

Review

Research progress in the treatment of an immune system disease—type 1 diabetes—by regulating the intestinal flora with Chinese medicine and food homologous drugs

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Type 1 diabetes (T1D) is a specific autoimmune disease related to genetic and autoimmune factors. Recent studies have found that the intestinal flora is one of the important environmental factors in the development of T1D. The gut microbiota is the largest microbiota in the human body and has a significant impact on material and energy metabolism. Related studies have found that the intestinal floras of T1D patients are unbalanced. Compared with normal patients, the abundance of beneficial bacteria is reduced, and various pathogenic bacteria are significantly increased, affecting the occurrence and development of diabetes. Medicinal and food homologous traditional Chinese medicine (TCM) has a multicomponent, multitarget, and biphasic regulatory effect. Its chemical composition can increase the abundance of beneficial bacteria, improve the diversity of the intestinal flora, reduce blood sugar, and achieve the purpose of preventing and treating T1D by regulating the intestinal flora and its metabolites. Therefore, based on a review of T1D, intestinal flora, and TCM derived from medicine and food, this review describes the relationship between T1D and the intestinal flora, as well as the research progress of TCM interventions for T1D through regulation of the intestinal flora. Medicine and food homologous TCM has certain advantages in treating diabetes and regulating the intestinal flora. It can be seen that there is still great research space and broad development prospects for the treatment of diabetes by regulating the intestinal flora with drug and food homologous TCM.

Key words: type 1 diabetes, intestinal flora, mechanism, traditional Chinese medicine with same origin as medicine and food, beneficial bacteria

INTRODUCTION

Type 1 diabetes (T1D) is a specific autoimmune disease related to genetic and autoimmune factors. According to the latest statistics of the International Alliance for Diabetes, the incidence rate of T1D is on the rise year by year worldwide. There are about 1.1 million children and adolescents (0–19 years old) suffering from diabetes, and more than 50% of them have not been diagnosed with diabetes [1]. T1D is the main disease of childhood diabetes, and its pathogenesis is not yet clear. It is mainly caused by genetic and environmental factors. At present, the treatment methods for T1D include lifestyle intervention, local insulin injection, and oral hypoglycemic drugs. However, the main group of T1DM patients is adolescents and children, and blood sugar usually fluctuates in this group, as it is usually poorly controlled through diet and exercise. In addition, long-term use of insulin

can cause a series of side effects, such as obesity, hypoglycemia, hyperinsulinemia, and injection site pain. Importantly, it can also lead to unhealthy psychology in adolescent patients [2]. Traditional Chinese medicine (TCM) has the advantages of low toxicity and adverse reactions, as well as mild effects. The idea that “medicine and food are homologous” has a long history and is a concept introduced by TCM [3, 4]. This is because our ancestors believed that TCM and food were interwoven. This is mainly due to the common root causes for which TCM products and food, which may bring multiple health benefits if combined, are used [4]. Nowadays, the concept of homology between medicine and food has gradually been accepted by the public. A large number of experiments have proved that TCM, which is derived from medicine and food, has a significant positive role in the treatment of T1D. These experimental results show that the TCM derived from food and medicine can effectively reduce the level of blood

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sugar and increase the secretion and sensitivity of insulin, thereby alleviating the symptoms of T1D [5]. Some studies have found that intestinal ecological imbalance is related to T1D [6]. The metabolites secreted by gut microbiota can regulate immune responses and slow down the development of T1D [7, 8]. In particular, the potential pathogenesis of T1D may occur via the reduction of pathogenic bacteria and the increase of probiotics. It can be seen that drug interventions targeting gut microbiota will provide new strategies for disease prevention. This article elaborates on the relationship between T1D and gut microbiota based on analysis of T1D, gut microbiota, and medicinal and food homologous TCM, as well as the research progress of TCM interventions for T1D via regulation of gut microbiota.

EXPLANATION OF T1D BY TRADITIONAL CHINESE AND WESTERN MEDICINE AND THE TREATMENT CONCEPT OF HOMOLOGOUS MEDICINE AND FOOD

Mechanism of Western medicine in the treatment of T1D

Diabetes mellitus (DM) is a metabolic disease with elevated blood sugar levels. Diabetes can lead to a variety of complications, including ischemic heart disease, peripheral vascular disease, cerebrovascular disease and other cardiovascular diseases, as well as retinopathy, nephropathy, neuropathy, and other diseases [9]. As shown in Fig. 1, diabetes can be divided into T1D, type 2 diabetes (T2D), gestational diabetes (GDM), and specific types of diabetes (American diabetes Association 2017) [10]. T1D is an autoimmune disease mainly mediated by effector T cells, which are activated by autoantigens, leading to islet destruction and insulin deficiency [11]. Western medicine usually adopts comprehensive measures, such as dietary control, moderate exercise, medication interventions, and blood pressure and lipid management to treat and prevent complications. During this period, there will inevitably be some treatment deficiencies

and side effects, such as the poor effect of Western medicine in regulating overall body function. Many patients taking increasing doses and types of hypoglycemic drugs can prolong their condition, easily damage the liver and kidneys, and develop drug resistance, toxic side effects, and various complications [12]. Compared with Western medicine treatment, TCM treatment can improve the structural composition of intestinal microbiota and balance gray energy supply and demand and have the advantages of small side effects and strong safety and control [13].

Understanding and treatment concept of Xiao Ke disease in TCM

In TCM, DM belongs to the category of disease called “*Xiao Ke*” [14]. The meaning of the word *Xiao Ke* focuses on the word “*Xiao*”. *Xiao* refers to the function of the spleen and stomach “*Xiaoshuigu*” under normal conditions, as well as to the abnormal hyperactivity of the function under pathological conditions, resulting in thirst, which is also called “*Xiao Ke*”. In a broad sense, *Xiao Ke* disease is equivalent to diabetes, diabetes insipidus, mental polydipsia, polyuria, and other diseases in modern medicine. The main causes of diabetes include eating inappropriately, heat accumulation and injury yin, insufficient endowment, asthenia of five viscera, emotional depression, excessive will hurt, exertion internal injury, two qi of dryness and dampness, and six exogenous causes. In addition, there is also the pathogenesis of diabetes, including spleen dysfunction, deficiency of vital energy, phlegm, and blood stasis [15].

Under the influence of the abovementioned causes, phlegm and dampness form directly or indirectly in the body, causing massive depletion of the patient’s fluids. The deficiency of yin and fluid in the body makes it difficult to moisten the tendons and internal organs. This results in a deficiency of both qi and yin, causing the person to urinate more frequently, consume more food when eating, and drink more when thirsty. Therefore, the disease is both symptomatic and real, with dry heat as the symptom and yin

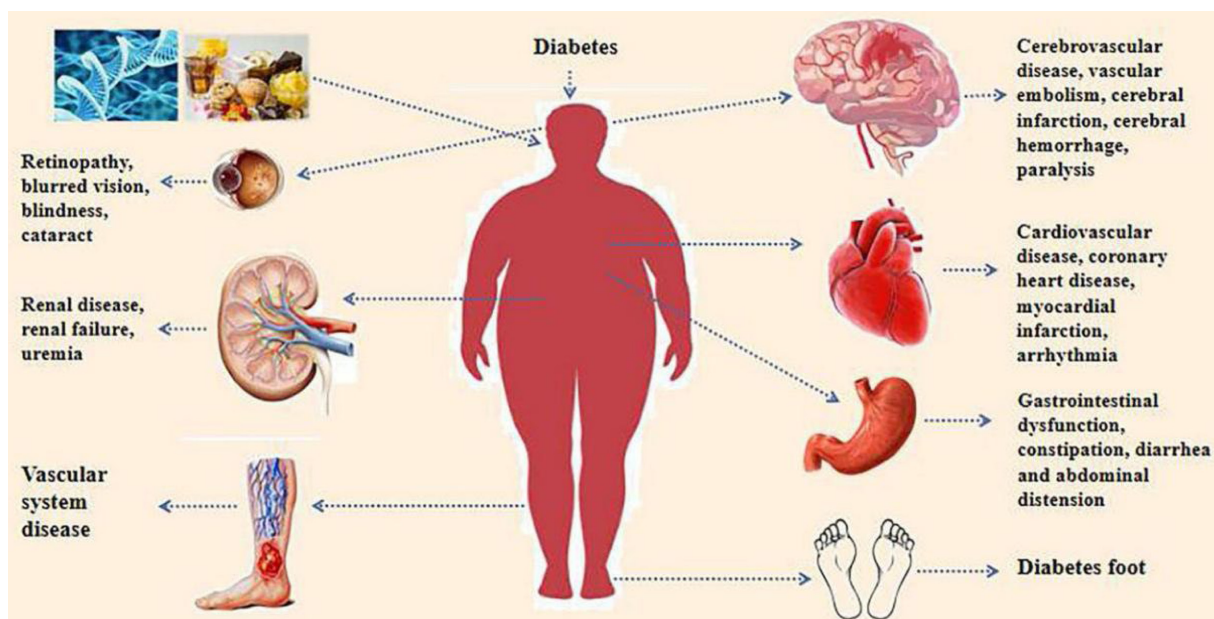


Fig. 1. Complications caused by diabetes.

deficiency as the basis. The clinical principles of TCM treatment are to nourish yin and clear heat, invigorate blood, and remove dampness and phlegm [16]. Diabetes has been treated using TCM for thousands of years. It focuses on regulation of the patient's overall body functions and makes full use of the characteristics of TCM, such as mild and long-lasting therapeutic effects, fewer toxic side effects, and lower chance of produce producing drug resistance, thus providing the key to prevention and treatment of diabetes.

Concept of homology between medicine and food

Traditional herbal therapies with multifunctional nutrients, known as “medicinal food homology”, have developed from ancient treatment systems [17, 18]. This concept can be traced back to 475–221 BC, and the “*Huangdi Neijing*” is China's first medical theory monograph that collected many dietary remedies. In 500 AD, food therapy entered an important stage. At that time, the medical expert Sun Simiao wrote a book called “Thousand Golden Prescriptions”, which was a monograph on “dietary therapy”. The book systematically expounded the theory of dietary therapy for the first time and comprehensively elaborated on how to combine food and drugs to treat diseases. Therefore, from a development perspective, Chinese food and medicine were homologous in ancient times [17]. In addition to the ability to treat specific diseases, TCM with the same origin as medicine and food is also widely used for disease prevention due to its easy inclusion in our daily diets [19]. The concept of medicinal and food homologous TCM is shown in Fig. 2. Nowadays, the viewpoint of “medicine and food are of the same origin” has deeply rooted in people's hearts.

HUMAN BODY AND INTESTINAL FLORA

Overall relationship between the human body and intestinal flora

TCM believes that the various parts of the human body are organically connected; that is, the human body is an organic whole [20]. As a relatively complete medical system, TCM is based on several theories, including the theory of yin and yang, the theory of five elements (five elements), the theory of visceral states (*zang fu*), and the meridian system (referred to as meridians) [21]. It advocates maintaining the coordination and balance of the functions of various organs and systems in the human body, including the gut microbiota. The human gut microbiota is a rich microecosystem [22] that has developed together with its host through the process of evolution. TCM improves the body's metabolism and immune function by regulating the gut microbiota. The gut microbiota can trigger the pharmacological activity or reduce the toxicity of drugs by regulating metabolism, thereby enabling TCM formulations to achieve the best therapeutic effect [23].

Overview of intestinal flora

In the human digestive system, there are many symbiotic microorganisms, approximately 10^{14} germs and about 1,000 bacterial species [24], which are collectively referred to as the “intestinal microbiota” [25]. Also known as the “second genome of the human body” [26], the intestinal microbiota is crucial for maintaining the integrity of the intestinal mucosal barrier function, absorbing nutrients, and regulating energy. The intestinal flora is mainly composed of 99% bacteria, as well as a small number of archaea, fungi, viruses, and protozoa [27]. These bacteria, which can be divided into beneficial bacteria, harmful bacteria, and

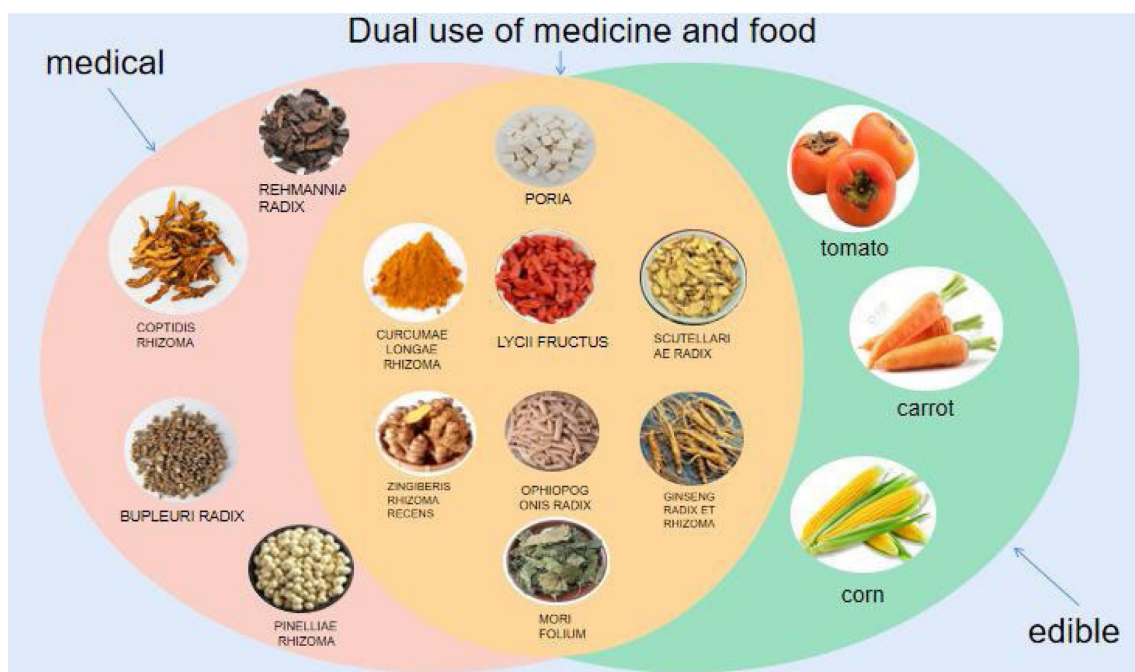


Fig. 2. Concept of homology between medicine and food.

Pink: medicinal herbs; Blue: food; Orange: traditional Chinese medicine with the same origin as medicine and food.

neutral bacteria according to their functions, compete and restrict each other and maintain an average dynamic balance in healthy individuals [28–32]. Beneficial bacteria account for 30% of them, and they can promote intestinal peristalsis, excrete harmful substances, and prevent the invasion of pathogens, such as lactic acid bacteria and *Pasteurella*. Harmful bacteria account for 10% of them and can produce harmful substances. They can also increase the reabsorption of harmful substances in the intestines, resulting in slow intestinal peristalsis and colonization by pathogenic bacteria easier, such as *Staphylococcus* and *Clostridium tetani*. Finally, neutral bacteria account for 60% of them and are also known as conditional pathogenic bacteria. They are beneficial to health under normal conditions, but when their proliferation is out of control, they are invasive and harmful to the human body. They include bacteria such as *Escherichia coli*, *Enterococcus*, and *Candida albicans*. The main physiological functions of the intestinal microbiota are as follows: (1) It maintains the integrity and position of the gastrointestinal tract, including maintaining the protein structure and resisting pathogens. (2) It regulates immune and inflammatory responses. The intestinal microbiota not only regulates host immunity by producing a variety of metabolites but also regulates its cellular components, such as lipopolysaccharide (LPS), lipoteichoic acid (LTA), peptidoglycan, flagellin, and DNA. It can also participate in the immune pathways of the body by preventing the colonization of pathogens in the intestine, regulating the inflammatory state, activating the complement bypass pathway, neutralizing metabolic waste, and other functions. (3) It regulates metabolism, mainly by helping to decompose plant polysaccharides and resistant starch. It also produces metabolites, such as short-chain fatty acids (SCFAs), to provide various vitamins and essential amino acids to the body and reduces the accumulation of body toxins [33–35]. As shown in Table 1. The human intestinal flora undergoes a dynamic colonization and development process at different stages of life, and its composition is affected by anatomical location, time, and personal health status [36, 37]. The gene pool of the microbial inhabitants is considerably diverse and almost 100 times larger than the gene pool of the host. Intestinal microorganisms contribute functional genes and metabolites that affect host metabolism, immunity, and endocrine and other physiological

processes. Therefore, it is increasingly recognized as a necessary and critical factor for maintaining health [38].

RELATIONSHIP BETWEEN INTESTINAL FLORA IMBALANCE AND DISEASES

In most cases, gut bacteria thrive in a dynamically balanced environment that is rather stable [39]. By occupying and competing for nutrients in bacterial membrane barriers, *Bifidobacterium* spp., for instance, can prevent the colonization and proliferation of harmful bacteria, preserving human health. By secreting rhodobactin, *Lactobacillus* can prevent enterohemorrhagic *E. coli*, *Salmonella*, *Shigella*, and *Vibrio cholerae* [40]. Once this equilibrium is upset, dysbiosis will follow, which will cause pathological changes in the host [39]. As shown in Fig. 3, dysbiosis is caused by an imbalance in the type, amount, proportion, and location of gut bacteria. For example, the intestinal flora provides energy for the body and affects fat absorption by regulating enzymes and regulatory factors that play an important role in lipid metabolism. When the intestinal environment changes, the growth of normal bacteria, such as bifidobacteria, lactobacilli, and butyric acid-producing bacteria, is inhibited, while the number of enterobacteria increases, resulting in an imbalance of the intestinal flora. This disorder can lead to abnormal lipid metabolism, which in turn can further aggravate the imbalance of the intestinal flora and form a vicious circle [41, 42]. Other studies have found a close relationship between obesity and gut microbiota imbalance. Intestinal microbiota may obtain energy from the diet and participate in energy metabolism by regulating energy storage, fat generation, and fatty acid oxidation, thereby affecting the development of obesity [43]. Ortega *et al.* [44] pointed out that obesity and T2D have consistent risk factors and pathophysiological mechanisms, among which those of the gut microbiota play a core role in the occurrence of obesity-related T2D.

At the same time, the gut is the largest immune organ in the human body, with a large number of microorganisms coexisting with the host. The immune system and gut microbiota interact and co-evolve to maintain the immune homeostasis of the body. The immune system plays an important role in the formation

Table 1. Functional classification of gut microbiota

	Beneficial bacteria	Neutral bacteria (conditional pathogenic bacteria)	Harmful bacteria
	<i>Bifidobacterium</i>	<i>Escherichia coli</i>	<i>Staphylococcus</i> sp.
	<i>Lactobacillus beijeirinck</i>	<i>Candida albicans</i>	<i>Shigella castellani</i>
	<i>Enterococcus</i>	<i>Enterococcus mundtii</i>	<i>Clostridium perfringen</i>
	<i>Akkermanisa</i>	<i>Bacteroides vulgatus</i>	<i>Pseudomonas aeruginosa</i>
	<i>Coprococcus</i>	<i>Actinomyces</i>	<i>Salmonella minnesota</i>
	<i>Ruminococcus</i>		
	<i>Lactobacillus</i>		
	<i>Bifidobacterium</i>		
	Butyric acid bacteria		
	Pectinolytic bacteria		
	<i>Enterococcus</i>		
	<i>Pseudomonas aeruginosa</i>		
Role	Can promote intestinal peristalsis, excrete harmful substances, and prevent pathogen invasion.	Beneficial to health under normal circumstances. Nevertheless, once proliferation is out of control, they will be invasive and harmful to the human body.	May produce harmful substances. It can increase the reabsorption of harmful substances in the intestinal tract, resulting in slow intestinal peristalsis and vulnerability to pathogenic bacteria.

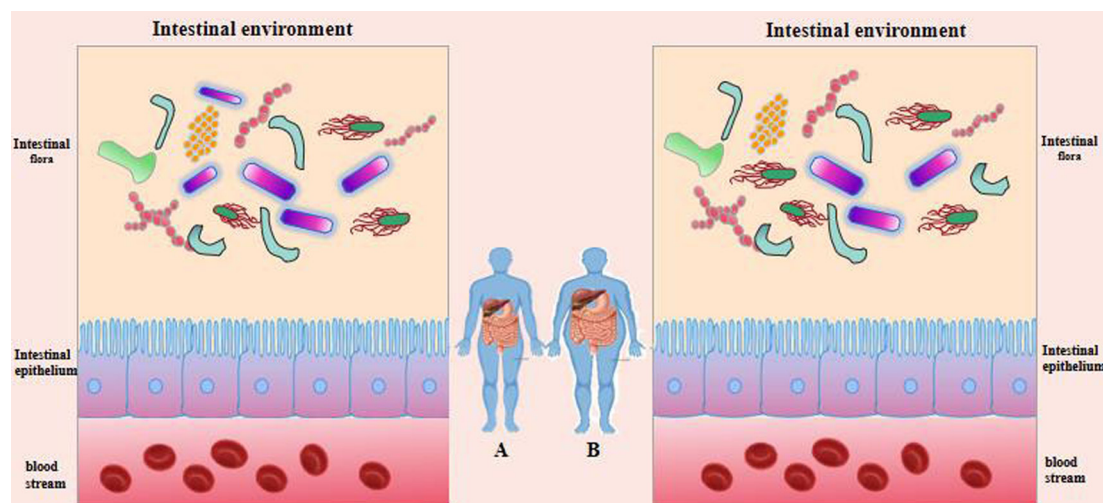


Fig. 3. Distribution of intestinal flora in healthy people and diabetes patients.

Purple: beneficial bacteria, Other colors: pathogenic and harmful bacteria (A: healthy people, B: diabetes patients).

and remodeling of gut microbiota [45]. When the homeostasis between microorganisms and the immune system is disrupted, autoimmune diseases may occur. More and more studies have found that gut microbiota disorders are associated with various autoimmune diseases, including inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, allergic asthma, and T1D [46]. In addition, the development of some diseases can lead to imbalances in the gut microbiota, which can also trigger the occurrence of such diseases. For example, in ischemic stroke [47], animal and clinical studies have found that gut microbiota imbalance is an important pathophysiological outcome of ischemic stroke [48, 49]. The imbalance of the intestinal flora may be one of the causes of stroke caused by abnormal glucose metabolism, atherosclerosis, and other risk factors [50, 51].

RELATIONSHIP BETWEEN T1D AND IMBALANCE OF THE INTESTINAL FLORA

In populations with certain genetic backgrounds and environmental factors, disruption of microbiota balance can trigger autoimmune diseases [52]. Many studies have found that ecological imbalances are also involved in the pathogenesis of T1D [53]. This means that the onset and development of T1D are jointly driven by genetic susceptibility and environmental factors [54]. These environmental factors are all related to the construction of the gut microbiota during the development of infants and young children. A series of studies have shown an imbalance of the gut microbiota in T1D patients and animal models. Biobreeding diabetes-prone (BBDP) rats (biologically screened diabetes rats) are an important animal model for studying spontaneous diseases of T1D. There are many similarities between diabetes in BBDP rats and human T1D, including gene susceptibility and the impact of environmental factors on the disease. Compared with BBDR (biobreeding diabetes-resistant rat) rats, BBDP rats showed a decrease in *Lactobacillus*, *Bryantella*, *Bifidobacterium*, and *Tubriciber*; while *Bacteroides*, *Eubacterium*, and *Ruminococcus* increased. Consistent with animal experimental results, there are

also differences in the gut microbiota between T1D patients and healthy controls, characterized by a decrease in the Firmicutes/Bacteroidetes ratio and an increase in *Clostridium*, *Bacteroides*, and *Veillonella* [55]. Moreover, the diversity and stability of gut microbiota in T1D patients also decreased. Demirci *et al.* [56] tested the levels of *Bacillus* and Bacteroidetes in 53 fecal samples from T1D patients. The results showed that compared with healthy individuals, the levels of Bacteroidetes in the gut microbiota of T1D patients increased. However, the level of Firmicutes decreased, and the Firmicutes/Bacteroidetes ratio significantly decreased. This indicates that there is an imbalance in the gut microbiota in the body before and after the onset of T1D. Buassoni *et al.* [57] compared the gut microbiota of 31 T1D children and 25 healthy children using 16s RNA sequencing technology. Their results showed that the abundance of *Bacteroides* and *Proteus* increased in children with T1D, while the abundance of *Proteus* decreased. Soyucen *et al.* [58] found that compared with healthy children, the number of bifidobacteria that colonized the intestines of T1D children was decreased, while the number of *C. albicans* and Enterobacteriaceae (excluding *E. coli*) was increased. Huang *et al.* [59] examined the intestinal microbiota in the feces of 12 Han (the main ethnic group in China and representing the vast majority of Chinese) children with T1D and compared it with that in healthy children. They found that the ratio of Bacteroidetes to Firmicutes in the intestinal microbiota of T1D children increased and that the abundance of fecal Bacteroidetes was negatively correlated with HbA1c levels. The abundance of Bacteroidetes was positively correlated with anti-pancreatic island autoantibodies. The above research indicates that intestinal microbiota imbalance is closely related to the onset of T1D. The gut microbiota can metabolize substances in the human diet that are difficult or impossible to digest and absorb and can produce metabolites that can be absorbed by the body, such as SCFAs, among which acetic acid, propionic acid, butyric acid, and their salts occupy a dominant position in the human gut [60, 61].

Sun *et al.* [62] found that compared with healthy controls, non-obese diabetic (NOD) mice showed a decrease in SCFAs,

especially butyric acid. In T1D patients, there is a decrease in butyrate-producing bacteria compared with healthy individuals. Therefore, butyric acid-producing bacteria play an important role in T1D. Butyric acid plays an important role in maintaining tight junctions between intestinal epithelial cells by inducing mucin synthesis, such as affecting the barrier function of the intestinal epithelium. Its function is to limit the content of intestinal contents (water, chyme, intestinal microbiota) and regulate immune responses. Disruption of the integrity of the intestinal epithelium can lead to “gut leakage”, thereby activating Toll-like receptor 4 (TLR4) and participating in the occurrence and development of T1D. From this, it can be concluded that the intestinal epithelial barrier requires a tightly connected cell layer (Fig. 4).

RESEARCH ON THE MECHANISM OF TCM, WHICH HAS THE SAME ORIGIN AS MEDICINE AND FOOD, REGULATING THE INTESTINAL FLORA TO INTERFERE WITH T1D

TCM has a long history of preventing and treating diabetes and has also achieved remarkable results in the field of medical care. In the process of searching for food, ancient sages discovered that various foods and medicines have the same taste and efficacy, and many foods can be used for both medicinal and edible purposes; that is, “medicine and food have the same origin”. Oral administration is the most important mode of administration in TCM. After entering the intestine, TCM inevitably comes into contact and interacts with the gut microbiota [63]. Research found that medicine and food homologous TCM can intervene and treat the development of T1D by regulating the intestinal flora. For example, *Poria cocos*, turmeric, ginger, *Lycium chinense*, *Scutellaria baicalensis*, *Ophiopogon japonicus*, ginseng, mulberry leaves, and other active ingredients of TCM can regulate the composition of the intestinal microbiota, increase beneficial bacteria, improve the intestinal microbiota, and further promote the conversion and utilization of bioactive ingredients of TCM. As shown in Table 2 and Fig. 5, it can be seen that there is a two-way relationship between the intestinal flora and TCM and that the intestinal flora is also a potential target of TCM for diabetes [61, 64].

Poria cocos

The dried sclerotia of the porous fungus *P. cocos* have functions such as beneficial effects on urination, spleen strengthening, and calming the nerves. The bioactive components in *P. cocos* include polysaccharides, triterpenes, fatty acids, sterols, and enzymes [65]. Consumption of *P. cocos* in China has a history of over two thousand years. The “Shennong Materia Medica Classic” states that it “soothes the soul and nourishes the soul for a long time, and does not starve and prolong the year” [66]. As a medicinal and edible homologous herb, *P. cocos* has medicinal tonifying properties but is not harsh, and its main components include triterpenes, polysaccharides, and fatty acids. In their research on the effects of *P. cocos* triterpenoids on intestinal epithelial integrity, scholars have found that *P. cocos* triterpenoids can improve intestinal barrier function [67]. Zhu *et al.* [68] found that *P. cocos* oligosaccharides (PCOs) can reduce blood sugar and insulin levels in high-fat diet (HFD)-induced obese mice. They also alleviated the damage to the gut barrier in HFD-fed mice, partially restored the imbalance of the gut microbiota in

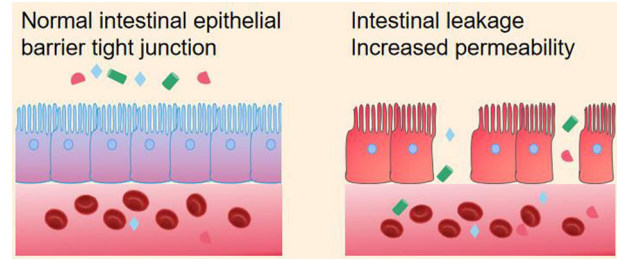


Fig. 4. Comparison of intestinal epithelial barriers.

On the left is the intact intestinal epithelium; on the right is the intestinal epithelium that flows out of the damaged intestinal content.

HFD-fed mice, including bile acid (BA), SCFA, and tryptophan metabolites. In recent years, studies have found that a *P. cocos* extract can treat T1D by regulating the intestinal flora. Liu *et al.* [69] found that after an intervention with a *Poria cocos* extract (PCE), PCOs can promote glucose consumption in Hep G2 cells of T1D model mice, exerting hypoglycemic effects. Triterpenoids can delay cell aging in mice, stimulate insulin secretion from pancreatic islet cells, and exert hypoglycemic effects. After the PCE intervention, the proportion of lactobacilli and rumen bacilli in the intestinal microbiota increased, improving the imbalance of the intestinal microbiota structure in the mice, enhancing immune regulation, inhibiting the development of intestinal inflammation, and thus alleviating progression of the disease. Wu *et al.* [70] found that administration of different extracts from *Poria cocos* effectively improved lipid metabolism in mouse intestinal microbiota dysbiosis models, repaired intestinal barriers, decreased the relative abundance of Firmicutes, and increased the relative abundance of Bacteroidetes, regulating the structure of the intestinal microbiota and increasing potential beneficial bacteria, such as *Lactobacillus*.

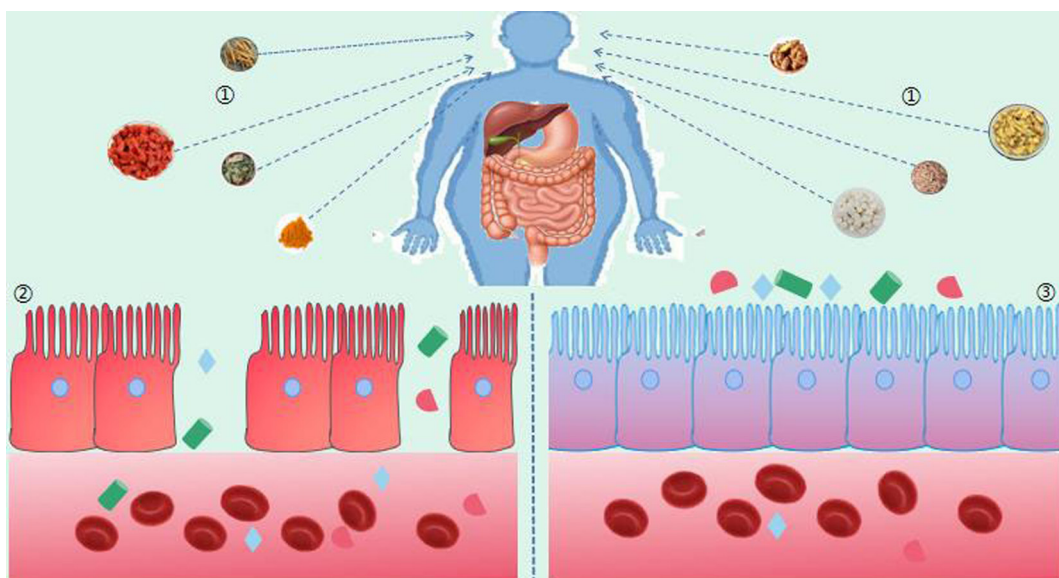
Turmeric

Turmeric is a perennial tuberous herbaceous plant with yellow flowers and wide leaves. It belongs to the ginger family and grows in tropical climates [71, 72]. TCM believes that turmeric is a type of TCM that has the effects of promoting qi and breaking blood, relieving pain through meridians, clearing the heart, and relieving depression [73]. Curcumin is a lipophilic polyphenol substance [74] that accounts for 2–5% of turmeric powder [74]. It has antioxidant, antibacterial, anti-inflammatory, antidiabetic, antiplatelet aggregation, and other characteristics [73, 75–77]. In some experimental animal models of diabetes, oral curcumin can reduce body weight, blood sugar, and glycosylated hemoglobin levels and improve insulin sensitivity. In patients with diabetes, curcumin treatment can reduce HbA1c and fasting blood glucose and improve pancreatic beta cell function. Some studies found that after treatment with curcumin, the abundances of Spirochaetae, Tenericutes, and Elusimicrobia at the phylum level in diabetes patients were significantly reduced. The abundances of Actinobacteria microbiota were significantly increased, with significant increases at the genus level in *Collinsella*, *Streptococcus*, *Sutterella*, *Gemella*, *Thalassospira*, *Gordonibacter*, and *Actinomyces* microbiota [78]. In the study of Liu *et al.* [79], as well as other studies, it was found that the flora structures of the normal control group and curcumin treatment

Table 2. Regulatory effects of medicinal and food homologous traditional Chinese medicine components on intestinal microbiota associated with T1DM (Ginkgo leaf content has been replaced)

Chinese herbal medicinal ingredient	Related Traditional Chinese Medicine	Regulating gut microbiota		Disease indicators
		Increase	Reduce	
Pachyman pachymic acid	Poria cocos	<i>Lactobacillus, Ruminococcus</i>	<i>Bacteroidetes</i>	Reduce blood sugar and induce insulin like growth factor
curcumin	turmeric	<i>Actinobacteria, Collinsella, Streptococcus, Sutterella, Gemella, Thalassospira, Gordonibacter, Actinomyces</i>	<i>Spirochaetae, Tenericutes, Elusimicrobia</i>	The body weight, liver index, blood ALT, LPS, HOMA - IR, intestinal coliform bacteria and the number of beneficial bacteria in the intestinal tract were significantly reduced.
Ginger polysaccharides	ginger	<i>Oscillospira, Adlercreutzia, Akkermansia, Lactobacillus</i>	<i>Prevotella, Oscillospira, Adlercreutzia</i>	Bacteria that produce short chain fatty acids and have anti-inflammatory effects, enhancing intestinal barrier function.
Lycium barbarum polysaccharides	Lycium chinensis	<i>Bacteroides, Ruminococcaceae_UCG-014, Mucispirillum, nestiimonas, Ruminococcaceae_UCG-009</i>	<i>Allobaculum, Dubosiella, Romboutsia</i>	Relieve hyperglycemia and insulin resistance, significantly alter intestinal composition, significantly increase levels of SCFAs, accompanied by an increase in SCFAs production genera
Baicalin	Scutellaria baicalensis	<i>Akkermanisa, Coprococcus, Ruminococcus</i>	<i>Odoribacter, Parabacteroides</i>	Increase the production of SCFAs and improve abnormal glucose and lipid metabolism.
Ophiopogon japonicus polysaccharides	Ophiopogon japonicus	<i>Lactobacillus, Bifidobacterium</i>	<i>Escherichia coli, Streptococcus thermophilus</i>	Improve dietary habits and lower blood sugar
ginsenoside	ginseng	<i>Phylum Firmicutes, Bacteroidetes</i>	<i>Proteobacteria, Actinomycesbovis</i>	Regulating intestinal immunity and promoting the repair of intestinal mucosa.
polysaccharide of mulberry leaves	mulberry leaves	<i>Proteus hauser</i>	<i>Bacteroides vulgatus</i>	Suppress the proliferation of harmful bacteria, restore intestinal function, and lower blood sugar.

ALT: alanine transaminase; LPS: lipopolysaccharide; HOMA: homeostatic model assessment; IR: infrared; SCFAs: short-chain fatty acids.

**Fig. 5.** Treatment of diabetes with TCM with the same origin as medicine and food by regulating the intestinal flora.

(1.TCM with same origin in medicine and food, 2. Intestinal leakage increased permeability, 3. Normal intestinal epithelial barrier tight junction).

group showed low *Chlamydia/Bacteroides* ratios and that the flora compositions and structures were similar. There was also a significantly increased proportion of Melainabacteria in the rectal contents of the diabetes model group, and this increase could be inhibited by curcumin perfusion. Hou *et al.* [80] found that the weight, liver index, and blood alanine transaminase (ALT), LPS, and HOMA-IR of rats fed a high-fat diet were significantly reduced when the rats subjected to a curcumin intervention. The coliform bacteria in the intestinal tract decreased, and the number of beneficial bacteria in the intestinal tract increased. This shows that curcumin can improve the imbalance of the intestinal flora in rats fed a high-fat diet.

Ginger

Ginger is a perennial herbaceous plant belonging to the family Zingiberaceae, order Zingiberales. Its rhizome is thick and branched, and it has a fragrant and spicy taste. It can be used for medicinal purposes, as a cooking ingredient, or in beverages and cosmetics. The Analects of Confucius state, “do not remove ginger food, do not eat too much”, and the Records of Famous Doctors state, “ginger can eliminate wind evil, cold and heat, typhoid fever, headache, nasal congestion... and stop vomiting” [81]. This indicates that since ancient times, ginger has been widely used as a food and medicine homologous material. Ginger polysaccharides are important components in ginger, with various biological activities, such as antioxidant activity [82], immune regulation [83], antitumor activity [84], anticoagulant activity [85], and hypoglycemic activity [86]. Wang *et al.* [87] found that ginger polysaccharide effectively reduced the blood sugar level of diabetic mice, increased the abundances of the beneficial bacteria *Oscillospira*, *Adlercreutzia*, *Akkermansia*, and *Lactobacillus*, and reduced the abundance of the harmful bacteria *Prevotella*. Among them, the genus *Oscillospira* is associated with obesity; *Adlercreutzia* is a bacterium that can produce SCFAs and has anti-inflammatory effects [88]. *Akkermansia* is a kind of mucin-degrading bacteria that colonizes the intestinal mucosa and can enhance the intestinal barrier function. It is negatively related to many diseases, such as obesity and diabetes [89]. *Prevotella* has been proven to induce insulin resistance [90]. To sum up, ginger polysaccharide can change the composition of the intestinal flora in diabetic mice and increase the abundance of relevant beneficial bacteria.

Lycium chinense

Lycium chinense is a member of the Solanaceae family and a famous Chinese herbal medicine with various benefits, including anti-inflammatory effects [91], immune regulatory effects [92], anticancer effects [93], blood sugar and lipid lowering effects [94], and antiaging effects [95]. Its fruit, goji berries, contains abundant endogenous molecules, such as polysaccharides, organic acids, alkaloids, flavonoids, and polyphenols, which are key to its biological effects [96, 97]. Research has shown [98–100] that polysaccharides may help regulate the composition of the gut microbiota and selectively increase the proportion of beneficial bacteria. Polysaccharides are important functional components of goji berries, with biological activities such as metabolism, antioxidant activity, and immune regulation [101]. Some reports suggest that *Lycium barbarum* polysaccharide (LBP) can affect the composition and structure of the gut microbiota [102–105]. Ma *et al.* [106] found that LBP significantly reduced the intake

of food and water in diabetic mice and alleviated hyperglycemia and insulin resistance by increasing the intake and utilization of blood sugar. Significantly altered intestinal composition, reduced *Allobaculum*, *Dubosiella*, and *Romboutsia*, and increased *Bacteroides* and *Ruminococcaceae_UCG-014*, *Mucispirillum*, *Intestinimonas*, and *Ruminococcaceae_UCG-009*. The levels of SCFAs in mice treated with LBP significantly increased, accompanied by an increase in SCFA-producing genera. *L. barbarum* polysaccharides may alleviate hyperglycemia and hyperlipidemia by regulating intestinal microbiota.

Scutellaria baicalensis

S. baicalensis is a commonly used TCM and a perennial herbaceous plant belonging to the *Lamiaceae* family. Its roots are the main part used as medicine. It is widely distributed in China, Japan, South Korea, and Russia [107]. So far, more than 40 compounds have been isolated and identified from *S. baicalensis*, including flavonoids, terpenoids, volatile oils, and polysaccharides. The compounds and extracts isolated from *S. baicalensis* have a wide range of pharmacological activities, including nervous system, immune system, antitumor, antibacterial, antiviral, antioxidant, and other pharmacological effects [108]. Xu [109] measured the effect of an *S. baicalensis* extract on the growth of intestinal flora in normal and diabetes rats by microplate turbidimetry. The results showed that *S. baicalensis* promoted the growth of beneficial *Bifidobacterium* and *Lactobacillus* bacteria and inhibited the growth of harmful bacteria such as *Enterococcus* and *Enterobacteriaceae*. Ju [110] found that a baicalin intervention increased the abundances of *Akkermansia*, *Coprococcus*, and *Ruminococcus* in high-fat model mice, while the abundances of *Odoribacter* and *Parabacteroides* decreased. Baicalin increases the production of SCFAs, indicating that it may improve glucose and lipid metabolism abnormalities caused by a high-fat diet by regulating intestinal microbiota disorder and increasing the production of SCFAs.

Ophiopogon japonicus

O. japonicus is a dry tuber in the lily family. It has a sweet and slightly bitter taste and the functions of generating fluid, moistening the lungs, nourishing yin, and clearing heat. It is mainly used in clinical practice for conditions such as heat damage, restlessness, and thirst [111]. *O. japonicus* is a homogeneous molecular weight β -D-fructan obtained by isolation and purification from *O. japonicus* tubers. It has a certain effect on lowering blood sugar and improving insulin resistance, while also improving and regulating the glucose tolerance and intestinal microbiota of normal mice. Wang *et al.* [112] found that different doses of *O. japonicus* can improve the symptoms of polydipsia and polydipsia in spontaneous diabetic mice. High doses of *O. japonicus* can reduce the fasting blood sugar of diabetic mice, reduce the numbers of *E. coli* and *Streptococcus*, and increase the numbers of lactic acid bacteria and bifidobacteria.

Ginseng

Ginseng is a dried root and rhizome of the genus *Panax*, family *Araliaceae*. It has a long history of application and is an essential medicine for restoring yang, relieving adversity, tonifying qi, and promoting fluid production; tonifying the kidneys and blood; and calming the mind and improving eyesight [113, 114]. Sun *et al.* [115] used 200 mg/kg of white ginseng and red ginseng

water extracts by gavage as an intervention in an HFD-induced diabetes model. They found that white ginseng and red ginseng water extracts could inhibit lipid metabolism disorder and insulin resistance in obese mice. White ginseng and red ginseng water extracts increased the relative abundances of Firmicutes and *Bacteroides*, reduced the relative abundances of Proteobacteria and Actinomycetes, improved the structure of intestinal microbiota, and promoted the growth of probiotics, balancing metabolic processes. Sun *et al.* [116] used an obesity-induced diabetes model and administered 150 mg/kg of a white ginseng extract by gavage for 12 weeks. It was found that the white ginseng extract could regulate liver glucose and lipid metabolism disorder and improve insulin sensitivity. The mechanism may be related to regulation of the intestinal flora by up-regulating acidophilus bacteria. Kim *et al.* [117] found that the glycosyl group of ginsenoside Rg3 stimulated the secretion of glucagon like peptide-1 (GLP-1) by intestinal cells through the sweet taste receptor-mediated signal transduction pathway and showed a strong antihyperglycemic effect in diabetic mice. To sum up, ginseng extract can improve the hyperglycemia level of diabetes by influencing intestinal cell metabolism, protecting the intestinal mucosa and regulating the intestinal flora.

Mulberry Leaves

Mulberry leaf is the dried leaf of the mulberry plant, family *Moraceae*, which is sweet, bitter, and cooling in nature and mainly affects the lung and liver meridians. It is used for dispersing wind-heat, clearing the lungs and moistening dryness, and clearing the liver and brightening the eyes and for wind-heat colds, lung-heat and dry cough, dizziness and headache, and redness and faintness of the eyes [118]. Mulberry leaves are rich in flavonoids and polysaccharide compounds, which can promote the absorption of nutrients in the intestines, thereby improving the intestinal function of the human body. At the same time, mulberry leaves are also rich in a large amount of organic acids, which can alter the intestinal environment and make it acidic. This effectively inhibits the proliferation of harmful bacteria, prevent the imbalance of the gut microbiota, restores normal intestinal function, and enhances the body's ability to absorb nutrients [119]. Chen *et al.* [120] induced intestinal flora imbalance in mice using lincomycin hydrochloride. After 7 days of intragastric administration of 0.6 mg/mL mulberry leaf polysaccharide, 16S rDNA was used as the target sequence for DNA amplification. Denaturation gradient gel electrophoresis (DGGE) and visual image analysis showed that the type and quantity of mouse flora in the mulberry leaf polysaccharide group were significantly increased compared with the natural recovery group but that the flora could not be restored to their original levels. It was proved that mulberry leaf polysaccharide could regulate intestinal flora disorder in mice.

SUMMARY

In summary, a large number of experimental studies have shown that intestinal flora disorders are closely related to the occurrence and development of diabetes. Homologous TCM can improve the symptoms of T1D by regulating the composition of the intestinal flora and increasing the abundances of beneficial bacteria. As the gut microbiota is further studied, the number and mechanisms of diseases caused by microbiota imbalance will

become clearer. In the study of disease prevention and treatment, effective interventions for disease treatment by regulating the balance of the intestinal flora will become an important research direction. In recent years, with the increasing prosperity of TCM health, “medicine comes from food, food with medicine function, medicine with food”, it has been found that some homologous TCM can support the growth of intestinal probiotics and inhibit the proliferation of harmful bacteria, thus maintaining the balance of the intestinal flora, improving the metabolic function of the body, and achieving the purpose of preventing and treating T1D. It is believed that with the deepening of relevant research, the relationship between the intestinal flora and diabetes will become clearer and that this clearer understanding will provide new directions for research and new treatment measures for the prevention and treatment of diabetes and its complications.

DATA AVAILABILITY STATEMENT

Data availability is not applicable to this article as no new data were created or analyzed in this study.

ETHICS APPROVAL

This article is a comprehensive paper and does not require ethical approval.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Yang Ping and Jianing Liu drafted of the manuscript. Huilin Wang and Yan Wang reviewed the previous literature, and Hongbin Qiu and Yu Zhang designed the study and revised the manuscript. All authors contributed to manuscript revision and read and approved the submitted version.

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CONFLICT OF INTEREST

The authors have no relevant financial or non-financial interests to disclose.

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