

Research Progress on the Multi-Target Modulation of the Gut-Brain Axis by Traditional Chinese Medicine to Improve Type 2 Diabetes Complicated by Obesity, Based on the ‘Spleen-Stomach–Heart-Mind’ Axis

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Abstract: Type 2 diabetes mellitus complicated by obesity has gradually emerged as a major global public health issue of increasing concern in recent years; its pathogenesis is closely linked to disturbances in energy metabolism within the endocrine system and dysfunction of the gut-brain axis resulting from long-term dietary indiscretion. Although Traditional Chinese Medicine (TCM) does not use this specific term for the condition, its theory of the ‘spleen-stomach–heart-mind’ axis aligns closely with the modern gut-brain axis theory in terms of core pathogenesis and the holistic perspective. This paper systematically proposes, for the first time, the ‘Spleen-Stomach–Mind-Spirit’ axis as a theoretical framework within Traditional Chinese Medicine, elucidating a new research paradigm in which Traditional Chinese Medicine improves T2DM complicated by obesity through multi-targeted, holistic regulation of the gut-brain axis. The paper outlines the theoretical correspondence between the spleen-stomach and mind-spirit system and the gut-brain axis, summarises the therapeutic advantages of numerous classical Chinese herbal formulae, and elucidates the mechanisms by which TCM improves glucose and lipid metabolism disorders through multi-target regulation. It also outlines future research directions for the multi-component, multi-network and holistic regulation of metabolic diseases by TCM, aiming to provide new theoretical foundations and research approaches for the integrated prevention and treatment of diabetes mellitus complicated by obesity using both Chinese and Western medicine.

Keywords: Spleen-Stomach–Mind Axis, Gut-Brain Axis, Type 2 diabetes, Obesity, Traditional Chinese Medicine.

1. Introduction

Type 2 diabetes is a common chronic condition characterised by persistently high blood glucose levels, and develops from a state of impaired glucose regulation (IGR) [1]. Patients often present with relatively insufficient endogenous insulin secretion. This insulin deficiency is caused by a variety of factors; the pathological mechanisms centre on either structural defects in the pancreas itself or a reduced response to insulin by target cells—such as muscle, fat and liver cells—leading to decreased sensitivity, which ultimately results in a chronic syndrome characterised by disturbances in carbohydrate and lipid metabolism. Type 2 diabetes is the most common form of diabetes among patients in China, accounting for over 90 per cent of cases [2]. As the Chinese population becomes increasingly overweight, the risk of developing type 2 diabetes mellitus (T2DM) is also rising, and the two are positively correlated [3]. In recent years, a large body of research has shown that type 2 diabetes is associated with rising levels of obesity, and the prevalence of newly diagnosed diabetes has consequently shown a significant upward trend. According to a 2013 report by the International Diabetes Federation (IDF), the total number of people with diabetes in the Chinese adult population stands at 92.4 million, with 85 per cent of those with type 2 diabetes (T2DM) suffering from varying degrees of obesity; over the past decade, the prevalence of diabetes among obese and overweight individuals has doubled [4]. “Diabetes and obesity influence each other; obesity leads to an increase in

circulating factors (FFA and LEP), which contribute to the development of hyperglycaemia” [5]. This results in a vicious cycle of pathological conditions; this complex metabolic disorder is closely associated with a significantly increased risk of a range of serious complications, such as cardiovascular disease [6]. In numerous previous data surveys, it has been found that, among patients with type 2 diabetes, those who are obese are at a higher risk than their non-obese counterparts of developing conditions such as hypertension and hyperlipidaemia, as well as macrovascular and microvascular complications and lesions affecting various organs. Consequently, the incidence of serious complications—and indeed the risk of disability—is significantly higher among obese patients, severely impacting their quality of life, mental health, physical functioning and even their lives.

The comorbidity of type 2 diabetes and obesity has gradually become a major public health issue in the field of modern medicine [7]. In the treatment of diabetes complicated by obesity, some traditional hypoglycaemic and weight-loss drugs previously used often come with a range of significant side effects; at the same time, certain drugs face limitations in efficacy during clinical application. Consequently, the field of clinical medicine is facing a bottleneck in their use. A wealth of research evidence indicates that the gut-brain axis is a bidirectional regulatory system linking intestinal function with the central nervous system, serving as a bridge through which the brain and gut ‘communicate’. This bridge regulates digestion, absorption, energy metabolism and inflammatory

responses within the body, maintaining glucose homeostasis, whilst also profoundly influencing psychological processes such as mood and cognition. As a key mechanism and central component of energy metabolism within the endocrine system, the gut-brain axis has emerged as a new therapeutic target for the treatment of type 2 diabetes complicated by obesity.

In traditional Chinese medicine theory, based on concepts such as the ‘holistic approach’ and the ‘interrelationship between the zang-fu organs’, there is a profound understanding of type 2 diabetes complicated by obesity. The pathogenesis of this condition is often categorised under terms such as ‘spleen deficiency’, ‘thirst’, ‘phlegm-dampness’ and ‘mental fatigue’. The core pathogenesis lies in the weakness of spleen and stomach function, resulting in impaired transport and transformation, which in turn generates phlegm-dampness and transforms into stasis and turbidity. This internal stasis and turbidity ascends to disturb the clear orifices and agitate the mind, ultimately forming a vicious cycle of ‘spleen-stomach–mind’ functional dysfunction. This pathological process is consistent with the ‘gut-brain axis’ theory in modern medicine, which posits that a series of immune and inflammatory responses caused by intestinal dysfunction ultimately lead to neuroendocrine and metabolic disorders, as well as central nervous system complications.

Based on the above, combined with the latest research advances in recent years, this review innovatively proposes the “Spleen-Stomach-Heart Spirit Axis” as a traditional Chinese medicine theoretical lens for the modern gut-brain axis. It reviews the research progress on multi-target regulation of intestinal flora by traditional Chinese medicine via the gut-brain axis for the prevention and treatment of type 2 diabetes mellitus combined with obesity, so as to provide novel ideas for the treatment and subsequent clinical mechanistic research of T2DM complicated with obesity, and open up new avenues for the integrated Chinese and Western medicine prevention and treatment of metabolic diseases.

2. The Theoretical Coupling and Scientific Implications of the ‘Spleen-Stomach – Heart-Mind’ Axis and the Gut-Brain Axis

2.1 The Significance of the ‘Spleen-Stomach–Heart-Mind’ Axis in Traditional Chinese Medicine

The Spleen-Stomach–Heart-Mind Axis is a mechanism, based on the fundamental theories of Traditional Chinese Medicine, in which the spleen and stomach serve as the central axis and the heart-mind acts as the guiding force, thereby facilitating mutual communication between the spleen-stomach and the heart-mind.

2.1.1 The Spleen and Stomach as the Pivot:

The spleen and stomach form the foundation of postnatal vitality. The spleen governs the transformation and transport of fluids and dampness, as well as the essence of food and drink. In Traditional Chinese Medicine, the functions of the ‘spleen’ encompass the role of the digestive system — including the pancreas, the small and large intestines—and even extend to the autonomic nervous system and endocrine and immune regulation; it is thus a functional complex

centred on digestion and absorption, energy conversion, blood formation, and fluid metabolism. The Stomach is responsible for receiving and digesting food; this corresponds to the mechanisms of digestion, absorption and fluid metabolism as explained by modern medicine. The Spleen and Stomach digest and absorb nutrients within the body, regulate the homeostasis of the gut microbiota, and participate in the body’s energy metabolism.

2.1.2 The Mind and Spirit as the Commander:

‘The heart governs the spirit’; the mind and spirit govern mental activities, intellect, consciousness and the physiological functions of the internal organs. As the source of the generation of qi and blood, the spleen and stomach are essential for the normal functioning of the mind and spirit, which depend on being nourished by sufficient qi and blood generated by the spleen and stomach; only when qi and blood are abundant can the mind and spirit be properly nourished and remain at peace.

2.1.3 The spleen and stomach are interconnected with the mind via the meridian pathways:

‘The Foot Taiyin Spleen Meridian, its branch [8], ..., flows into the heart’; the branch of the Spleen Meridian ultimately flows into the heart. From this, it can be seen that the spleen and stomach are interconnected with the mind through the course of the meridians. In Traditional Chinese Medicine theory, the spleen and stomach are situated in the middle jiao of the human body and serve as the pivotal point for the ascending and descending movements of qi; the spleen and stomach are also interconnected with the mind through these movements of qi. When the ascending and descending functions of the spleen and stomach are disrupted—with clear qi failing to rise and turbid qi failing to descend—the spleen loses its ability to transport and transform, giving rise to phlegm-dampness. This dampness and turbidity then obscure the clear orifices, disturbing the mind, resulting in spleen deficiency and mental decline, which manifest as insomnia, anxiety, mental fatigue, forgetfulness and other emotional disturbances. Conversely, as the brain is the seat of the primordial spirit, prolonged excessive worry depletes spleen qi, leading to poor appetite, abdominal distension, loss of appetite and a sensation of fullness and oppression in the chest and epigastrium; this exemplifies the classical TCM theory that ‘excessive thinking injures the spleen’. The *Lingshu: Five Transformations* states: ‘When anger arises, qi rises in reverse; heat accumulates in the chest and transforms into heat; heat consumes the skin and flesh, hence causing xiaoke’ [9], clearly indicating that mental disturbance and the upward reversal of anger can induce xiaoke.

2.2 The Theoretical Implications of the Gut-Brain Axis

In modern medicine, the gut-brain axis refers to the interaction between the gut and the brain, forming a complex bidirectional regulatory network that connects the brain and the gut. Signalling occurs via the vagus nerve pathway, endocrine signals related to gut hormones, cytokine-mediated immune signals, and bioactive metabolites secreted by gut microbiota. The mechanism of action of this bidirectional communication system indicates that gut health closely

influences brain functions such as mood, cognition and behaviour, whilst brain activity, in turn, modulates gut functions such as digestion and immunity.

The gut microbiota serves as the source of signals for the gut-brain axis and is a key initiating factor in the onset and progression of type 2 diabetes complicated by obesity. An imbalance in the gut microbiota leads to damage to the intestinal barrier, a decrease in the expression of tight junction proteins in the intestinal epithelium, and an abnormal increase in the permeability of the intestinal mucosa, thereby resulting in leaky gut. Lipopolysaccharides (LPS), a component of the cell walls of Gram-negative bacteria, subsequently leak in large quantities into the bloodstream through the compromised barrier, triggering metabolic endotoxemia. LPS binds to the TLR4 receptor on the surface of immune cells, activating the NF- κ B signalling pathway, which prompts macrophages and adipocytes to release large amounts of pro-inflammatory factors such as tumour necrosis factor and interleukins, thereby inducing a chronic, low-grade inflammatory response. Inflammatory factors inhibit insulin signalling via multiple pathways, reducing insulin receptor sensitivity, thereby diminishing the efficacy of insulin action and leading to insulin resistance. The vagus nerve acts as a 'physical bridge' between the gut and the brain. Neurons within the gut can detect signals such as gut microbiota metabolites and lipopolysaccharides, transmitting information regarding metabolic dysregulation to the central nervous system [10], triggering an inflammatory response in the central nervous system. This leads to disruption of appetite regulation, causing fat accumulation in the body and inducing insulin resistance.

2.3 Points of Convergence with the Modern Gut-brain Axis Theory

In Traditional Chinese Medicine (TCM), the functions of the spleen and stomach correspond to aspects of modern medicine such as the intestinal barrier, digestion and absorption, and the gut microbiota. The functions of the heart and mind in TCM correspond to modern medical concepts of brain cognition, emotional regulation, and the control of the appetite centre.

The vagus nerve, acting as a 'physical bridge' between the gut and the brain, bears a striking resemblance to the Ren Meridian, the Spleen and Stomach Meridians, and the Heart Meridian in Traditional Chinese Medicine in terms of its anatomical course, bidirectional transmission function, and regulation of internal organs. Numerous modern medical studies have confirmed that stimulating acupoints such as Zusanli (ST36), Zhongwan (CV12), Tianshu (ST25), Shenmen (HT7) and Neiguan (PC6) can activate the vagus nerve, increase its tone, and thereby regulate the gut microbiota, repair the intestinal barrier, reduce inflammation in the central nervous system, and consequently modulate insulin resistance.

Spleen deficiency gives rise to dampness; the accumulation of dampness forms phlegm; phlegm and blood stasis become intertwined; and when stagnation persists, it transforms into heat. This progression of pathogenesis in Traditional Chinese Medicine reflects an imbalance in the gut microbiota, damage to the intestinal barrier, the entry of LPS into the bloodstream,

and the subsequent accumulation of inflammatory factors, which damage the pancreas and nerves. Persistent, low-grade systemic inflammation further exacerbates this pathological process. Beneficial metabolites produced by the microbiota, such as short-chain fatty acids—referred to as 'clear yang'—provide nutrition, anti-inflammatory effects and neuroprotection. They represent, at a microscopic level, the process by which the essence of food and drink is transported upwards to the heart and lungs to nourish the mind. Harmful metabolites, known as 'turbid yin', disrupt metabolic balance; they symbolise how bodily waste products can obstruct the flow of qi, disturb the mind. Harmful metabolic by-products and waste in the gut must be promptly eliminated to maintain a clean internal environment.

3. Classic Traditional Chinese Medicine Formulations for Regulating the 'Spleen-Stomach-Heart-Mind' Axis

Numerous classic formulations substantially regulate the gut-brain axis through mechanisms such as harmonising the spleen and stomach, resolving phlegm and opening the orifices, and clearing the heart and calming the mind.

3.1 Banxia Xiexin Decoction – Gastrointestinal Disharmony with Mixed Symptoms of Cold and Heat

Banxia Xiexin Decoction is a well-known classical prescription derived from the ancient medical monograph *Treatise on Febrile Diseases*, consists of Pinellia, Coptis, Scutellaria, Dried Ginger, Ginseng, Jujube and Fried Licorice. The formula as a whole works to harmonise cold and heat, utilising pungent properties to disperse and bitter properties to descend, whilst combining tonification and purgation. It can significantly improve clinical conditions characterised by gastrointestinal disharmony and a mixture of cold and heat in patients with diabetes complicated by obesity. Modern pharmacological and clinical studies have confirmed that Banxia Xiexin Decoction can effectively regulate blood glucose and gastrointestinal hormone levels, improve dysbiosis of the gut microbiota [11], increase beneficial bacteria, inhibit harmful bacteria, strengthen the intestinal barrier, upregulate the expression of tight junction proteins (such as ZO-1), repair 'leaky gut', and reduce the entry of endotoxins (LPS) into the bloodstream, thereby treating symptoms of gastroparesis in diabetic patients. Han Xinyao et al. [12] found that Banxia Xiexin Decoction can upregulate the level of autophagy in pancreatic β -cells by activating the SIRT6/CAV1 signalling pathway, thereby restoring islet function in T2DM mice, promoting lipid metabolism, and exerting a therapeutic effect on T2DM. Through the aforementioned mechanisms, Banxia Xiexin Decoction can effectively reduce low-grade inflammation in diabetic patients, as chronic inflammation is a key factor in the development of insulin resistance and nerve damage. By 'cleansing the gut' to 'clear the mind', it improves central insulin signalling and emotional well-being.

3.2 Huanglian Wendan Decoction for Excessive Internal Phlegm-Heat Syndrome

Huanglian Wendan Decoction is modified from Wendan Decoction, an ancient prescription recorded in *Essential*

Prescriptions Worth a Thousand Gold. It consists of Coptidis Rhizoma, Pinelliae Rhizoma, Citri Reticulatae Pericarpium, Poria Cocos, Bambusae Caulis in Taeniam, Aurantii Fructus Immaturus, Glycyrrhizae Radix et Rhizoma and Zingiberis Rhizoma Recens. The original formula treats syndromes of disharmony between gallbladder and stomach disturbed by internal phlegm-heat, such as restlessness and insomnia, chest distress, bitter taste in mouth and nausea. This decoction markedly alleviates symptoms of obese type 2 diabetes mellitus with excessive internal phlegm-heat syndrome. Berberine, the monarch ingredient extracted from Coptidis Rhizoma, acts as a natural AMPK activator with definite hypoglycemic and weight-losing effects. Moreover, berberine suppresses the activity of cholesterol synthetase to reduce cholesterol biosynthesis and lower blood lipid levels [13]. Studies have validated that BBR competitively inhibits 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) activity and upregulates the expression of cholesterol reverse transport proteins ABCA1 and ABCG1, thereby decreasing plasma LDL concentrations [14]. Berberine also exerts vital therapeutic effects on the microbiota-gut-brain axis: it remodels intestinal flora and elevates the abundance of short-chain fatty acid (SCFA)-producing bacteria. SCFAs (e.g., butyrate) exert anti-inflammatory effects, preserve intestinal barrier integrity, cross the blood-brain barrier to regulate cerebral appetite centers and hypothalamic function, and further improve insulin sensitivity as well as emotional and cognitive conditions, which perfectly reflects the TCM theory of “clearing intestinal heat to calm the spirit”. Li and Kang et al. [15] conducted an experiment on 32 T2DM model mice. After six weeks of berberine intervention, pathological lesions including disordered hepatocyte arrangement and lipid vacuolation in liver tissues were obviously alleviated in the high-dose group. The results confirmed that high-dose berberine significantly reduced serum ceramide levels in model mice ($P<0.05$), so as to reverse insulin resistance effectively.

3.3 Chengqi Decoction: Unblock Fu-Qi to Clear Mind

Da Chengqi Decoction and Xiao Chengqi Decoction are classical herbal formulas recorded in *Treatise on Febrile Diseases*. The prescriptions exert drastic purgation to eliminate heat bind, and are suitable for patients with type 2 diabetes mellitus complicated with severe constipation. Severe constipation leads to massive absorption of intestinal endotoxins and microbial metabolites (such as ammonia and indole), which aggravates hepatic burden and systemic inflammatory level. Based on the “fu-unblocking therapy”, these decoctions can rapidly eliminate intestinal endotoxins and metabolic wastes to cut off the source of inflammation, which embodies the therapeutic principle that “unblocked fu-qi clears disturbed consciousness”. Wang et al. [16] conducted a clinical trial on diabetic patients with constipation. The results showed that the reductions of fasting blood glucose (FBG) and 2-hour postprandial blood glucose (2hPG) in the treatment group were significantly greater than those in the control group, indicating that the adjuvant administration of San Yi Chengqi Decoction can effectively reduce blood glucose in T2DM patients with constipation. Pharmacological studies have demonstrated that anthraquinone components extracted from Rhei Radix et Rhizoma stimulate the intestinal nerve plexus, accelerate

intestinal peristalsis and shorten the retention time of feces in the intestinal tract [17]. Natrii Sulfas produces an osmotic purgative effect by drawing abundant water into the intestinal lumen to soften stool and facilitate defecation [18]. The decoctions should be discontinued once symptoms are relieved and long-term administration is prohibited.

3.4 Shenling Baizhu Powder for Syndrome of Excessive Internal Dampness due to Spleen Deficiency

Shenling Baizhu Powder was first documented in *Prescriptions of the Peaceful Benevolent Dispensary* compiled in the Northern Song Dynasty. This prescription invigorates the spleen and eliminates dampness. It restores intestinal homeostasis by enriching beneficial bacteria such as Bifidobacterium and Lactobacillus, and boosts the production of short-chain fatty acids (SCFAs), thereby ameliorating systemic metabolism and cerebral function. Modern pharmacological studies have verified [19] that Shenling Baizhu Powder suppresses the release of pro-inflammatory cytokines including TNF- α , IL-1 and IL-8, and downregulates the mRNA expression of inflammation-related genes NLRP3, Toll-like receptor 4 and NF- κ B, which further alleviates insulin resistance. Basic researches demonstrate that Shenling Baizhu Powder reduces body weight in patients with obese type 2 diabetes mellitus [20]. It activates the AMPK signaling pathway to regulate lipid and glucose metabolism, thus relieving glycolipid metabolic disorders in obese T2DM patients [21]. Other studies have reported that polysaccharides extracted from Shenling Baizhu Powder alleviate colitis and diarrhea [22,23]. In addition, piperlongumine [24], the active ingredient in this formula, activates the peroxisome proliferator-activated receptor gamma coactivator 1 α (PGC-1 α) pathway and targets mtDNA copy number to effectively enhance mitochondrial function, so as to improve metabolic syndrome.

3.5 Buzhong Yiqi Decoction for Spleen-Stomach Qi Deficiency Syndrome

Buzhong Yiqi Decoction was created by Li Dongyuan and recorded in *Treatise on the Spleen and Stomach*. Its core therapeutic principles are tonifying middle jiao qi, ascending yang and invigorating the spleen. When applied to intervene obese patients with type 2 diabetes mellitus, this decoction exerts comprehensive regulatory effects via multiple targets. Angelicae Sinensis Radix contained in the formula is rich in sucrose and amino acids, which can regulate lipid metabolism, lower blood pressure, boost hematopoietic function, ameliorate insulin resistance and reduce HOMA-IR index [25]. This formula activates qi movement of the spleen and stomach in the middle jiao, alleviating gastroparesis caused by diabetic gastrointestinal neuropathy. It accelerates peristalsis of gastrointestinal smooth muscle and coordinates gastric emptying rhythm, thus relieving digestive disorders such as postprandial abdominal distension and poor appetite. Meanwhile, it modulates innate immunity and chronic inflammatory pathways to suppress low-grade chronic inflammation induced by adipose tissue infiltration, removing the pathological basis of insulin resistance. While resolving phlegm-damp and lipid accumulation caused by dysfunctional transportation and transformation of the spleen and stomach and controlling body weight, the decoction also assists in

stabilizing blood glucose, realizing integrated intervention for the pathogenesis of obesity, gastric motility disorder and insulin resistance.

3.6 Gegen Qinlian Decoction for Intestinal Damp-Heat Syndrome

Gegen Qinlian Decoction was formulated by Zhang Zhongjing and recorded in *Treatise on Febrile Diseases*. The original prescription treats heat-induced diarrhea resulting from improper purgation in Taiyang disease, with typical manifestations including fever and sweating, foul-smelling loose stool, chest and epigastric distress, dry mouth with preference for cold drinks, red tongue covered with yellow greasy coating, and slippery rapid pulse. Clinical researches have expanded its application to endocrine and metabolic diseases in modern medicine, especially for obese patients with type 2 diabetes mellitus differentiated as intestinal damp-heat syndrome in TCM. Apart from elevated blood glucose and abdominal obesity, such patients usually present loose stool or diarrhea, dull abdominal pain, spontaneous and night sweats, dry bitter mouth, excessive appetite and easy hunger, which are highly consistent with the pathogenesis targeted by the original formula. A clinical trial conducted by Zhang et al. [26] verified that combined therapy of Gegen Qinlian Decoction and long-acting insulin achieved more significant reductions in fasting blood glucose, 2-hour postprandial blood glucose and glycated hemoglobin, optimized serum lipid profiles, and brought about a lower incidence of adverse reactions compared with long-acting insulin monotherapy. Puerarin extracted from *Puerariae Radix* promotes insulin secretion and upregulates GLUT-4 gene expression to enhance glucose uptake by stimulating the release of β -endorphin [27]. Furthermore, puerarin activates the Akt pathway related to insulin sensitivity and downregulates the mRNA level of uncoupling protein 2 (UCP2), which inhibits insulin secretion, so as to regulate blood glucose [28]. *Pueraria polysaccharides* exert hypoglycemic and hypolipidemic effects, whose mechanism may be attributed to their antioxidant capacity [29]. Centered on the core pathogenesis of intestinal damp-heat, Gegen Qinlian Decoction takes clearing heat and arresting diarrhea as its fundamental therapeutic method. It firstly regulates intestinal microecology and repairs intestinal mucosal barrier to block LPS-mediated endotoxin inflammation. Secondly, it alleviates insulin resistance by suppressing systemic inflammation to improve obesity and hyperglycemia. Meanwhile, it reduces central neuroinflammation and repairs bidirectional signal transmission of the gut-brain axis, realizing integrated regulation of the “intestine-peripheral metabolism-central nervous system”. This decoction provides definite modern biological mechanism evidence for TCM treatment of obese type 2 diabetes mellitus, and offers a novel gut-brain axis research direction for prescriptions targeting metabolic diseases with intestinal damp-heat syndrome.

3.7 Xuefu Zhuyu Decoction for Turbid Stasis Obstruction Syndrome

Xuefu Zhuyu Decoction, recorded in *Correction on Errors in Medical Works*, specializes in activating blood circulation to dissipate stasis and promoting qi movement to relieve pain, and is indicated for syndromes of qi stagnation and blood

stasis caused by chronic diseases invading collaterals. Patients with type 2 diabetes mellitus combined with obesity usually suffer a prolonged disease course; phlegm-damp and turbid stasis linger in collaterals for a long time, eventually obstructing blood and qi circulation, which highly matches the core pathogenesis of collateral blockage by stasis treated by this decoction. This formula markedly improves systemic and intestinal microcirculation, unclogs stagnated collaterals and optimizes tissue blood supply to guarantee oxygen, blood and nutrient metabolism of systemic nerves and blood vessels, thus alleviating collateral injuries induced by hyperglycemia and hyperlipidemia. Meanwhile, Xuefu Zhuyu Decoction exerts definite anti-fibrosis and tissue remodeling-improving pharmacological effects. It relieves vascular sclerosis and microcirculation disorders resulting from ectopic fat deposition, interstitial fibrosis and glycolipid metabolic disturbance, further ameliorating insulin resistance and suppressing low-grade chronic inflammation. Through multi-target regulation on unbalanced glycolipid metabolism, it is suitable for comprehensive intervention and disease progression control in obese type 2 diabetes mellitus patients with collateral blood stasis syndrome. Numerous clinical studies have verified that Xuefu Zhuyu Decoction can regulate abnormal glycolipid metabolism. Xiong [30] conducted a randomized controlled trial including 86 subjects with non-proliferative diabetic retinopathy. The results demonstrated that after 4 months of modified Xuefu Zhuyu Decoction combined with standardized hypoglycemic therapy, the observation group obtained obviously decreased levels of fasting blood glucose, glycated hemoglobin, total cholesterol and triglyceride compared with the routine hypoglycemic monotherapy group, indicating that combined intervention with this decoction can effectively regulate glycolipid metabolism in diabetic patients. Wu et al. [31] carried out a clinical study, which revealed that compared with metformin monotherapy, combined treatment of Xuefu Zhuyu Decoction and Erchen Decoction significantly reduced fasting blood glucose, improved body mass index and elevated total clinical effective rate in obese type 2 diabetes mellitus patients ($P < 0.05$). In summary, multiple clinical trials have proven that this formula can lower blood glucose, blood lipid and body mass index, and its curative effect is superior when combined with western hypoglycemic drugs.

4. Multi-Target Regulatory Mechanisms of TCM on Gut-Brain Axis

Traditional Chinese Medicine exerts multi-dimensional and networked regulation on the gut-brain axis (GBA) relying on the multi-component characteristics of herbal compound prescriptions.

4.1 Target 1: Remodel Intestinal Flora Homeostasis — The Root Therapy for Regulating the Spleen

Herbal active ingredients including polysaccharides (astragalus polysaccharide, poria cocos polysaccharide), alkaloids (berberine) and flavonoids act as prebiotics. They selectively boost the proliferation of beneficial bacteria and suppress conditional pathogenic bacteria, restore the α -diversity and structural balance of gut microbiota, and further improve metabolism at the source.

4.2 Target 2: Restore Intestinal Barrier Integrity — Consolidate the Defensive Barrier of the Spleen

Chinese herbal medicines upregulate the expression of tight junction proteins (Occludin, ZO-1) to reduce intestinal mucosal permeability, repair intestinal leak, effectively block inflammatory mediators such as LPS from entering the circulatory system, and alleviate metabolic endotoxemia.

4.3 Target 3: Regulate Secretion of Gut-Brain Peptides — Modulate Messengers Linking Spleen-Stomach and Mind-Spirit

Herbal ingredients act on intestinal L cells and gastric cells to promote the secretion of anorectic hormones GLP-1 and PYY, while inhibiting the production of orexigenic hormone Ghrelin, thus bidirectionally regulating appetite and energy homeostasis.

4.4 Target 4: Suppress Immune and Inflammatory Responses — Eliminate Pathogens of Phlegm-Damp and Turbid Stasis

Herbal therapy inhibits core inflammatory signaling pathways including NF- κ B and NLRP3 inflammasome, reduces the generation of pro-inflammatory cytokines TNF- α , IL-1 β and IL-6, breaks the vicious cycle of “inflammation-insulin resistance”, protects the blood-brain barrier and alleviates neuroinflammation.

4.5 Target 5: Modulate Central Nervous System Function — Calm the Mind-Spirit

Via the above indirect pathways as well as direct neurotrophic and neuroprotective effects (such as regulating the levels of BDNF and 5-HT), traditional Chinese medicine improves the sensitivity of leptin/insulin signaling in the hypothalamus, modulates the appetite center, and relieves diabetes-related anxiety, depression and cognitive dysfunction.

5. Conclusion

Framed by the TCM theory of the “spleen-stomach and mind-spirit axis”, exploring the multi-target regulatory effects of traditional Chinese medicine on the gut-brain axis for the prevention and treatment of type 2 diabetes mellitus combined with obesity realizes an in-depth dialogue between the wisdom of traditional medicine and cutting-edge modern science. It also provides a holistic and systematic therapeutic strategy to address the therapeutic dilemma of complex metabolic diseases. In the future, the integration of modern scientific technologies and research paradigms will further reveal the underlying mechanisms of traditional Chinese medicine, promote the transformation of integrated Chinese and Western medicine from theoretical research to clinical practice, and ultimately yield pioneering original research achievements.

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