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Study on the Mechanism by Which Traditional Chinese Herbal Formulations Improve Insulin Resistance via Regulation of the Gut Microbiota–Adipose Tissue Oxidative Stress–Glucose and Lipid Metabolism Axis

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Abstract: ***Type 2 diabetes mellitus (T2DM), a globally prevalent metabolic disorder, has its core pathological mechanisms—specifically the development and progression of insulin resistance—closely associated with gut microbiota dysbiosis, adipose tissue oxidative stress, and dysregulation of glucose and lipid metabolism. Traditional Chinese herbal compound prescriptions offer unique advantages in ameliorating insulin resistance and preventing or treating T2DM, owing to their multi-target and holistic regulatory properties. This review systematically examines the mechanisms by which traditional Chinese herbal formulas alleviate insulin resistance through three interrelated pathways: modulating gut microbiota composition, inhibiting adipose tissue oxidative stress, and improving glucose and lipid metabolism. Particular emphasis is placed on the regulatory effects of specific compound prescriptions—such as Ge Gen Qin Lian Tang, Huang Qin Tang, and Shou Hui Tong Ban Capsules—and their active constituents on gut microbiota, as well as their comprehensive regulation of insulin signaling pathways via the microbiota-metabolism-immunity axis. Furthermore, this study explores the pharmacological mechanisms by which active components of traditional Chinese medicine, including polysaccharides and flavonoids, restore gut microecological balance, mitigate systemic chronic inflammatory states, and enhance insulin sensitivity, thereby providing a scientific foundation for the clinical application of traditional Chinese medicine in the prevention and treatment of T2DM [1].***

Keywords: Traditional Chinese herbal compound prescriptions, Type 2 diabetes mellitus, Insulin resistance, Gut microbiota, Oxidative stress, Glucose and lipid metabolism**.**

1. Introduction

Type 2 Diabetes Mellitus (T2DM) has become a major global public health challenge. According to statistics from the International Diabetes Federation (IDF), the number of people with diabetes worldwide has been steadily increasing, and it is projected to reach 783 million by 2045. Recent studies have demonstrated that gut microbiota dysbiosis, oxidative stress in adipose tissue, and disturbances in glucose and lipid metabolism [2] are critical factors in the development and progression of insulin resistance.

In traditional Chinese medicine (TCM) theory, type 2 diabetes mellitus (T2DM) falls under the category of "Xiao Ke," and its pathogenesis is primarily associated with dysfunction of the spleen and stomach, internal accumulation of damp-heat, and deficiency of both qi and yin. TCM emphasizes the "holistic approach" and "pattern differentiation and treatment," and has accumulated [3] extensive experience in the prevention and management of T2DM. With advancements in modern pharmacological research technologies, the mechanisms underlying the therapeutic effects of TCM compound prescriptions in treating T2DM have been progressively elucidated; in particular, the discovery of the "TCM–gut microbiota–metabolism axis" has provided a novel perspective for understanding the multi-target actions of TCM.

The gut microbiota serves as an important "virtual organ" in the human body, influencing host metabolic health through multiple pathways, including modulation of energy metabolism, immune responses, and hormone secretion. Studies have demonstrated that patients with type 2 diabetes mellitus (T2DM) exhibit significant dysbiosis of their gut microbiota, characterized by a reduction in beneficial bacteria (e.g., Akkermansia, *Faecalibacterium prausnitzii*, etc.) and an increase in opportunistic pathogens. This microbial imbalance can exacerbate insulin resistance via mechanisms such as disruption of intestinal barrier function, induction of chronic low-grade inflammation, and interference with bile acid metabolism. Concurrently, adipose tissue functions not only as an energy storage organ but also as a critical endocrine organ. In obese individuals, excessive proliferation and hypertrophy of adipose tissue lead to hypoxia and oxidative stress, prompting adipocytes to secrete various pro-inflammatory cytokines (e.g., TNF-α, IL-6, etc.), thereby disrupting insulin signaling pathways. Disruptions in glucose and lipid metabolism directly reflect the metabolic abnormalities observed in T2DM patients, including elevated levels of free fatty acids, increased hepatic glucose output, and reduced muscle glycogen synthesis [4].

The advantage of traditional Chinese medicine (TCM) compound formulations in the treatment of type 2 diabetes mellitus (T2DM) lies in their multi-component, multi-target, and holistic regulatory characteristics. Unlike conventional chemical drugs, which target a single pathway, TCM compound formulations can exert synergistic effects through

multiple mechanisms to comprehensively regulate the body's metabolic balance. This article systematically elucidates the mechanisms by which TCM compound formulations ameliorate insulin resistance from three interrelated perspectives—intestinal microbiota modulation, inhibition of oxidative stress in adipose tissue, and improvement of glucose and lipid metabolism—thereby providing new insights and directions for modern research on the prevention and treatment of T2DM using traditional Chinese medicine [5].

2. 2. Traditional Chinese herbal formulations modulate gut microbiota to ameliorate insulin resistance

The gut microbiota plays a pivotal role in maintaining host metabolic health, and dysbiosis is closely associated with the pathogenesis of insulin resistance. Recent studies have demonstrated that various traditional Chinese medicine (TCM) compound prescriptions can improve insulin sensitivity and glucose metabolic homeostasis by modulating the gut microbiota composition and enriching beneficial microbial taxa. The mechanistic pathways linking gut microbiota to insulin resistance primarily include: reduced production of short-chain fatty acids (SCFAs), compromised intestinal barrier function leading to systemic translocation of endotoxins, and dysregulation of bile acid metabolism. The following sections elaborate on the therapeutic effects of these TCM formulations in this context [6].

2.1 Regulation of Gut Microbiota Composition by Traditional Chinese Medicine Formulations

Shouhui Defecation Capsules (SHTB) represent another typical herbal formulation used to ameliorate type 2 diabetes mellitus (T2DM) by modulating the gut microbiota. A study conducted by the team led by Liu Hongwei at the Institute of Microbiology, Chinese Academy of Sciences, revealed that SHTB is composed of seven traditional Chinese medicinal herbs—Aloe vera, Polygonum multiflorum, Cassia seed, Barbary wolfberry, Atractylodes macrocephala, Citrus aurantium, and Panax ginseng—and contains representative chemical constituents. In diabetic mouse models, SHTB significantly enriches beneficial bacterial populations such as Akkermansia and Parabacteroides; these microbes metabolize branched-chain amino acids (BCAAs) into branched-chain short-chain fatty acids (BSCFAs), thereby alleviating T2DM symptoms by regulating the mTORC1-mediated IRS1/PI3K/AKT insulin signaling pathway. This study is the first to characterize the signature components within this traditional Chinese herbal compound using molecular network analysis techniques and systematically elucidates the complete functional axis of "traditional Chinese medicine – microbiota – metabolites – insulin signaling pathway."

Table 1: Regulatory Effects of Traditional Chinese Medicine Formulas on Intestinal Microbiota in Patients with T2DM or in Model Rodent Animals (Traditional Chinese Medicine Compound Formula: Increase in beneficial bacteria, decrease in harmful bacteria; Mechanism of Action)

Traditional Chinese Medicine Compound Formula	Beneficial bacteria increased	Reduction of harmful bacteria	mechanism of action
Puerariae and Scutellariae and Coptidis Decoction	Faecalibacterium prausnitzii, Akkermansia, Muribaculaceae	Bacilli, Clostridia	Increases butyrate production, reduces inflammation, and improves the intestinal barrier.
Shouhui Laxative Capsules	Akkermansia, Parabacteroides	Not otherwise specified	Metabolizing BCAAs to BSCAAs regulates the IRS1/PI3K/AKT pathway.
Huangqin Decoction	Bifidobacterium, Lactobacillus	Normalization of the ratio between Firmicutes and Bacteroidetes	Upregulation of IRS1/2 and downregulation of SOCS3 improve insulin signal transduction.
Jianpi Sanjing Decoction	Bifidobacterium, Lactobacillus, Clostridium	Yeast, Enterobacteriaceae, Enterococcus	Regulates immune function and alleviates insulin resistance

2.2 Gut Microbiota-derived Metabolites Regulate the Insulin Signaling Pathway

The gut microbiota's role in the metabolic transformation of traditional Chinese medicine (TCM) components is a critical factor in mediating the hypoglycemic effects of TCM. On one hand, the microbiota can convert macromolecular substances — such as polysaccharides and polyphenols—present in TCM into small-molecule active compounds with higher bioavailability; on the other hand, TCM components can modulate the metabolic functions of the microbiota, influencing the synthesis of metabolites—including short-chain fatty acids, bile acids, and branched-chain amino acids—which can directly or indirectly affect the insulin signaling pathway [7].

The Jianpi Sanjing method has also demonstrated a favorable probiotic modulation effect in the treatment of T2DM. A clinical study involving 118 patients revealed that the intestinal colonization by opportunistic pathogens—such as Saccharomyces, Enterobacter, and Enterococcus—was significantly reduced in the Jianpi Sanjing decoction treatment group, whereas the levels of beneficial bacteria — including Bifidobacterium, Lactobacillus, and Clostridium — were significantly elevated. Additionally, immune parameters such as CD3+, CD4+, and the CD4+/CD8+ ratio were improved, and insulin resistance was alleviated. These findings suggest that the Jianpi Sanjing method may influence insulin sensitivity through the "microbiota–immune system" axis. The restoration of intestinal microbiota balance helps regulate immune function and mitigate systemic chronic inflammatory states, thereby reducing insulin resistance [8].

3. Traditional Chinese Medicine Modulates Oxidative Stress in Adipose Tissue to Improve Insulin Resistance

Adipose tissue serves not only as an organ for energy storage but also as an important endocrine organ. In conditions of obesity, excessive adipose tissue proliferation leads to hypoxia and oxidative stress, which in turn trigger chronic inflammatory responses and disrupt insulin signaling. The various active components present in traditional Chinese

medicinal formulations exhibit significant antioxidant and anti-inflammatory properties, enabling them to mitigate oxidative stress in adipose tissue and improve insulin sensitivity [9].

3.1 The Relationship Between Oxidative Stress and Insulin Resistance

Oxidative stress refers to a state in which the production and clearance of reactive oxygen species (ROS) in the body are out of balance, leading to excessive accumulation of ROS. In obesity-associated insulin resistance, adipose tissue serves as an important source of oxidative stress. Lipid droplet accumulation and hypertrophy in adipocytes result in relatively inadequate blood supply, inducing cellular hypoxia, which in turn triggers mitochondrial dysfunction and the generation of large amounts of ROS. Excessive ROS can interfere with insulin signaling through various mechanisms: activating stress kinase pathways (e.g.JNK, p38 MAPK), promoting serine phosphorylation of IRS-1 and reducing its tyrosine phosphorylation capacity; activating inflammatory pathways (e.g., NF-κB), increasing the expression of inflammatory cytokines such as TNF-α and IL-6; and inducing endoplasmic reticulum stress, further exacerbating insulin signaling impairment [10].

3.2 Antioxidant Mechanisms of Active Compounds in Traditional Chinese Medicine

Traditional Chinese medicine is rich in antioxidant compounds such as polyphenols, flavonoids, and saponins; these components can directly scavenge free radicals, activate the endogenous antioxidant system, and mitigate oxidative stress-induced damage. For example, constituents such as scutellaria and berberine in the GeGen QinLian Decoction exhibit significant antioxidant activity. Studies have demonstrated that berberine can activate the Nrf2/ARE antioxidant signaling pathway, upregulate the expression of antioxidant enzymes—including superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px)—and alleviate oxidative stress in adipose tissue [11].

Astragalus polysaccharides and Angelica sinensis polysaccharides exert indirect antioxidant effects by modulating the gut microbiota. Studies have demonstrated that these polysaccharides can promote the growth of beneficial bacteria in the gut, which in turn produce antioxidant metabolites such as butyrate—a type of short-chain fatty acid. Butyrate not only enhances intestinal barrier function but also enters the systemic circulation, thereby alleviating oxidative stress in peripheral tissues, including adipose tissue [12].

Table 2: Regulatory Effects of Active Compounds in Traditional Chinese Medicine on Oxidative Stress in Adipose Tissue

Active ingredient	Traditional Chinese Medicine Source	Antioxidant mechanism	Effects on insulin signaling
Baicalein/Berberine	Puerariae and Scutellariae and Coptidis Decoction	Activates the Nrf2/ARE pathway, upregulating SOD and GSHPx.	Inhibits the JNK pathway and reduces IRS1 serine phosphorylation.
Astragalus polysaccharides	Astragalus mongholicus	Promote the production of butyrate by probiotics and activate the AMPK pathway.	Increase insulin receptor tyrosine phosphorylation
lycium barbarum polysaccharide	gojiberry	Scavenge free radicals and inhibit NADPH oxidase expression	Reduces NF-κB activation and decreases the expression of inflammatory cytokines
ginsenoside	ginseng	Activates the PI3K/Akt pathway and inhibits mitochondrial ROS production.	Promotes GLUT4 translocation and enhances glucose uptake

4. Traditional Chinese Medicine Regulates Glucose and Lipid Metabolism Disorders and Improves Insulin Resistance

Disruption of glucose and lipid metabolism constitutes the core pathological hallmark of type 2 diabetes mellitus (T2DM), manifesting as hyperglycemia, abnormal lipid profiles (elevated free fatty acids, triglyceride accumulation, etc.), and impaired energy metabolism. Traditional Chinese herbal compound formulations can intervene at multiple key nodes of glucose and lipid metabolism, thereby restoring metabolic homeostasis and enhancing insulin sensitivity [13].

4.1 Traditional Chinese Medicine's Regulation of Glucose Metabolism

Traditional Chinese medicine formulations regulate glucose metabolism through multiple organs and key physiological processes: inhibiting glucose absorption at the intestinal level; suppressing gluconeogenesis in the liver; promoting glucose uptake in muscle tissue; and improving glucose transport in adipose tissue.

Multiple active constituents in Puerariae Radix et Gentianae Decoction have been demonstrated to exhibit significant hypoglycemic effects. Among these, puerarin and berberine are the two components that have been most extensively studied. Berberine can inhibit the activity of intestinal α-glucosidase, thereby delaying the digestion and absorption of carbohydrates, and reducing postprandial blood glucose peaks; additionally, berberine can activate AMP-activated protein kinase (AMPK) and suppress the expression of key enzymes involved in hepatic gluconeogenesis (e.g., G6Pase and PEPCK), consequently decreasing hepatic glucose output^4. Puerarin, on the other hand, primarily enhances glucose uptake and utilization in peripheral tissues by promoting the translocation of glucose transporter type 4 (GLUT4) in adipose and skeletal muscle tissues.

A clinical study evaluating the combined use of Huangqin Decoction and metformin in the treatment of type 2 diabetes mellitus (T2DM) demonstrated that adding Huangqin Decoction can further enhance glycemic control efficacy and significantly reduce fasting blood glucose levels, 2-hour postprandial blood glucose levels, and glycated hemoglobin (HbA1c) levels^3. Mechanistic studies indicate that the active components in Huangqin Decoction can upregulate the expression of insulin receptor substrates (IRS-1/2), thereby strengthening insulin signaling; simultaneously, they downregulate negative regulatory factors such as SOCS-3, thereby alleviating the inhibition of insulin signaling [14].

4.2 Regulation of Lipid Metabolism by Traditional Chinese Medicine

Lipid metabolism disorders are a significant driving factor of insulin resistance. Elevated levels of circulating free fatty acids (FFA) can lead to lipotoxicity, inhibit insulin signaling, and induce impaired β-cell function. Traditional Chinese medicine formulations mitigate lipotoxicity by regulating lipid metabolism through multiple pathways [15].

The study on Shouhui Defecation Capsules demonstrated that this formulation can ameliorate insulin resistance by modulating branched-chain amino acid (BCAA) metabolism mediated by the gut microbiota^1. BCAAs (leucine, isoleucine, valine) and their metabolites play an important role in obesity and insulin resistance. Elevated BCAA levels can inhibit insulin signaling by activating the mTORC1 pathway and inducing IRS-1 serine phosphorylation. The SHTB-enriched microbiota metabolizes BCAAs into branched-chain short-chain fatty acids (BSCFAs), thereby reducing BCAA levels; moreover, BSCFAs themselves possess the ability to improve insulin sensitivity.

5. Conclusions

Traditional Chinese medicine (TCM), as a unique healthcare resource in China, holds broad application prospects in the prevention and treatment of type 2 diabetes mellitus (T2DM). Elucidating the mechanistic basis of TCM's therapeutic effects through modern scientific and technological approaches not only facilitates the modernization and internationalization of TCM but also provides novel insights and strategies for the global prevention and management of T2DM.

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