1, Glucose-Dependent Insulinotropic Polypeptide, and Glucagon Receptor Agonists in Metabolic Dysfunction-Associated Steatotic Liver Disease: novel Medication in New Liver Disease Nomenclature. *Int J Mol Sci.* 2024;25(7):3832. doi:10.3390/ijms25073832
18. Zheng S, Xue C, Li S, et al. Chinese medicine in the treatment of non-alcoholic fatty liver disease based on network pharmacology: a review. *Front Pharmacol.* 2024;15:1381712. doi:10.3389/fphar.2024.1381712
19. Li X, Zhu R, Liu Q, Sun H, Sheng H, Zhu L. Effects of traditional Chinese medicine polysaccharides on chronic diseases by modulating gut microbiota: a review. *Int J Biol Macromol.* 2024;282(Pt 2):136691. doi:10.1016/j.ijbiomac.2024.136691
20. Li Z, Ouyang H, Zhu J. Traditional Chinese medicines and natural products targeting immune cells in the treatment of metabolic-related fatty liver disease. *Front Pharmacol.* 2023;14:1195146. doi:10.3389/fphar.2023.1195146
21. Qi Y, Wang L, Wang N, et al. A comprehensive review of the botany, phytochemistry, pharmacology, and toxicology of *Murrayae Folium* et *Cacumen*. *Front Pharmacol.* 2024;15:1337161. doi:10.3389/fphar.2024.1337161
22. Khol M, Ma F, Lei L, Liu W, Liu X. A Frontier Review of Nutraceutical Chinese Yam. *Foods.* 2024;13(10):1426. doi:10.3390/foods13101426
23. Liu H, Yang J, Yang W, et al. Focus on Notoginsenoside R1 in Metabolism and Prevention Against Human Diseases. *Drug Des Devel Ther.* 2020;14:551–565. doi:10.2147/DDDT.S240511
24. Zhang Y, Yang Y, Ding L, Wang Z, Xiao Y, Xiao W. Emerging Applications of Metabolomics to Assess the Efficacy of Traditional Chinese Medicines for Treating Type 2 Diabetes Mellitus. *Front Pharmacol.* 2021;12:735410. doi:10.3389/fphar.2021.735410
25. Gao K, Yang R, Zhang J, et al. Effects of Qijian mixture on type 2 diabetes assessed by metabolomics, gut microbiota and network pharmacology. *Pharmacol Res.* 2018;130:93–109. doi:10.1016/j.phrs.2018.01.011
26. Pan L, Li Z, Wang Y, Zhang B, Liu G, Liu J. Network pharmacology and metabolomics study on the intervention of traditional Chinese medicine Huanglian Decoction in rats with type 2 diabetes mellitus. *J Ethnopharmacol.* 2020;258:112842. doi:10.1016/j.jep.2020.112842
27. Tong XL, Zhao LH, Lian FM, et al. Clinical observations on the dose-effect relationship of gegen qin lian decoction on 54 out-patients with type 2 diabetes. *J trad Chin med.* 2011;31(1):56–59. doi:10.1016/s0254-6272(11)60013-7
28. Xue J, Shi Y, Li C, Song H. Network pharmacology-based prediction of the active ingredients, potential targets, and signaling pathways in compound Lian-Ge granules for treatment of diabetes. *J Cell Biochem.* 2019;120(4):6431–6440. doi:10.1002/jcb.27933
29. Li J, Huang Y, Zhao S, et al. Based on network pharmacology to explore the molecular mechanisms of astragalus membranaceus for treating T2 diabetes mellitus. *Ann transl Med.* 2019;7(22):633. doi:10.21037/atm.2019.10.118
30. Qin J, Li Y, Cai Z, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature.* 2012;490(7418):55–60. doi:10.1038/nature11450
31. Karlsson FH, Tremaroli V, Nookaew I, et al. Gut metagenome in European women with normal, impaired and diabetic glucose control. *Nature.* 2013;498(7452):99–103. doi:10.1038/nature12198
32. Cani PD, Amar J, Iglesias MA, et al. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes.* 2007;56(7):1761–1772. doi:10.2337/db06-1491
33. Xu X, Gao Z, Yang F, et al. Antidiabetic Effects of Gegen Qinlian Decoction via the Gut Microbiota Are Attributable to Its Key Ingredient Berberine. *Genomics proteomics bioinfo.* 2020;18(6):721–736. doi:10.1016/j.gpb.2019.09.007
34. Shao J, Liu Y, Wang H, Luo Y, Chen L. An Integrated Fecal Microbiome and Metabolomics in T2DM Rats Reveal Antidiabetes Effects from Host-Microbial Metabolic Axis of EtOAc Extract from *Sophora flavescens*. *Oxid Med Cell Longev.* 2020;2020:1805418. doi:10.1155/2020/1805418
35. Li S, Zhan JK, Wang YJ, et al. Exosomes from hyperglycemia-stimulated vascular endothelial cells contain versican that regulate calcification/senescence in vascular smooth muscle cells. *Cell Biosci.* 2019;9:1. doi:10.1186/s13578-018-0263-x
36. Wang G, Han B, Zhang R, et al. C1q/TNF-Related Protein 9 Attenuates Atherosclerosis by Inhibiting Hyperglycemia-Induced Endothelial Cell Senescence Through the AMPK α /KLF4 Signaling Pathway. *Front Pharmacol.* 2021;12:758792. doi:10.3389/fphar.2021.758792
37. Wan Y, Liu Z, Wu A, et al. Hyperglycemia Promotes Endothelial Cell Senescence through AQR/PLAU Signaling Axis. *Int J Mol Sci.* 2022;23(5):2879. doi:10.3390/ijms23052879
38. Gao Y, Zhang L, Zhang F, et al. Traditional Chinese medicine and its active substances reduce vascular injury in diabetes via regulating autophagic activity. *Front Pharmacol.* 2024;15:1355246. doi:10.3389/fphar.2024.1355246
39. Zheng H, He B, Wu T, Cai J, Wei J. Extraction, purification and anti-osteoporotic activity of a polysaccharide from *Epimedium brevicornum* Maxim. in vitro. *Int J Biol Macromol.* 2020;156:1135–1145. doi:10.1016/j.ijbiomac.2019.11.145
40. Lei SS, Li B, Huang XW, et al. Structural identification of a polysaccharide isolated from *Epimedium brevicornum* and its beneficial effect on promoting osteogenesis in osteoblasts induced by high glucose. *Biomed Pharmacoth.* 2023;169:115893. doi:10.1016/j.biopha.2023.115893
41. Wang N, Xu P, Yao W, et al. Structural elucidation and anti-diabetic osteoporotic activity of an arabinogalactan from *Phellodendron chinense* Schneid. *Carbohydr Polym.* 2021;271:118438. doi:10.1016/j.carbpol.2021.118438

42. Xu P, Lin B, Deng X, He S, Chen N, Wang N. Anti-osteoporosis effects of Anemarrhenae Rhizoma / Phellodendri Chinensis Cortex herb pair and its major active components in diabetic rats and zebrafish. *J Ethnopharmacol.* 2022;293:115269. doi:10.1016/j.jep.2022.115269
43. Fu F, Luo H, Du Y, et al. AR/PCC herb pair inhibits osteoblast pyroptosis to alleviate diabetes-related osteoporosis by activating Nrf2/Keap1 pathway. *J Cell & Mol Med.* 2023;27(22):3601–3613. doi:10.1111/jcmm.17928
44. Feng R, Ding F, Mi XH, et al. Protective Effects of Ligustroflavone, an Active Compound from *Ligustrum lucidum*, on Diabetes-Induced Osteoporosis in Mice: a Potential Candidate as Calcium-Sensing Receptor Antagonist. *Am J Chin Med.* 2019;47(2):457–476. doi:10.1142/S0192415X1950023X
45. Gong W, Zhang N, Cheng G, et al. Rehmannia glutinosa Libosch Extracts Prevent Bone Loss and Architectural Deterioration and Enhance Osteoblastic Bone Formation by Regulating the IGF-1/PI3K/mTOR Pathway in Streptozotocin-Induced Diabetic Rats. *Int J Mol Sci.* 2019;20(16):3964. doi:10.3390/ijms20163964
46. Zhang Q, Hu S, Jin Z, Wang S, Zhang B, Zhao L. Mechanism of traditional Chinese medicine in elderly diabetes mellitus and a systematic review of its clinical application. *Front Pharmacol.* 2024;15:1339148. doi:10.3389/fphar.2024.1339148
47. She M, Huang M, Zhang J, et al. Astragalus embranaceus (Fisch.) Bge-Dioscorea opposita Thunb herb pair ameliorates sarcopenia in senile type 2 diabetes mellitus through Rab5a/mTOR-mediated mitochondrial dysfunction. *J Ethnopharmacol.* 2023;317:116737. doi:10.1016/j.jep.2023.116737
48. Zhang J, Zhuang P, Wang Y, et al. Reversal of muscle atrophy by Zhimu-Huangbai herb-pair via Akt/mTOR/FoxO3 signal pathway in streptozotocin-induced diabetic mice. *PLoS One.* 2014;9(6):e100918. doi:10.1371/journal.pone.0100918
49. Ping Y, Liu J, Wang L, Qiu H, Zhang Y. Research progress on the mechanism of TCM regulating intestinal microbiota in the treatment of DM mellitus. *Front Endocrinol.* 2024;15:1308016. doi:10.3389/fendo.2024.1308016
50. Ma CC, Jiang YH, Wang Y, Xu RR. The Latest Research Advances of Danggui Buxue Tang as an Effective Prescription for Various Diseases: a Comprehensive Review. *Current Med Sci.* 2022;42(5):913–924. doi:10.1007/s11596-022-2642-0
51. Zhang L, He S, Liu L, Huang J. Saponin monomers: potential candidates for the treatment of type 2 diabetes mellitus and its complications. *Phytother Res.* 2024;38(7):3564–3582. doi:10.1002/ptr.8229
52. Zhu M, Sun Y, Su Y, et al. Luteolin: a promising multifunctional natural flavonoid for human diseases. *Phytother Res.* 2024;38(7):3417–3443. doi:10.1002/ptr.8217
53. Yao YX, Yu YJ, Dai S, et al. Kaempferol efficacy in metabolic diseases: molecular mechanisms of action in diabetes mellitus, obesity, non-alcoholic fatty liver disease, steatohepatitis, and atherosclerosis. *Biomed Pharmacoth.* 2024;175:116694. doi:10.1016/j.biopha.2024.116694
54. Deng L, Shi C, Li R, et al. The mechanisms underlying Chinese medicines to treat inflammation in diabetic kidney disease. *J Ethnopharmacol.* 2024;333:118424. doi:10.1016/j.jep.2024.118424
55. Gao Y, Li Z, Wang Y, et al. Analysis of clinical evidence on traditional Chinese medicine for the treatment of diabetic nephropathy: a comprehensive review with evidence mapping. *Front Endocrinol.* 2024;15:1324782. doi:10.3389/fendo.2024.1324782
56. Guo X, Wu Y, Zhang C, Wu L, Qin L, Liu T. Network Pharmacology Analysis of ZiShenWan for Diabetic Nephropathy and Experimental Verification of Its Anti-Inflammatory Mechanism. *Drug Des Devel Ther.* 2021;15:1577–1594. doi:10.2147/DDDT.S297683
57. Wu JS, Liu Y, Shi R, Lu X, Ma YM, Cheng NN. Effects of combinations of Xiexin decoction constituents on diabetic nephropathy in rats. *J Ethnopharmacol.* 2014;157:126–133. doi:10.1016/j.jep.2014.09.024
58. Hong JN, Li WW, Wang LL, et al. JIANGTANG decoction ameliorate diabetic nephropathy through the regulation of PI3K/Akt-mediated NF-κB pathways in KK-Ay mice. *ChinMed.* 2017;12:13. doi:10.1186/s13020-017-0134-0
59. Cheng H, Fan X, Moeckel GW, Harris RC. Podocyte COX-2 exacerbates diabetic nephropathy by increasing podocyte (pro)renin receptor expression. *J Am Soc Nephrol.* 2011;22(7):1240–1251. doi:10.1681/ASN.2010111149
60. Xu ZG, Li SL, Lanting L, et al. Relationship between 12/15-lipoxygenase and COX-2 in mesangial cells: potential role in diabetic nephropathy. *Kidney Int.* 2006;69(3):512–519. doi:10.1038/sj.ki.5000137
61. Sun M, Bu W, Li Y, et al. Danzhi JIANGTANG Capsule ameliorates kidney injury via inhibition of the JAK-STAT signaling pathway and increased antioxidant capacity in STZ-induced diabetic nephropathy rats. *Biosci Trends.* 2019;12(6):595–604. doi:10.5582/bst.2018.01255
62. Zhang C, Li Q, Lai S, et al. Attenuation of diabetic nephropathy by Sanziguben Granule inhibiting EMT through Nrf2-mediated anti-oxidative effects in streptozotocin (STZ)-induced diabetic rats. *J Ethnopharmacol.* 2017;205:207–216. doi:10.1016/j.jep.2017.05.009
63. Li S, Zheng L, Zhang J, Liu X, Wu Z. Inhibition of ferroptosis by up-regulating Nrf2 delayed the progression of diabetic nephropathy. *Free Radic Biol Med.* 2021;162:435–449. doi:10.1016/j.freeradbiomed.2020.10.323
64. Yang S, Liu M, Chen Y, et al. NaoXinTong Capsules inhibit the development of diabetic nephropathy in db/db mice. *Sci Rep.* 2018;8(1):9158.
65. Chen X, Wang H, Jiang M, et al. Huangqi (astragalus) decoction ameliorates diabetic nephropathy via IRS1-PI3K-GLUT signaling pathway. *Am J Transl Res.* 2018;10(8):2491–2501.
66. Zhao TT, Zhang HJ, Lu XG, et al. Chaihuang-Yishen granule inhibits diabetic kidney disease in rats through blocking TGF-β/Smad3 signaling. *PLoS One.* 2014;9(3):e90807. doi:10.1371/journal.pone.0090807
67. Wang JY, Gao YB, Zhang N, et al. Tongxinluo ameliorates renal structure and function by regulating miR-21-induced epithelial-to-mesenchymal transition in diabetic nephropathy. *Am J Physiol Renal Physiol.* 2014;306(5):F486–495. doi:10.1152/ajprenal.00528.2013
68. Xin C, Xia Z, Jiang C, Lin M, Li G. Xiaoeping mixture inhibits diabetic nephropathy in streptozotocin-induced rats through blocking TGF-β1/Smad7 signaling. *Drug Des Devel Ther.* 2015;9:6269–6274. doi:10.2147/DDDT.S93964
69. Zheng W, Qian C, Xu F, et al. Fuxin Granules ameliorate diabetic nephropathy in db/db mice through TGF-β1/Smad and VEGF/VEGFR2 signaling pathways. *Biomed Pharmacoth.* 2021;141:111806. doi:10.1016/j.biopha.2021.111806
70. Jin J, Zhang Z, Chen J, Liu Y, Chen Q, Wang Q. Jixuepaidu Tang-I inhibits epithelial-mesenchymal transition and alleviates renal damage in DN mice through suppressing long non-coding RNA LOC498759. *Cell Cycle.* 2019;18(22):3125–3136. doi:10.1080/15384101.2019.1669986
71. Cai Y, Chen J, Jiang J, Cao W, He L. Zhen-wu-tang, a blended traditional Chinese herbal medicine, ameliorates proteinuria and renal damage of streptozotocin-induced diabetic nephropathy in rats. *J Ethnopharmacol.* 2010;131(1):88–94. doi:10.1016/j.jep.2010.06.004
72. Liu Y, Liu W, Zhang Z, et al. Yishen capsule promotes podocyte autophagy through regulating SIRT1/NF-κB signaling pathway to improve diabetic nephropathy. *Renal Failure.* 2021;43(1):128–140. doi:10.1080/0886022X.2020.1869043

73. Wang W, Long H, Huang W, et al. Bu-Shen-Huo-Xue Decoction Ameliorates Diabetic Nephropathy by Inhibiting Rac1/PAK1/p38MAPK Signaling Pathway in High-Fat Diet/Streptozotocin-Induced Diabetic Mice. *Front Pharmacol.* 2020;11:587663. doi:10.3389/fphar.2020.587663
74. Fernandes R, Viana SD, Nunes S, Reis F. Diabetic gut microbiota dysbiosis as an inflammaging and immunosenescence condition that fosters progression of retinopathy and nephropathy. *Biochim Biophys Acta Mol Basis Dis.* 2019;1865(7):1876–1897. doi:10.1016/j.bbadis.2018.09.032
75. Wei H, Wang L, An Z, et al. QiDiTangShen granules modulated the gut microbiome composition and improved bile acid profiles in a mouse model of diabetic nephropathy. *Biomed Pharmacothe.* 2021;133:111061. doi:10.1016/j.biopha.2020.111061
76. Meng X, Ma J, Kang SY, Jung HW, Park YK. Jowiseungki decoction affects diabetic nephropathy in mice through renal injury inhibition as evidenced by network pharmacology and gut microbiota analyses. *ChinMed.* 2020;15:24. doi:10.1186/s13020-020-00306-0
77. Liu Y, Chen X, Liu Y, et al. Metabolomic study of the protective effect of Gandi capsule for diabetic nephropathy. *Chem Biol Interact.* 2019;314:108815. doi:10.1016/j.cbi.2019.108815
78. Yang WJ, Li YR, Gao H, et al. Protective effect of the ethanol extract from Ligusticum chuanxiong rhizome against streptozotocin-induced diabetic nephropathy in mice. *J Ethnopharmacol.* 2018;227:166–175. doi:10.1016/j.jep.2018.08.037
79. Koulis C, Watson AMD, Gray SP, Jandeleit-Dahm KA. Linking RAGE and Nox in diabetic micro- and macrovascular complications. *Diab Metab.* 2015;41(4):272–281. doi:10.1016/j.diabet.2015.01.006
80. Xu GK, Sun CY, Qin XY, et al. Effects of ethanol extract of Bombax ceiba leaves and its main constituent mangiferin on diabetic nephropathy in mice. *Chinese J Nat Med.* 2017;15(8):597–605. doi:10.1016/S1875-5364(17)30087-0
81. Huang S, Tan M, Guo F, et al. Nepeta angustifolia C. Y. Wu improves renal injury in HFD/STZ-induced diabetic nephropathy and inhibits oxidative stress-induced apoptosis of mesangial cells. *J Ethnopharmacol.* 2020;255:112771. doi:10.1016/j.jep.2020.112771
82. An L, Zhou M, Marikar F, et al. Salvia miltiorrhiza Lipophilic Fraction Attenuates Oxidative Stress in Diabetic Nephropathy through Activation of Nuclear Factor Erythroid 2-Related Factor 2. *Am J Chin Med.* 2017;45(7):1441–1457. doi:10.1142/S0192415X17500781
83. Xiang X, Cai HD, Su SL, et al. Salvia miltiorrhiza protects against diabetic nephropathy through metabolome regulation and wnt/ β -catenin and TGF- β signaling inhibition. *Pharmacol Res.* 2019;139:26–40. doi:10.1016/j.phrs.2018.10.030
84. Wu Q, Guan YB, Zhang KJ, Li L, Zhou Y. Tanshinone IIA mediates protection from diabetes kidney disease by inhibiting oxidative stress induced pyroptosis. *J Ethnopharmacol.* 2023;316:116667. doi:10.1016/j.jep.2023.116667
85. Chen HW, Yang MY, Hung TW, Chang YC, Wang CJ. Nelumbo nucifera leaves extract attenuate the pathological progression of diabetic nephropathy in high-fat diet-fed and streptozotocin-induced diabetic rats. *J Food Drug Anal.* 2019;27(3):736–748. doi:10.1016/j.jfda.2018.12.009
86. Zhang X, Hu C, Kong CY, et al. FNDC5 alleviates oxidative stress and cardiomyocyte apoptosis in doxorubicin-induced cardiotoxicity via activating AKT. *Cell Death Differ.* 2020;27(2):540–555. doi:10.1038/s41418-019-0372-z
87. Kajal A, Singh R. Coriandrum sativum seeds extract mitigate progression of diabetic nephropathy in experimental rats via AGEs inhibition. *PLoS One.* 2019;14(3):e0213147. doi:10.1371/journal.pone.0213147
88. Chang B, Jin C, Zhang W, et al. Eonymus alatus in the treatment of diabetic nephropathy in rats. *Am J Chin Med.* 2012;40(6):1177–1187. doi:10.1142/S0192415X12500875
89. Menzies RI, Booth JWR, Mullins JJ, et al. Hyperglycemia-induced Renal P2X7 Receptor Activation Enhances Diabetes-related Injury. *EBioMedicine.* 2017;19:73–83. doi:10.1016/j.ebiom.2017.04.011
90. Hou Y, Lin S, Qiu J, et al. NLRP3 inflammasome negatively regulates podocyte autophagy in diabetic nephropathy. *Biochem Biophys Res Commun.* 2020;521(3):791–798. doi:10.1016/j.bbrc.2019.10.194
91. Wang C, Hou XX, Rui HL, et al. Artificially Cultivated Ophiocordyceps sinensis Alleviates Diabetic Nephropathy and Its Podocyte Injury via Inhibiting P2X7R Expression and NLRP3 Inflammasome Activation. *J Diab Res.* 2018;2018:1390418. doi:10.1155/2018/1390418
92. Yoon JJ, Park JH, Lee YJ, et al. Protective Effects of Ethanolic Extract from Rhizome of Polygoni avicularis against Renal Fibrosis and Inflammation in a Diabetic Nephropathy Model. *Int J Mol Sci.* 2021;22(13):7230. doi:10.3390/ijms22137230
93. Yao Y, Yang J, Wang D, et al. The aqueous extract of Lycopus lucidus Turcz ameliorates streptozotocin-induced diabetic renal damage via inhibiting TGF- β 1 signaling pathway. *Phytomedicine.* 2013;20(13):1160–1167. doi:10.1016/j.phymed.2013.06.004
94. Zhang M, Liu M, Xiong M, Gong J, Tan X. Schisandra chinensis fruit extract attenuates albuminuria and protects podocyte integrity in a mouse model of streptozotocin-induced diabetic nephropathy. *J Ethnopharmacol.* 2012;141(1):111–118. doi:10.1016/j.jep.2012.02.007
95. Grahammer F, Schell C, Huber TB. Molecular understanding of the slit diaphragm. *Pediatr Nephrol.* 2013;28(10):1957–1962. doi:10.1007/s00467-012-2375-6
96. Shukla R, Pandey N, Banerjee S, Tripathi YB. Effect of extract of Pueraria tuberosa on expression of hypoxia inducible factor-1 α and vascular endothelial growth factor in kidney of diabetic rats. *Biomed Pharmacothe.* 2017;93:276–285. doi:10.1016/j.biopha.2017.06.045
97. Zhang XX, Jiang CH, Y L, et al. Cyclocarya paliurus triterpenic acids fraction attenuates kidney injury via AMPK-mTOR-regulated autophagy pathway in diabetic rats. *Phytomedicine.* 2019;64:153060. doi:10.1016/j.phymed.2019.153060
98. Kim BH, Lee ES, Choi R, et al. Protective Effects of Curcumin on Renal Oxidative Stress and Lipid Metabolism in a Rat Model of Type 2 Diabetic Nephropathy. *Yonsei med j.* 2016;57(3):664–673. doi:10.3349/yjm.2016.57.3.664
99. Lu M, Yin N, Liu W, Cui X, Chen S, Wang E. Curcumin Ameliorates Diabetic Nephropathy by Suppressing NLRP3 Inflammasome Signaling. *Biomed Res Int.* 2017;2017:1516985. doi:10.1155/2017/1516985
100. Ding T, Wang S, Zhang X, et al. Kidney protection effects of dihydroquercetin on diabetic nephropathy through suppressing ROS and NLRP3 inflammasome. *Phytomedicine.* 2018;41:45–53. doi:10.1016/j.phymed.2018.01.026
101. Liu W, Liang L, Zhang Q, et al. Effects of andrographolide on renal tubulointerstitial injury and fibrosis. Evidence of its mechanism of action. *Phytomedicine.* 2021;91:153650. doi:10.1016/j.phymed.2021.153650
102. Zhu L, Han J, Yuan R, Xue L, Pang W. Berberine ameliorates diabetic nephropathy by inhibiting TLR4/NF- κ B pathway. *Biol Res.* 2018;51(1):9. doi:10.1186/s40659-018-0157-8
103. Bao L, Li J, Zha D, et al. Chlorogenic acid prevents diabetic nephropathy by inhibiting oxidative stress and inflammation through modulation of the Nrf2/HO-1 and NF- κ B pathways. *Int Immunopharmacol.* 2018;54:245–253. doi:10.1016/j.intimp.2017.11.021
104. Hu X, Zhang X, Jin G, Shi Z, Sun W, Chen F. Geniposide reduces development of streptozotocin-induced diabetic nephropathy via regulating nuclear factor-kappa B signaling pathways. *Fundament Clin Pharmacol.* 2017;31(1):54–63. doi:10.1111/fcp.12231

105. Xue H, Li P, Luo Y, et al. Salidroside stimulates the Sirt1/PGC-1 α axis and ameliorates diabetic nephropathy in mice. *Phytomedicine*. 2019;54:240–247. doi:10.1016/j.phymed.2018.10.031
106. Davidovici BB, Sattar N, Joerg PC, et al. Psoriasis and Systemic Inflammatory Diseases: potential Mechanistic Links between Skin Disease and Co-Morbid Conditions. *J Invest Dermatol*. 2010;130(7):1785–1796. doi:10.1038/jid.2010.103
107. He T, Guan X, Wang S, et al. Resveratrol prevents high glucose-induced epithelial-mesenchymal transition in renal tubular epithelial cells by inhibiting NADPH oxidase/ROS/ERK pathway. *Mol Cell Endocrinol*. 2015;402:13–20. doi:10.1016/j.mce.2014.12.010
108. Xu X, Zheng N, Chen Z, Huang W, Liang T, Kuang H. Puerarin, isolated from *Pueraria lobata* (Willd.), protects against diabetic nephropathy by attenuating oxidative stress. *Gene*. 2016;591(2):411–416. doi:10.1016/j.gene.2016.06.032
109. Mou Z, Feng Z, Xu Z, et al. Corrigendum to “Schisandrin B alleviates diabetic nephropathy through suppressing excessive inflammation and oxidative stress” *Biochem. Biophys. Res. Commun.* 508 (2019): 243–249. *Biochem Biophys Res Commun*. 2019;511(1):199–200. doi:10.1016/j.bbrc.2019.02.027
110. Rai U, Kosuru R, Prakash S, Tiwari V, Singh S. Tetramethylpyrazine alleviates diabetic nephropathy through the activation of Akt signalling pathway in rats. *Eur J Pharmacol*. 2019;865:172763. doi:10.1016/j.ejphar.2019.172763
111. Chen J, Chen Y, Luo Y, Gui D, Huang J, He D. Astragaloside IV ameliorates diabetic nephropathy involving protection of podocytes in streptozotocin induced diabetic rats. *Eur J Pharmacol*. 2014;736:86–94. doi:10.1016/j.ejphar.2014.04.037
112. Zhang Y, Wang B, Guo F, Li Z, Qin G. Involvement of the TGF β 1- ILK-Akt signaling pathway in the effects of hesperidin in type 2 diabetic nephropathy. *Biomed Pharmacoth*. 2018;105:766–772. doi:10.1016/j.biopha.2018.06.036
113. Tian N, Gao Y, Wang X, et al. Emodin mitigates podocytes apoptosis induced by endoplasmic reticulum stress through the inhibition of the PERK pathway in diabetic nephropathy. *Drug Des Devel Ther*. 2018;12:2195–2211. doi:10.2147/DDDT.S167405
114. Wang X, Gao L, Lin H, et al. Mangiferin prevents diabetic nephropathy progression and protects podocyte function via autophagy in diabetic rat glomeruli. *Eur J Pharmacol*. 2018;824:170–178. doi:10.1016/j.ejphar.2018.02.009
115. Yuan YL, Guo CR, Cui LL, et al. Timosaponin B-II ameliorates diabetic nephropathy via TXNIP, mTOR, and NF- κ B signaling pathways in alloxan-induced mice. *Drug Des Devel Ther*. 2015;9:6247–6258. doi:10.2147/DDDT.S96435
116. Zhang H, Qi S, Song Y, Ling C. Artemisinin attenuates early renal damage on diabetic nephropathy rats through suppressing TGF- β 1 regulator and activating the Nrf2 signaling pathway. *Life Sci*. 2020;256:117966. doi:10.1016/j.lfs.2020.117966
117. Yang J, Kan M, Wu GY. Bergenin ameliorates diabetic nephropathy in rats via suppressing renal inflammation and TGF- β 1-Smads pathway. *Immuno Immunotoxicol*. 2016;38(2):145–152. doi:10.3109/08923973.2016.1142560
118. Yan N, Wen L, Peng R, et al. Naringenin Ameliorated Kidney Injury through Let-7a/TGFBR1 Signaling in Diabetic Nephropathy. *J Diab Res*. 2016;2016:8738760. doi:10.1155/2016/8738760
119. Lai PB, Zhang L, Yang LY. Quercetin ameliorates diabetic nephropathy by reducing the expressions of transforming growth factor- β 1 and connective tissue growth factor in streptozotocin-induced diabetic rats. *Renal Failure*. 2012;34(1):83–87. doi:10.3109/0886022X.2011.623564
120. Lei D, Chengcheng L, Xuan Q, et al. Quercetin inhibited mesangial cell proliferation of early diabetic nephropathy through the Hippo pathway. *Pharmacol Res*. 2019;146:104320. doi:10.1016/j.phrs.2019.104320
121. Dong Z, Chen CX. Effect of catalpol on diabetic nephropathy in rats. *Phytomedicine*. 2013;20(11):1023–1029. doi:10.1016/j.phymed.2013.04.007
122. Zhou TY, Tian N, Li L, Yu R. Iridoids modulate inflammation in diabetic kidney disease: a review. *J Integr Med*. 2024;22(3):210–222. doi:10.1016/j.joim.2024.03.010
123. Bai Y, Zhu R, Tian Y, et al. Catalpol in Diabetes and its Complications: a Review of Pharmacology, Pharmacokinetics, and Safety. *Molecules*. 2019;24(18):3302. doi:10.3390/molecules24183302
124. Bhattamisra SK, Yap KH, Rao V, Choudhury H. Multiple Biological Effects of an Iridoid Glucoside, Catalpol and Its Underlying Molecular Mechanisms. *Biomolecules*. 2019;10(1). doi:10.3390/biom10010032
125. Jiang P, Xiang L, Chen Z, et al. Catalpol alleviates renal damage by improving lipid metabolism in diabetic db/db mice. *Am J Transl Res*. 2018;10(6):1750–1761.
126. Yang S, Deng H, Zhang Q, et al. Amelioration of Diabetic Mouse Nephropathy by Catalpol Correlates with Down-Regulation of Grb10 Expression and Activation of Insulin-Like Growth Factor 1 / Insulin-Like Growth Factor 1 Receptor Signaling. *PLoS One*. 2016;11(3):e0151857. doi:10.1371/journal.pone.0151857
127. Chen J, Yang Y, Lv Z, et al. Study on the inhibitive effect of Catalpol on diabetic nephropathy. *Life Sci*. 2020;257:118120. doi:10.1016/j.lfs.2020.118120
128. Chen Y, Liu Q, Shan Z, et al. The protective effect and mechanism of catalpol on high glucose-induced podocyte injury. *BMC Complementary Alternative Med*. 2019;19(1):244. doi:10.1186/s12906-019-2656-8
129. Shu A, Du Q, Chen J, et al. Catalpol ameliorates endothelial dysfunction and inflammation in diabetic nephropathy via suppression of RAGE/RhoA/ROCK signaling pathway. *Chem Biol Interact*. 2021;348:109625. doi:10.1016/j.cbi.2021.109625
130. Chen Y, Liu Q, Shan Z, et al. Catalpol Ameliorates Podocyte Injury by Stabilizing Cytoskeleton and Enhancing Autophagy in Diabetic Nephropathy. *Front Pharmacol*. 2019;10:1477. doi:10.3389/fphar.2019.01477
131. Sun W, Gao Y, Ding Y, et al. Catalpol ameliorates advanced glycation end product-induced dysfunction of glomerular endothelial cells via regulating nitric oxide synthesis by inducible nitric oxide synthase and endothelial nitric oxide synthase. *IUBMB Life*. 2019;71(9):1268–1283. doi:10.1002/iub.2032
132. Cong C, Yuan X, Hu Y, Chen W, Wang Y, Tao L. Catalpol Alleviates Ang II-Induced Renal Injury Through NF- κ B Pathway and TGF- β 1/Smads Pathway. *J Cardiovas Pharmacol*. 2022;79(1):e116–e121. doi:10.1097/FJC.0000000000001148
133. Sun WX, Gao YY, Cao Y, Lu JF, Lv GH, Xu HQ. Catalpol Prevents Glomerular Angiogenesis Induced by Advanced Glycation End Products via Inhibiting Galectin-3. *Current Med Sci*. 2023;43(4):668–678. doi:10.1007/s11596-023-2750-5
134. Zhang J, Bi R, Meng Q, et al. Catalpol alleviates Adriamycin-induced nephropathy by activating the SIRT1 signalling pathway in vivo and in vitro. *Br J Pharmacol*. 2019;176(23):4558–4573. doi:10.1111/bph.14822
135. Zhang J, Liu L, Li F, Wang Z, Zhao J. Treatment with catalpol protects against cisplatin-induced renal injury through Nrf2 and NF- κ B signaling pathways. *Exp Ther Med*. 2020;20(4):3025–3032. doi:10.3892/etm.2020.9077

136. Zhang J, Zhao T, Wang C, et al. Catalpol-Induced AMPK Activation Alleviates Cisplatin-Induced Nephrotoxicity through the Mitochondrial-Dependent Pathway without Compromising Its Anticancer Properties. *Oxid Med Cell Longev*. 2021;2021:7467156. doi:10.1155/2021/7467156
137. Zhang F, Yan Y, Zhang J, et al. Phytochemistry, synthesis, analytical methods, pharmacological activity, and pharmacokinetics of loganin: a comprehensive review. *Phytother Res*. 2022;36(6):2272–2299. doi:10.1002/ptr.7347
138. Xu H, Shen J, Liu H, Shi Y, Li L, Wei M. Morroniside and loganin extracted from *Cornus officinalis* have protective effects on rat mesangial cell proliferation exposed to advanced glycation end products by preventing oxidative stress. *Can J Physiol Pharmacol*. 2006;84(12):1267–1273. doi:10.1139/y06-075
139. Yamabe N, Noh JS, Park CH, et al. Evaluation of loganin, iridoid glycoside from *Corni Fructus*, on hepatic and renal glucolipototoxicity and inflammation in type 2 diabetic db/db mice. *Eur J Pharmacol*. 2010;648(1–3):179–187. doi:10.1016/j.ejphar.2010.08.044
140. Wan H, Li C, Yang Y, Chen D. Loganin attenuates interleukin-1 β -induced chondrocyte inflammation, cartilage degeneration, and rat synovial inflammation by regulating TLR4/MyD88/NF- κ B. *J Int Med Res*. 2022;50(8):3000605221104764. doi:10.1177/03000605221104764
141. Zhou Y, Luo D, Shi J, et al. Loganin alleviated cognitive impairment in 3 \times Tg-AD mice through promoting mitophagy mediated by optineurin. *J Ethnopharmacol*. 2023;312:116455. doi:10.1016/j.jep.2023.116455
142. Jiang WL, Zhang SP, Hou J, Zhu HB. Effect of loganin on experimental diabetic nephropathy. *Phytomedicine*. 2012;19(3–4):217–222. doi:10.1016/j.phymed.2011.08.064
143. Chen Y, Chen J, Jiang M, et al. Loganin and catalpol exert cooperative ameliorating effects on podocyte apoptosis upon diabetic nephropathy by targeting AGEs-RAGE signaling. *Life Sci*. 2020;252:117653. doi:10.1016/j.lfs.2020.117653
144. Du Q, Fu YX, Shu AM, et al. Loganin alleviates macrophage infiltration and activation by inhibiting the MCP-1/CCR2 axis in diabetic nephropathy. *Life Sci*. 2021;272:118808. doi:10.1016/j.lfs.2020.118808
145. Kong X, Zhao Y, Wang X, et al. Loganin reduces diabetic kidney injury by inhibiting the activation of NLRP3 inflammasome-mediated pyroptosis. *Chem Biol Interact*. 2023;382:110640. doi:10.1016/j.cbi.2023.110640
146. Wang DD, Zhu HZ, Li SW, et al. Crude Saponins of *Panax notoginseng* Have Neuroprotective Effects To Inhibit Palmitate-Triggered Endoplasmic Reticulum Stress-Associated Apoptosis and Loss of Postsynaptic Proteins in Staurosporine Differentiated RGC-5 Retinal Ganglion Cells. *J Agri Food Chem*. 2016;64(7):1528–1539. doi:10.1021/acs.jafc.5b05864
147. Wang MX, Wang MM, Liu C, et al. A geniposide-phospholipid complex ameliorates posthyperuricemia chronic kidney disease induced by inflammatory reactions and oxidative stress. *Eur J Pharmacol*. 2022;930:175157. doi:10.1016/j.ejphar.2022.175157
148. Ran D, Yan W, Yanhong B, Hong W. Geniposide augments apoptosis in fibroblast-like synoviocytes by restoring hypoxia-enhanced JNK-BNIP3-mediated autophagy. *Infl res*. 2023;72(8):1745–1760. doi:10.1007/s00011-023-01782-4
149. Huang J, Ye Y, Xiao Y, et al. Geniposide ameliorates glucocorticoid-induced osteoblast apoptosis by activating autophagy. *Biomed Pharmacother*. 2022;155:113829. doi:10.1016/j.biopha.2022.113829
150. Jiang P, Zhang Y, Li X, Chen J. Geniposidic acid attenuates DSS-induced colitis through inhibiting inflammation and regulating gut microbiota. *Phytother Res*. 2023;37(8):3453–3466. doi:10.1002/ptr.7819
151. Gao S, Feng Q. The Beneficial Effects of Geniposide on Glucose and Lipid Metabolism: a Review. *Drug Des Devel Ther*. 2022;16:3365–3383. doi:10.2147/DDDT.S378976
152. Li F, Chen Y, Li Y, Huang M, Zhao W. Geniposide alleviates diabetic nephropathy of mice through AMPK/SIRT1/NF- κ B pathway. *Eur J Pharmacol*. 2020;886:173449. doi:10.1016/j.ejphar.2020.173449
153. Dai SJ, Zhang QY, Lan Q, Chen Y, Zhang YZ, Huang Q. [PK2/PKR1 signaling pathway participates in geniposide protection against diabetic nephropathy in mice]. *Zhongguo Zhong Yao Za Zhi = Zhongguo Zhongyao Zazhi = China Journal of Chinese Materia Medica*. 2022;47(6):1611–1617. doi:10.19540/j.cnki.cjcmm.20211122.401
154. Dusabimana T, Park EJ, Je J, et al. Geniposide Improves Diabetic Nephropathy by Enhancing ULK1-Mediated Autophagy and Reducing Oxidative Stress through AMPK Activation. *Int J Mol Sci*. 2021;22(4):1651. doi:10.3390/ijms22041651
155. Muhamad Fadzil NS, Sekar M, Gan SH, et al. Chemistry, Pharmacology and Therapeutic Potential of Swertiamarin - A Promising Natural Lead for New Drug Discovery and Development. *Drug Des Devel Ther*. 2021;15:2721–2746. doi:10.2147/DDDT.S299753
156. Sonawane RD, Vishwakarma SL, Lakshmi S, Rajani M, Padh H, Goyal RK. Amelioration of STZ-induced type 1 diabetic nephropathy by aqueous extract of *Enicostemma littorale* Blume and swertiamarin in rats. *Mol Cell Biochem*. 2010;340(1–2):1–6. doi:10.1007/s11010-010-0393-x
157. Parwani K, Patel F, Patel D, Mandal P. Protective Effects of Swertiamarin against Methylglyoxal-Induced Epithelial-Mesenchymal Transition by Improving Oxidative Stress in Rat Kidney Epithelial (NRK-52E) Cells. *Molecules*. 2021;26(9):2748. doi:10.3390/molecules26092748
158. Xu L, Li D, Zhu Y, et al. Swertiamarin supplementation prevents obesity-related chronic inflammation and insulin resistance in mice fed a high-fat diet. *Adipocyte*. 2021;10(1):160–173. doi:10.1080/21623945.2021.1906510
159. Patel TP, Soni S, Parikh P, Gosai J, Chruvattil R, Gupta S. Swertiamarin: an Active Lead from *Enicostemma littorale* Regulates Hepatic and Adipose Tissue Gene Expression by Targeting PPAR- γ and Improves Insulin Sensitivity in Experimental NIDDM Rat Model. *Evidence-Based Complementary Alternative Med*. 2013;2013:358673. doi:10.1155/2013/358673
160. Xiao H, Sun X, Liu R, et al. Gentiopicroside activates the bile acid receptor Gpbar1 (TGR5) to repress NF- κ B pathway and ameliorate diabetic nephropathy. *Pharmacol Res*. 2020;151:104559. doi:10.1016/j.phrs.2019.104559
161. Xu Z, Zhang M, Wang Y, et al. Gentiopicroside Ameliorates Diabetic Renal Tubulointerstitial Fibrosis via Inhibiting the AT1R/CK2/NF- κ B Pathway. *Front Pharmacol*. 2022;13:848915. doi:10.3389/fphar.2022.848915
162. Micheli L, Bertini L, Bonato A, et al. Role of Hydroxytyrosol and Oleuropein in the Prevention of Aging and Related Disorders: focus on Neurodegeneration, Skeletal Muscle Dysfunction and Gut Microbiota. *Nutrients*. 2023;15(7). doi:10.3390/nu15071767
163. Liu Y, Dai W, Ye S. The olive constituent oleuropein exerts nephritic protective effects on diabetic nephropathy in db/db mice. *Arch Physiol Biochem*. 2022;128(2):455–462. doi:10.1080/13813455.2019.1691603
164. Ahmadvand H, Shahsavari G, Tavafi M, et al. Protective effects of oleuropein against renal injury oxidative damage in alloxan-induced diabetic rats; a histological and biochemical study. *J Nephropathol*. 2017;6(3):204–209. doi:10.15171/jnp.2017.34
165. Yokozawa T, Yamabe N, Kim HY, et al. Protective effects of morroniside isolated from *Corni Fructus* against renal damage in streptozotocin-induced diabetic rats. *Biol Pharm Bull*. 2008;31(7):1422–1428. doi:10.1248/bpb.31.1422

166. Lv G, Lv X, Tao Y, Xu H. Effect of morroniside on glomerular mesangial cells through AGE-RAGE pathway. *Human Cell*. 2016;29(4):148–154. doi:10.1007/s13577-015-0128-0
167. Gao X, Liu Y, Wang L, Sai N, Liu Y, Ni J. Morroniside Inhibits H(2)O(2)-Induced Podocyte Apoptosis by Down-Regulating NOX4 Expression Controlled by Autophagy In Vitro. *Front Pharmacol*. 2020;11:533809. doi:10.3389/fphar.2020.533809
168. Gao J, Liu P, Shen Z, et al. Morroniside Promotes PGC-1 α -Mediated Cholesterol Efflux in Sodium Palmitate or High Glucose-Induced Mouse Renal Tubular Epithelial Cells. *Biomed Res Int*. 2021;2021:9942152. doi:10.1155/2021/9942152
169. Chen W, Yao X, Zhou C, Zhang Z, Gui G, Lin B. Danhong Huayu Koufuye Prevents Diabetic Retinopathy in Streptozotocin-Induced Diabetic Rats via Antioxidation and Anti-Inflammation. *Mediators Inflammation*. 2017;2017:3059763. doi:10.1155/2017/3059763
170. Li Y, Huang Y, Tu C. Systems-Pharmacology-Based Identification of Antitumor Necrosis Factor Effect in Mimeng Flower Decoction for the Treatment of Diabetic Retinopathy. *Evidence-Based Complementary Alternative Med*. 2019;2019:5107103. doi:10.1155/2019/5107103
171. Gao D, Guo Y, Li X, et al. An Aqueous Extract of Radix Astragali, Angelica sinensis, and Panax notoginseng Is Effective in Preventing Diabetic Retinopathy. *Evidence-Based Complementary Alternative Med*. 2013;2013:578165. doi:10.1155/2013/578165
172. Wang N, Zhang C, Xu Y, et al. OMICs approaches-assisted identification of macrophages-derived MIP-1 γ as the therapeutic target of botanical products TNTL in diabetic retinopathy. *Cell commun signaling*. 2019;17(1):81. doi:10.1186/s12964-019-0396-5
173. Wang X, Li Y, Xie M, Deng L, Zhang M, Xie X. Urine metabolomics study of Bushen Huoxue Prescription on diabetic retinopathy rats by UPLC-Q-exactive Orbitrap-MS. *Biomed Chromatography*. 2020;34(4):e4792. doi:10.1002/bmc.4792
174. Zhang C, Xu Y, Tan HY, et al. Neuroprotective effect of He-Ying-Qing-Re formula on retinal ganglion cell in diabetic retinopathy. *J Ethnopharmacol*. 2018;214:179–189. doi:10.1016/j.jep.2017.12.018
175. Lk H, Ee J, Gm S, et al. Serotonin reciprocally regulates melanocortin neurons to modulate food intake. *Neuron*. 2006;51(2):239–249. doi:10.1016/j.neuron.2006.06.004
176. Li RL, Wang JX, Chai LJ, et al. Xueshuantong for Injection (Lyophilized,) Alleviates Streptozotocin-Induced Diabetic Retinopathy in Rats. *Chin J Integr Med*. 2020;26(11):825–832. doi:10.1007/s11655-020-3088-5
177. Xing W, Song Y, Li H, et al. Fufang Xueshuantong protects retinal vascular endothelial cells from high glucose by targeting YAP. *Biomed Pharmacother*. 2019;120:109470. doi:10.1016/j.biopha.2019.109470
178. He M, Long P, Guo L, Zhang M, Wang S, He H. Fushinging Capsule Attenuates Diabetic Rat Retina Damage via Antioxidation and Anti-Inflammation. *Evidence-Based Complementary Alternative Med*. 2019;2019:5376439. doi:10.1155/2019/5376439
179. Zhao Y, Yu J, Liu J, An X. The Role of Liuwei Dihuang Pills and Ginkgo Leaf Tablets in Treating Diabetic Complications. *Evidence-Based Complementary Alternative Med*. 2016;2016:7931314. doi:10.1155/2016/7931314
180. Liu M, Pan Q, Chen Y, et al. Administration of Danhong Injection to diabetic db/db mice inhibits the development of diabetic retinopathy and nephropathy. *Sci Rep*. 2015;5:11219. doi:10.1038/srep11219
181. Liu M, Pan Q, Chen Y, et al. NaoXinTong Inhibits the Development of Diabetic Retinopathy in db/db Mice. *Evidence-Based Complementary Alternative Med*. 2015;2015:242517. doi:10.1155/2015/242517
182. Wang H, Xing W, Tang S, et al. HuoXueJieDu Formula Alleviates Diabetic Retinopathy in Rats by Inhibiting SOCS3-STAT3 and TIMP1-A2M Pathways. *Int J Genomics*. 2017;2017:4832125. doi:10.1155/2017/4832125
183. Ren Y, Liang H, Xie M, Zhang M. Natural plant medications for the treatment of retinal diseases: the blood-retinal barrier as a clue. *Phytomedicine*. 2024;130:155568. doi:10.1016/j.phymed.2024.155568
184. Wang J, Yao Y, Liu X, Wang K, Zhou Q, Tang Y. Protective effects of lycium barbarum polysaccharides on blood-retinal barrier via ROCK1 pathway in diabetic rats. *Am J Transl Res*. 2019;11(10):6304–6315.
185. Dy O, Walenta E, Te A, et al. A Gpr120-selective agonist improves insulin resistance and chronic inflammation in obese mice. *Nature Med*. 2014;20(8):942–947. doi:10.1038/nm.3614
186. Dátilo MN, Sant'Ana MR, Formigari GP, et al. Omega-3 from Flaxseed Oil Protects Obese Mice Against Diabetic Retinopathy Through GPR120 Receptor. *Sci Rep*. 2018;8(1):14318. doi:10.1038/s41598-018-32553-5
187. Gong CY, Yu ZY, Lu B, et al. Ethanol extract of Dendrobium chrysotoxum Lindl ameliorates diabetic retinopathy and its mechanism. *Vasc Pharmacol*. 2014;62(3):134–142. doi:10.1016/j.vph.2014.04.007
188. Yu Z, Gong C, Lu B, et al. Dendrobium chrysotoxum Lindl. alleviates diabetic retinopathy by preventing retinal inflammation and tight junction protein decrease. *J Diab Res*. 2015;2015:518317. doi:10.1155/2015/518317
189. Sohn E, Kim J, Kim CS, Lee YM, Kim JS. Extract of Polygonum cuspidatum Attenuates Diabetic Retinopathy by Inhibiting the High-Mobility Group Box-1 (HMGB1) Signaling Pathway in Streptozotocin-Induced Diabetic Rats. *Nutrients*. 2016;8(3):140. doi:10.3390/nu8030140
190. Js M, Jh K, jh K, et al. Impaired RBC deformability is associated with diabetic retinopathy in patients with type 2 diabetes. *Diab Metab*. 2016;42(6):448–452. doi:10.1016/j.diabet.2016.04.008
191. Youngblood H, Robinson R, Sharma A, Sharma S. Proteomic Biomarkers of Retinal Inflammation in Diabetic Retinopathy. *Int J Mol Sci*. 2019;20(19):4755. doi:10.3390/ijms20194755
192. Liang XC, Hagino N, Guo SS, Tsutsumi T, Kobayashi S. Therapeutic efficacy of Stephania tetrandra S. Moore for treatment of neovascularization of retinal capillary (retinopathy) in diabetes--in vitro study. *Phytomedicine*. 2002;9(5):377–384. doi:10.1078/09447110260571599
193. Kim J, Kim CS, Lee YM, Sohn E, Jo K, Kim JS. Vaccinium myrtillus extract prevents or delays the onset of diabetes--induced blood-retinal barrier breakdown. *Int J Food Sci Nutr*. 2015;66(2):236–242. doi:10.3109/09637486.2014.979319
194. Zhou L, Zhang T, Lu B, et al. Lonicerae Japonicae Flos attenuates diabetic retinopathy by inhibiting retinal angiogenesis. *J Ethnopharmacol*. 2016;189:117–125. doi:10.1016/j.jep.2016.05.039
195. Lei X, Zhou Y, Ren C, et al. Typhae pollen polysaccharides ameliorate diabetic retinal injury in a streptozotocin-induced diabetic rat model. *J Ethnopharmacol*. 2018;224:169–176. doi:10.1016/j.jep.2018.05.030
196. Tzeng TF, Liu WY, Liou SS, Hong TY, Liu IM. Antioxidant-Rich Extract from Plantaginis Semen Ameliorates Diabetic Retinal Injury in a Streptozotocin-Induced Diabetic Rat Model. *Nutrients*. 2016;8(9):572. doi:10.3390/nu8090572
197. Ys K, Kim M, My C, et al. Aralia elata (Miq) Seem Extract Decreases O-GlcNAc Transferase Expression and Retinal Cell Death in Diabetic Mice. *J Med Food*. 2017;20(10):989–1001. doi:10.1089/jmf.2016.3891
198. Adki KM, Kulkarni YA. Paeonol attenuates retinopathy in streptozotocin-induced diabetes in rats by regulating the oxidative stress and polyol pathway. *Front Pharmacol*. 2022;13:891485. doi:10.3389/fphar.2022.891485

199. Kilari EK, Putta S. Delayed progression of diabetic cataractogenesis and retinopathy by *Litchi chinensis* in STZ-induced diabetic rats. *Cutaneous Ocular Toxicol.* **2017**;36(1):52–59. doi:10.3109/15569527.2016.1144610
200. Veeresham C, Swetha E, Rao AR, Asres K. In vitro and in vivo aldose reductase inhibitory activity of standardized extracts and the major constituent of *Andrographis paniculata*. *Phytother Res.* **2013**;27(3):412–416. doi:10.1002/ptr.4722
201. Fan C, Ma Q, Xu M, et al. Ginsenoside Rb1 Attenuates High Glucose-Induced Oxidative Injury via the NAD-PARP-SIRT Axis in Rat Retinal Capillary Endothelial Cells. *Int J Mol Sci.* **2019**;20(19):4936. doi:10.3390/ijms20194936
202. Xu Y, Zhao Y, Sui Y, Lei X. Protective effect of *Pterocarpus marsupium* bark extracts against cataract through the inhibition of aldose reductase activity in streptozotocin-induced diabetic male albino rats. *3 Biotech.* **2018**;8(4):188. doi:10.1007/s13205-018-1210-6
203. Sun HQ, Zhou ZY. Effect of ginsenoside-Rg3 on the expression of VEGF and TNF- α in retina with diabetic rats. *Int Jophthalmol.* **2010**;3(3):220–223. doi:10.3980/j.issn.2222-3959.2010.03.09
204. Qiao Y, Fan CL, Tang MK. Astragaloside IV protects rat retinal capillary endothelial cells against high glucose-induced oxidative injury. *Drug Des Devel Ther.* **2017**;11:3567–3577. doi:10.2147/DDDT.S152489
205. Yang Y, Zhou M, Liu H. Luteolin, an aryl hydrocarbon receptor antagonist, alleviates diabetic retinopathy by regulating the NLRP/NOX4 signalling pathway: experimental and molecular docking study. *Physiol Int.* **2021**;108(2):172–184. doi:10.1556/2060.2021.00148
206. Gao LM, Fu S, Liu F, Wu HB, Li WJ. Astragalus Polysaccharide Regulates miR-182/Bcl-2 Axis to Relieve Metabolic Memory through Suppressing Mitochondrial Damage-Mediated Apoptosis in Retinal Pigment Epithelial Cells. *Pharmacology.* **2021**;106(9–10):520–533. doi:10.1159/000515901
207. Liu P, Peng QH, Tong P, Li WJ. Astragalus polysaccharides suppresses high glucose-induced metabolic memory in retinal pigment epithelial cells through inhibiting mitochondrial dysfunction-induced apoptosis by regulating miR-195. *Mol Med.* **2019**;25(1):21. doi:10.1186/s10020-019-0088-z
208. Gupta SK, Kumar B, Nag TC, et al. Effects of *Trigonella foenum-graecum* (L.) on retinal oxidative stress, and proinflammatory and angiogenic molecular biomarkers in streptozotocin-induced diabetic rats. *Mol Cell Biochem.* **2014**;388(1–2):1–9. doi:10.1007/s11010-013-1893-2
209. Kumar Gupta S, Kumar B, Srinivasan BP, et al. Retinoprotective effects of *Moringa oleifera* via antioxidant, anti-inflammatory, and anti-angiogenic mechanisms in streptozotocin-induced diabetic rats. *J Ocular Pharmacol Therapeutics.* **2013**;29(4):419–426. doi:10.1089/jop.2012.0089
210. Fan C, Qiao Y, Tang M. Notoginsenoside R1 attenuates high glucose-induced endothelial damage in rat retinal capillary endothelial cells by modulating the intracellular redox state. *Drug Des Devel Ther.* **2017**;11:3343–3354. doi:10.2147/DDDT.S149700
211. Fu D, Yu JY, Connell AR, et al. Beneficial Effects of Berberine on Oxidized LDL-Induced Cytotoxicity to Human Retinal Müller Cells. *Invest Ophthalmol Visual Sci.* **2016**;57(7):3369–3379. doi:10.1167/iovs.16-19291
212. Liu WY, Liou SS, Hong TY, Liu IM. Protective Effects of Hesperidin (Citrus Flavonone) on High Glucose Induced Oxidative Stress and Apoptosis in a Cellular Model for Diabetic Retinopathy. *Nutrients.* **2017**;9(12):1312. doi:10.3390/nu9121312
213. Lacombe J, Al RO, Loter L, et al. Measurement of bioactive osteocalcin in humans using a novel immunoassay reveals association with glucose metabolism and beta-cell function. *Am J Physiol Endocrinol Metab.* **2020**;318(3):E381–E391. doi:10.1152/ajpendo.00321.2019
214. Qian S, Qian Y, Huo D, Wang S, Qian Q. Tanshinone Ila protects retinal endothelial cells against mitochondrial fission induced by methylglyoxal through glyoxalase 1. *Eur J Pharmacol.* **2019**;857:172419. doi:10.1016/j.ejphar.2019.172419
215. Wang J, Zhang J, Nr ZY. Calycosin Alleviates Oxidative Stress and Pyroptosis Induced by High Glucose in Human Retinal Capillary Endothelial Cells Induced by High Glucose. *Current Topics in Nutraceutical Research.* **2022**;21(1):40–46. doi:10.37290/ctrn2641-452X.21:40-46
216. Wu Q, Liu H, Zhou M. Fangchinoline Ameliorates Diabetic Retinopathy by Inhibiting Receptor for Advanced Glycation End-Products (RAGE)-Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells (NF- κ B) Pathway in Streptozotocin (STZ)-Induced Diabetic Rats. *Med Sci Monitor.* **2019**;25:1113–1121. doi:10.12659/MSM.912927
217. Fang M, Wan W, Li Q, et al. Asiatic acid attenuates diabetic retinopathy through TLR4/MyD88/NF- κ B p65 mediated modulation of microglia polarization. *Life Sci.* **2021**;277:119567. doi:10.1016/j.lfs.2021.119567
218. Zhang TH, Huang CM, Gao X, Wang JW, Hao LL, Ji Q. Gastrodin inhibits high glucose-induced human retinal endothelial cell apoptosis by regulating the SIRT1/TLR4/NF- κ Bp65 signaling pathway. *Mol med rep.* **2018**;17(6):7774–7780. doi:10.3892/mmr.2018.8841
219. Zhu Q, Liu M, He Y, Yang B. Quercetin protect cigarette smoke extracts induced inflammation and apoptosis in RPE cells. *Artif Cells Nanomed Biotechnol.* **2019**;47(1):2010–2015. doi:10.1080/21691401.2019.1608217
220. Oh JH, Oh J, Togloom A, Kim SW, Huh K. Effects of ginkgo biloba extract on cultured human retinal pigment epithelial cells under chemical hypoxia. *Current Eye Res.* **2013**;38(10):1072–1082. doi:10.3109/02713683.2013.804093
221. Wu J, Ke X, Fu W, et al. Inhibition of Hypoxia-Induced Retinal Angiogenesis by Specnuezhenide, an Effective Constituent of *Ligustrum lucidum* Ait. through Suppression of the HIF-1 α /VEGF Signaling Pathway. *Molecules.* **2016**;21(12):1756. doi:10.3390/molecules21121756
222. Ai X, Yu P, Luo L, et al. Berberis dictyophylla F. inhibits angiogenesis and apoptosis of diabetic retinopathy via suppressing HIF-1 α /VEGF/DLL-4/Notch-1 pathway. *J Ethnopharmacol.* **2022**;296:115453. doi:10.1016/j.jep.2022.115453
223. Shi X, Liao S, Mi H, et al. Hesperidin prevents retinal and plasma abnormalities in streptozotocin-induced diabetic rats. *Molecules.* **2012**;17(11):12868–12881. doi:10.3390/molecules171112868
224. Abdulqader A, Ali F, Ismail A, Esa NM. Gac fruit extracts ameliorate proliferation and modulate angiogenic markers of human retinal pigment epithelial cells under high glucose conditions. **2018**;8(12):571–579.
225. Chen H, Ji Y, Yan X, Su G, Chen L, Xiao J. Berberine attenuates apoptosis in rat retinal Müller cells stimulated with high glucose via enhancing autophagy and the AMPK/mTOR signaling. *Biomed Pharmacothe.* **2018**;108:1201–1207. doi:10.1016/j.biopha.2018.09.140
226. Li L, Chen J, Zhou Y, Zhang J, Chen L. Artesunate alleviates diabetic retinopathy by activating autophagy via the regulation of AMPK/SIRT1 pathway. *Arch Physiol Biochem.* **2023**;129(4):943–950. doi:10.1080/13813455.2021.1887266
227. Peng QH, Tong P, Gu LM, Li WJ. Astragalus polysaccharide attenuates metabolic memory-triggered ER stress and apoptosis via regulation of miR-204/SIRT1 axis in retinal pigment epithelial cells. *Biosci Rep.* **2020**;40(1). doi:10.1042/BSR20192121
228. Chen W, Zhang Y, Li X, Yang G, Liu JP. Chinese herbal medicine for diabetic peripheral neuropathy. *Cochrane Database Syst Rev.* **2013**;2013(10):Cd007796. doi:10.1002/14651858.CD007796.pub3

229. Bai L, Xu D, Zhou YM, et al. Antioxidant Activities of Natural Polysaccharides and Their Derivatives for Biomedical and Medicinal Applications. *Antioxidants*. 2022;11(12):2491. doi:10.3390/antiox11122491
230. Guo H, Fu MX, Wu DT, et al. Structural Characteristics of Crude Polysaccharides from 12 Selected Chinese Teas, and Their Antioxidant and Anti-Diabetic Activities. *Antioxidants*. 2021;10(10):1562. doi:10.3390/antiox10101562
231. Ji N, Liu P, Zhang N, Yang S, Zhang M. Comparison on Bioactivities and Characteristics of Polysaccharides From Four Varieties of *Gastrodia elata* Blume. *Front Chem*. 2022;10:956724. doi:10.3389/fchem.2022.956724
232. Huang F, Zhang R, Dong L, et al. Antioxidant and antiproliferative activities of polysaccharide fractions from litchi pulp. *Food Funct*. 2015;6(8):2598–2606. doi:10.1039/C5FO00249D
233. Wang Y, Bian X, Park J, Ying L, Qian L, Xu P. Physicochemical properties, in vitro antioxidant activities and inhibitory potential against α -glucosidase of polysaccharides from *Ampelopsis grossedentata* leaves and stems. *Molecules*. 2011;16(9):7762–7772. doi:10.3390/molecules16097762
234. Ka-Chai S, Xia C, Jian-Yong W. Constituents actually responsible for the antioxidant activities of crude polysaccharides isolated from mushrooms. *J Functional Foods*. 2014;11:548–556. doi:10.1016/j.jff.2014.08.012
235. Li P, Jiang Z, Sun T, et al. Comparison of structural, antioxidant and immuno-stimulating activities of polysaccharides from *Tremella fuciformis* in two different regions of China. *Int J Food Sci Technol*. 2018;53(8):1942–1953. doi:10.1111/ijfs.13782
236. Keum YS. Regulation of Nrf2-Mediated Phase II Detoxification and Anti-oxidant Genes. *Biomolecules Ther*. 2012;20(2):144–151. doi:10.4062/biomolther.2012.20.2.144
237. Li S, Song Z, Liu T, et al. Polysaccharide from *Ostrea rivularis* attenuates reproductive oxidative stress damage via activating Keap1-Nrf2/ARE pathway. *Carbohydr Polym*. 2018;186:321–331. doi:10.1016/j.carbpol.2018.01.075
238. Han Y, Zhao M, Ouyang K, et al. Sulfated modification, structures, antioxidant activities and mechanism of *Cyclocarya paliurus* polysaccharides protecting dendritic cells against oxidant stress. *Ind Crops Prod*. 2021;164:113353. doi:10.1016/j.indcrop.2021.113353
239. Yun L, Wu T, Mao Z, Li W, Zhang M, Sun X. A novel wheat germ polysaccharide: structural characterization, potential antioxidant activities and mechanism. *Int J Biol Macromol*. 2020;165(Pt B):1978–1987. doi:10.1016/j.ijbiomac.2020.10.112
240. Jiang S, Wang Y, Ren D, et al. Antidiabetic mechanism of *Coptis chinensis* polysaccharide through its antioxidant property involving the JNK pathway. *Pharm Biol*. 2015;53(7):1022–1029. doi:10.3109/13880209.2014.952838
241. Zhuang C, Ni S, Yang ZC, Liu RP. Oxidative Stress Induces Chondrocyte Apoptosis through Caspase-Dependent and Caspase-Independent Mitochondrial Pathways and the Antioxidant Mechanism of *Angelica Sinensis* Polysaccharide. *Oxid Med Cell Longev*. 2020;2020:3240820. doi:10.1155/2020/3240820
242. Yue C, Chen J, Hou R, et al. The antioxidant action and mechanism of selenizing *Schisandra chinensis* polysaccharide in chicken embryo hepatocyte. *Int J Biol Macromol*. 2017;98:506–514. doi:10.1016/j.ijbiomac.2017.02.015
243. Chen F, Huang S, Huang G. Preparation, activity, and antioxidant mechanism of rice bran polysaccharide. *Food Funct*. 2021;12(2):834–839. doi:10.1039/D0FO02498H
244. Peng H, Yang M, Guo Q, Su T, Xiao Y, Xia ZY. *Dendrobium officinale* polysaccharides regulate age-related lineage commitment between osteogenic and adipogenic differentiation. *Cell Proliferation*. 2019;52(4):e12624. doi:10.1111/cpr.12624
245. Zhang Y, Wang H, Zhang L, Yuan Y, Yu D. *Codonopsis lanceolata* polysaccharide CLPS alleviates high fat/high sucrose diet-induced insulin resistance via anti-oxidative stress. *Int J Biol Macromol*. 2020;145:944–949. doi:10.1016/j.ijbiomac.2019.09.185
246. Zhuang C, Wang Y, Zhang Y, Xu N. Oxidative stress in osteoarthritis and antioxidant effect of polysaccharide from *angelica sinensis*. *Int J Biol Macromol*. 2018;115:281–286. doi:10.1016/j.ijbiomac.2018.04.083
247. Pengzhan Y, Ning L, Xiguang L, Gefei Z, Quanbin Z, Pengcheng L. Antihyperlipidemic effects of different molecular weight sulfated polysaccharides from *Ulva pertusa* (Chlorophyta). *Pharmacol Res*. 2003;48(6):543–549. doi:10.1016/S1043-6618(03)00215-9
248. Tian X, Liang T, Liu Y, Ding G, Zhang F, Ma Z. Extraction, Structural Characterization, and Biological Functions of *Lycium Barbarum* Polysaccharides: a Review. *Biomolecules*. 2019;9(9):389. doi:10.3390/biom9090389
249. Liu J, Pu Q, Qiu H, Di D. Polysaccharides isolated from *Lycium barbarum* L. by integrated tandem hybrid membrane technology exert antioxidant activities in mitochondria. *Ind Crops Prod*. 2021;168:113547. doi:10.1016/j.indcrop.2021.113547
250. Fan H, Meng Q, Xiao T, Zhang L. Partial characterization and antioxidant activities of polysaccharides sequentially extracted from *Dendrobium officinale*. *J Food Measurement Characterization*. 2018;12(2):1054–1064. doi:10.1007/s11694-018-9721-8
251. Zhang Y, Zhang L, Liu J, Liang J, Si J, Wu S. *Dendrobium officinale* leaves as a new antioxidant source. *J Functional Foods*. 2017;37:400–415. doi:10.1016/j.jff.2017.08.006
252. Niu X, Zhang J, Ling C, et al. Polysaccharide from *Angelica sinensis* protects H9c2 cells against oxidative injury and endoplasmic reticulum stress by activating the ATF6 pathway. *J Int Med Res*. 2018;46(5):1717–1733. doi:10.1177/0300060518758863
253. Tian S, Hao C, Xu G, Yang J, Sun R. Optimization conditions for extracting polysaccharide from *Angelica sinensis* and its antioxidant activities. *J Food Drug Anal*. 2017;25(4):766–775. doi:10.1016/j.jfda.2016.08.012
254. Zhu ZY, Chen CJ, Sun HQ, Chen LJ. Structural characterisation and ACE-inhibitory activities of polysaccharide from *Gastrodia elata* Blume. *Nat Product Res*. 2019;33(12):1721–1726. doi:10.1080/14786419.2018.1434643
255. Zhou B, Tan J, Zhang C, Wu Y. Neuroprotective effect of polysaccharides from *Gastrodia elata* blume against corticosterone-induced apoptosis in PC12 cells via inhibition of the endoplasmic reticulum stress-mediated pathway. *Mol med rep*. 2018;17(1):1182–1190. doi:10.3892/mmr.2017.7948
256. Huo J, Lei M, Li F, et al. Structural Characterization of a Polysaccharide from *Gastrodia elata* and Its Bioactivity on Gut Microbiota. *Molecules*. 2021;26(15):4443. doi:10.3390/molecules26154443
257. Li N, Wang D, Wen X, et al. Effects of polysaccharides from *Gastrodia elata* on the immunomodulatory activity and gut microbiota regulation in cyclophosphamide-treated mice. *J Sci Food Agric*. 2023;103(7):3390–3401. doi:10.1002/jsfa.12491
258. Chen L, Zhang YP, Jin LX. Preparation, characterization and anti-ageing activity of *Gastrodia elata* blume polysaccharide. *Acta Aliment*. 2018;47(2):210–219. doi:10.1556/066.2018.47.2.10
259. Li Y, Hu Y, Shi S, Jiang L. Evaluation of antioxidant and immuno-enhancing activities of Purslane polysaccharides in gastric cancer rats. *Int J Biol Macromol*. 2014;68:113–116. doi:10.1016/j.ijbiomac.2014.04.038

260. YouGuo C, ZongJi S, XiaoPing C. Evaluation of free radicals scavenging and immunity-modulatory activities of Purslane polysaccharides. *Int J Biol Macromol.* 2009;45(5):448–452. doi:10.1016/j.ijbiomac.2009.07.009
261. Cui X, Wang S, Cao H, et al. A Review: the Bioactivities and Pharmacological Applications of Polygonatum sibiricum polysaccharides. *Molecules.* 2018;23(5):1170. doi:10.3390/molecules23051170
262. Shen F, Song Z, Xie P, et al. Polygonatum sibiricum polysaccharide prevents depression-like behaviors by reducing oxidative stress, inflammation, and cellular and synaptic damage. *J Ethnopharmacol.* 2021;275:114164. doi:10.1016/j.jep.2021.114164
263. Yang H, Zhang X. Polysaccharides from Polygonatum odoratum strengthen antioxidant defense system and attenuate lipid peroxidation against exhaustive exercise-induced oxidative stress in mice. *Trop J Pharm Res.* 2017;16(4):795–801. doi:10.4314/tjpr.v16i4.8
264. Zhang Z, Wang F, Wang X, Liu X, Hou Y, Zhang Q. Extraction of the polysaccharides from five algae and their potential antioxidant activity in vitro. *Carbohydr Polym.* 2010;82(1):118–121. doi:10.1016/j.carbpol.2010.04.031
265. Yuan Y, Macquarrie D. Microwave assisted extraction of sulfated polysaccharides (fucoidan) from *Ascophyllum nodosum* and its antioxidant activity. *Carbohydr Polym.* 2015;129:101–107. doi:10.1016/j.carbpol.2015.04.057
266. Le B, Golokvast KS, Yang SH, Sun S. Optimization of Microwave-Assisted Extraction of Polysaccharides from *Ulva pertusa* and Evaluation of Their Antioxidant Activity. *Antioxidants.* 2019;8(5):129. doi:10.3390/antiox8050129
267. Mohd Fauzee NA, Chang LS, Wan Mustapha WA, Md Nor AR, Lim SJ. Functional polysaccharides of fucoidan, laminaran and alginate from Malaysian brown seaweeds (*Sargassum polycystum*, *Turbinaria ornata* and *Padina boryana*). *Int J Biol Macromol.* 2021;167:1135–1145. doi:10.1016/j.ijbiomac.2020.11.067
268. Sarithakumari CH, Renju GL, Kurup GM. Anti-inflammatory and antioxidant potential of alginic acid isolated from the marine algae, *Sargassum wightii* on adjuvant-induced arthritic rats. *Inflammopharmacology.* 2013;21(3):261–268. doi:10.1007/s10787-012-0159-z
269. Hifney AF, Fawzy MA, Abdel-Gawad KM, Gomaa M. Upgrading the antioxidant properties of fucoidan and alginate from *Cystoseira trinodis* by fungal fermentation or enzymatic pretreatment of the seaweed biomass. *Food Chem.* 2018;269:387–395. doi:10.1016/j.foodchem.2018.07.026
270. Sen M. Effects of molecular weight and ratio of guluronic acid to mannuronic acid on the antioxidant properties of sodium alginate fractions prepared by radiation-induced degradation. *Applied Radiation Isotopes.* 2011;69(1):126–129. doi:10.1016/j.apradiso.2010.08.017
271. Kelishomi ZH, Goliaei B, Mahdavi H, et al. Antioxidant activity of low molecular weight alginate produced by thermal treatment. *Food Chem.* 2016;196:897–902. doi:10.1016/j.foodchem.2015.09.091
272. Chen H, Ju Y, Li J, Yu M. Antioxidant activities of polysaccharides from *Lentinus edodes* and their significance for disease prevention. *Int J Biol Macromol.* 2012;50(1):214–218. doi:10.1016/j.ijbiomac.2011.10.027
273. You R, Wang K, Liu J, Liu M, Luo L, Zhang Y. A comparison study between different molecular weight polysaccharides derived from *Lentinus edodes* and their antioxidant activities in vivo. *Pharm Biol.* 2011;49(12):1298–1305. doi:10.3109/13880209.2011.621960
274. Yan J, Zhu L, Qu Y, et al. Analyses of active antioxidant polysaccharides from four edible mushrooms. *Int J Biol Macromol.* 2019;123:945–956. doi:10.1016/j.ijbiomac.2018.11.079
275. He JZ, Ru QM, Dong DD, Sun PL. Chemical characteristics and antioxidant properties of crude water soluble polysaccharides from four common edible mushrooms. *Molecules.* 2012;17(4):4373–4387. doi:10.3390/molecules17044373
276. Chen GT, Ma XM, Liu ST, Liao YL, Zhao GQ. Isolation, purification and antioxidant activities of polysaccharides from *Grifola frondosa*. *Carbohydr Polym.* 2012;89(1):61–66. doi:10.1016/j.carbpol.2012.02.045
277. Chen Z, Tang Y, Liu A, Jin X, Zhu J, Lu X. Oral administration of *Grifola frondosa* polysaccharides improves memory impairment in aged rats via antioxidant action. *Mol Nutr Food Res.* 2017;61(11). doi:10.1002/mnfr.201700313
278. Cör D, Knez Ž, Knez Hrnčič M. Antitumour, Antimicrobial, Antioxidant and Antiacetylcholinesterase Effect of *Ganoderma Lucidum* Terpenoids and Polysaccharides: a Review. *Molecules.* 2018;23(3):649. doi:10.3390/molecules23030649
279. Xue Z, Zhao L, Wang D, et al. Structural characterization of a polysaccharide from *Radix Hedysari* and its protective effects against H(2)O (2)-induced injury in human gastric epithelium cells. *Int J Biol Macromol.* 2021;189:503–515. doi:10.1016/j.ijbiomac.2021.08.151
280. Fan S, Huang X, Wang S, et al. Combinatorial usage of fungal polysaccharides from *Cordyceps sinensis* and *Ganoderma atrum* ameliorate drug-induced liver injury in mice. *Food Chemical Toxicol.* 2018;119:66–72. doi:10.1016/j.ftc.2018.05.027
281. Fan ST, Nie SP, Huang XJ, et al. Protective properties of combined fungal polysaccharides from *Cordyceps sinensis* and *Ganoderma atrum* on colon immune dysfunction. *Int J Biol Macromol.* 2018;114:1049–1055. doi:10.1016/j.ijbiomac.2018.04.004
282. Mahdhi A, Leban N, Chakroun I, et al. Extracellular polysaccharide derived from potential probiotic strain with antioxidant and antibacterial activities as a prebiotic agent to control pathogenic bacterial biofilm formation. *Microb Pathogenesis.* 2017;109:214–220. doi:10.1016/j.micpath.2017.05.046
283. Asker MMS, Shawky BT. Structural characterization and antioxidant activity of an extracellular polysaccharide isolated from *Brevibacterium otitidis* BTS 44. *Food Chem.* 2010;123(2):315–320. doi:10.1016/j.foodchem.2010.04.037
284. Diao Y, Xin Y, Zhou Y, et al. Extracellular polysaccharide from *Bacillus* sp. strain LBP32 prevents LPS-induced inflammation in RAW 264.7 macrophages by inhibiting NF-κB and MAPKs activation and ROS production. *Int Immunopharmacol.* 2014;18(1):12–19.
285. Elnahas MO, Amin MA, Hussein MMD, Shanbhag VC, Ali AE, Wall JD. Isolation, Characterization and Bioactivities of an Extracellular Polysaccharide Produced from *Streptomyces* sp. MOE6. *Molecules.* 2017;22(9):1396. doi:10.3390/molecules22091396
286. Manivasagan P, Sivasankar P, Venkatesan J, Senthilkumar K, Sivakumar K, Kim SK. Production and characterization of an extracellular polysaccharide from *Streptomyces violaceus* MM72. *Int J Biol Macromol.* 2013;59:29–38. doi:10.1016/j.ijbiomac.2013.04.012
287. Xiong Q, Song Z, Hu W, et al. Methods of extraction, separation, purification, structural characterization for polysaccharides from aquatic animals and their major pharmacological activities. *Crit Rev Food Sci Nutr.* 2020;60(1):48–63. doi:10.1080/10408398.2018.1512472
288. Xue W, Zeng Q, Lin S, et al. Recovery of high-value and scarce resources from biological wastewater treatment: sulfated polysaccharides. *Water Res.* 2019;163:114889. doi:10.1016/j.watres.2019.114889
289. Pomin VH. Review: an overview about the structure-function relationship of marine sulfated homopolysaccharides with regular chemical structures. *Biopolymers.* 2009;91(8):601–609. doi:10.1002/bip.21200
290. Zou S, Pan R, Dong X, He M, Wang C. Physicochemical properties and antioxidant activities of two fucosylated chondroitin sulfate from sea cucumber *Acaudina molpadioidea* and *Holothuria nobilis*. *Process Biochem.* 2016;51(5):650–658. doi:10.1016/j.procbio.2016.02.009

291. Wang Z, Zhao Y, Su T. Extraction and antioxidant activity of polysaccharides from *Rana chensinensis* skin. *Carbohydr Polym.* 2015;115:25–31. doi:10.1016/j.carbpol.2014.08.082
292. Wang Z, Zhao Y, Su T, Zhang J, Wang F. Characterization and antioxidant activity in vitro and in vivo of polysaccharide purified from *Rana chensinensis* skin. *Carbohydr Polym.* 2015;126:17–22. doi:10.1016/j.carbpol.2015.03.031
293. Ghormade V, Pathan EK, Deshpande MV. Can fungi compete with marine sources for chitosan production? *Int J Biol Macromol.* 2017;104(Pt B):1415–1421. doi:10.1016/j.ijbiomac.2017.01.112
294. Anraku M, Kabashima M, Namura H, et al. Antioxidant protection of human serum albumin by chitosan. *Int J Biol Macromol.* 2008;43(2):159–164. doi:10.1016/j.ijbiomac.2008.04.006
295. Yuan F, Gao Z, Liu W, et al. Characterization, Antioxidant, Anti-Aging and Organ Protective Effects of Sulfated Polysaccharides from *Flammulina velutipes*. *Molecules.* 2019;24(19):3517. doi:10.3390/molecules24193517
296. Chen F, Huang G, Huang H. Preparation, analysis, antioxidant activities in vivo of phosphorylated polysaccharide from *Momordica charantia*. *Carbohydr Polym.* 2021;252:117179. doi:10.1016/j.carbpol.2020.117179
297. Chen L, Huang G. Antioxidant activities of sulfated pumpkin polysaccharides. *Int J Biol Macromol.* 2019;126:743–746. doi:10.1016/j.ijbiomac.2018.12.261
298. Xie J-H, Wang Z-J, Shen M-Y, et al. Sulfated modification, characterization and antioxidant activities of polysaccharide from *Cyclocarya paliurus*. *Food Hydrocoll.* 2016;53:7–15. doi:10.1016/j.foodhyd.2015.02.018
299. Chen L, Huang G. Antioxidant activities of phosphorylated pumpkin polysaccharide. *Int J Biol Macromol.* 2019;125:256–261. doi:10.1016/j.ijbiomac.2018.12.069
300. Xiong X, Huang G, Huang H. The antioxidant activities of phosphorylated polysaccharide from native ginseng. *Int J Biol Macromol.* 2019;126:842–845. doi:10.1016/j.ijbiomac.2018.12.266
301. Chen J, Huang G. Antioxidant activities of garlic polysaccharide and its phosphorylated derivative. *Int J Biol Macromol.* 2019;125:432–435. doi:10.1016/j.ijbiomac.2018.12.073
302. Duan Z, Zhang Y, Zhu C, Wu Y, Du B, Ji H. Structural characterization of phosphorylated *Pleurotus ostreatus* polysaccharide and its hepatoprotective effect on carbon tetrachloride-induced liver injury in mice. *Int J Biol Macromol.* 2020;162:533–547. doi:10.1016/j.ijbiomac.2020.06.107
303. Liu Y, Huang G. The antioxidant activities of carboxymethylated cushaw polysaccharide. *Int J Biol Macromol.* 2019;121:666–670. doi:10.1016/j.ijbiomac.2018.10.108
304. Li YT, Chen BJ, Wu WD, et al. Antioxidant and antimicrobial evaluation of carboxymethylated and hydroxamated degraded polysaccharides from *Sargassum fusiforme*. *Int J Biol Macromol.* 2018;118(Pt B):1550–1557. doi:10.1016/j.ijbiomac.2018.06.196
305. Shi MJ, Wei X, Xu J, et al. Carboxymethylated degraded polysaccharides from *Enteromorpha prolifera*: preparation and in vitro antioxidant activity. *Food Chem.* 2017;215:76–83. doi:10.1016/j.foodchem.2016.07.151
306. Wen S, Li Y, Xu C, et al. The Relationship Between Computerized Face and Tongue Image Segmentation and Metabolic Parameters in Patients with Type 2 Diabetes Based on Machine Learning. *Diabetes Metab Syndrome Obes.* 2024;17:4049–4068. doi:10.2147/DMSO.S491897

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