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REVIEW

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

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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 Chines 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 opposite (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

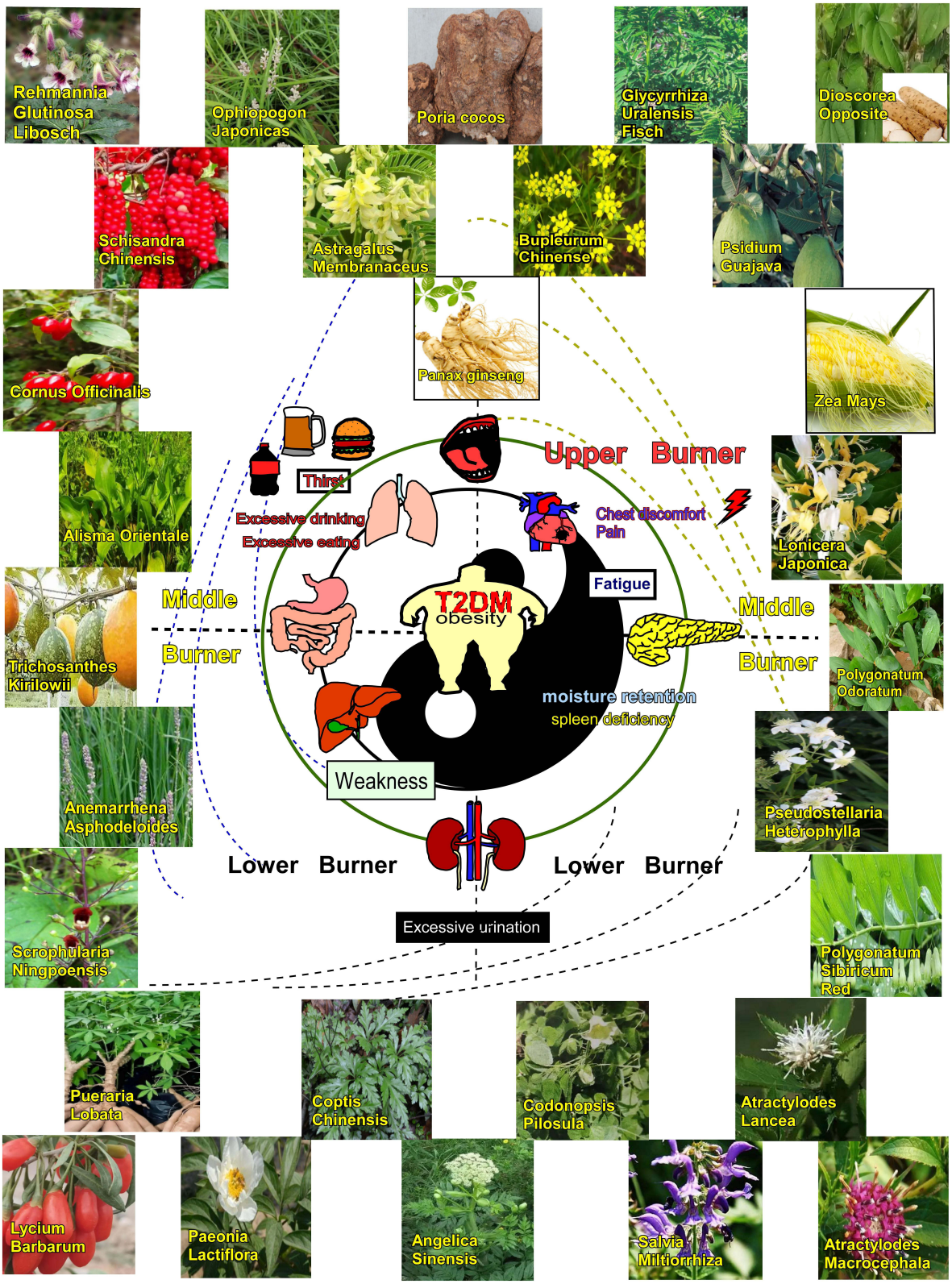

Figure 1 The most referenced TCM herbs to treat T2DM which were also known as the "XiaoKe" syndrome, classically characterized by the symptoms belongs to "Three Burns" - also termed as "Three Xiao" or "Three exhausting symptoms". The "Upper Xiao", which is comprised by the organs from "Upper Burner" 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".

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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: siamenoside I, mogroside III, mogroside IV, mogroside V; Triterpenoids such as: catalpol, oleanolic acid, asiatic acid, glycyrrhetinic 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]

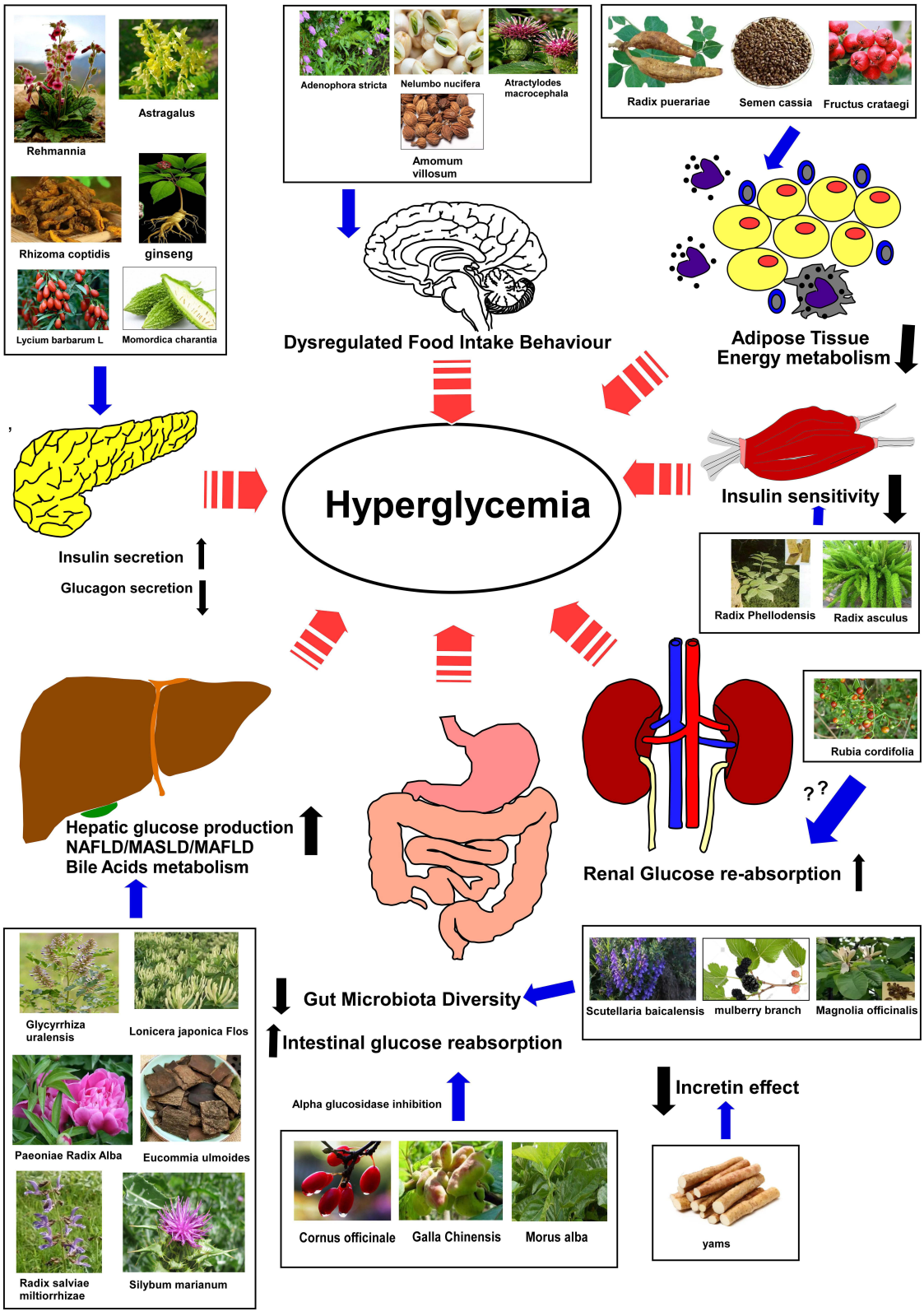

Figure 2 The therapeutic role of TCM herbs in the pathophysiology of T2DM represented as classical "ominous octet" theory proposed by the recipient of Banting Reward Prof. Defronzo based on the major pathophysiology of T2DM and intervention or pharmacological targets: 1) the pathophysiology of pancreas: decreased islet β cell insulin secretion; 2) the increased islet α cell glucagon secretion; 3) the overproduction of hepatic glucose production; 4) the attenuated "incretion 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.

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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-1β, 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-3β; inhibited TGFβ and collagen I expression; inhibited oxidative stress, inflammation, and apoptosis; reduced VEGF expression in retinopathy; and reduced p62/SQSTMI expression. Increased PINK1, Parkin activation, and LC3-II/LC3-I ratio to reduce fine-grained damage. α3β1 integrin deficiency induces adhesion to the glomerular basement membrane, resulting in diabetic nephropathy (DN), NG-R1 improving α3β1 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] Georgi 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 glycyrcholic 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 extracts[38] 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-κB signaling upstream of the NLPR3 inflammatory body and promoting of Nfr2 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-1β, 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 autophage 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, Shenyan Kangfu tablets, Yishenhuashi Granules, Jinshuibao capsules, Huangkui capsules, Cichongyishen granules, Jinlida granules, Uiduqing 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-1β, IL-6 and TNF-α;[56] 2) "Xiexin Decoction" can reduce the expression of inflammatory cytokines in kidney, possibly by regulating the NF-κB 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-κB 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-β1 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 SOC3 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 fibrosisc.[62]

The TGF-β1/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-β1 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-β1 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-β1/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-κB;[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-κB/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-κB 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 studies[80] and Nepeta Angustifolia (C.Y.W) were found to inhibit peroxisase-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, fibril-binding protein, and laminin, and downregulate the expression of TGF-β1.[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-β1/Smad signaling pathway.[93] Schisandra fruit can improve pathological changes in the kidney by down-regulating 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-1α (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 NLPR3 inflammasome activity, thus playing an antifibrotic role.[98,99] Dihydroquercetin, also known as dihydroquercetin, can significantly inhibit ROS and NLPR3 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-κB signaling pathway, thereby improving mitochondrial dysfunction and NLPR3 inflammasome activation.[101] Berberine can inhibit the Toll-like receptor 4 (TLR4)/NF-κB 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 N2rf/HO-1 and NF-κB pathways.[103] Geniposide inhibits NF-κB-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-1α axis, a conserved member of the NAD+-dependent deacetylase family sirtuins.[105] Resveratrol can inhibit gotang-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 α3/β1, and inhibits the Wnt/β-catenin pathway, thus lessening oxidative stress damage and inflammation, delaying the progression of EMT, inhibiting the TGF-β1-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 2α (eIF2α) 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-κB, a linking molecule in the inflammatory pathway mediated by ROS and the NLPR3 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-1β expression and inflammatory pathways.[116] Bergenin can also reduce the production of TGF-β1, down-regulate p-Smad2/3, and promote the expression of Smad7 to alleviate kidney injury;[117] naringenin can inhibit TGF-β1/Smad pathway by up-regulating let-7α of miRNA-let-7 family.[118] Quercetin can inhibit TGF-β1 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-β1, and CTGF levels.[121] Simultaneously, the NF-κB pathway was downregulated. In AGE-treated mouse glomerular endothelial cells (mGECs), catalpol inhibited the RAGE/NF-κBp65/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-κB activation, regulating p38 MAPK and TLR4/MyD88 signaling pathways.[128] Catalpol can also inhibit oxidative stress, inflammation, and pyroptosis through the AMPK/SIRT1/NF-κB pathway[127] via the TGF-β1/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-κB, 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-κB,[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-κB, up-regulate TGR5, regulate the TGR5-B-arrestin2-NF-κB pathway, inhibit ECM aggregation, and can also act on AT1R/CK2/NF-κB, to delay glomerular and renal tubule fibrosis.[160,161]

Oleuropein, derived from whole olive plant or crude gentian, can improve inflammation[162] and injury by acting on the MAPK signaling pathway[163] 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-1α, 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-1β, IL-6, NF-κB, MCP-1, ICAM-1, and VCAM-1.[171] "Tongluo tangning" may block retinal MMP-2/9/13 by acting on the MIP1γ/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 T1MP1-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] ω3 in flaxseed oil alleviates DR and retinal electrical stimulation by inhibiting inflammation and upregulating GPR120 (a receptor for ω3).[185] The ethanol extract of Sannai alleviates retinal inflammation by inhibiting extracellular signal-regulated kinase (ERK1/2) and nuclear transcription factor (NF-κB) signaling pathways.[186] Similarly, Dendrobium chrysotoxum Lindl inhibits the NF-κB 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-κB, thereby improving vascular permeability. P. cuspidatum extract can inhibit the HMGB1-RAGe-NF-κB 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, Lonicerae japonicae 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 PKCβ2 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-κB.[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 eIF2α/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-κB 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 PCβ 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-κB pathway, whereas curcumin interacts with ROS-Akt/mTOR to inhibit inflammatory expression.[216] Gastrodin, Asiatic acid, and paeoniflorin block the TLR4/NF-κB 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 Pl3K/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] Qiying granules showed no significant improvement in DPN symptoms compared to cobamamide 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 mecobalamine 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 mecobalamine did not improve the symptoms better than mecobalamine 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 mecobalamine did not increase significantly. Xuesaitong capsules or injections contained notoginseng saponins and flavonoids. Adding Xuesaitong capsules based on mecobalamine 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 3β (GSK3β) 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-picrohydrazine (DPPH) scavenging test. At the same time, it also has strong activity in 2,2′ -azidine (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 pluviata, 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.

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