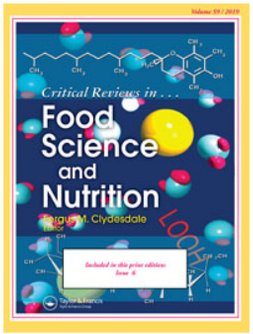

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REVIEW

Dietary compounds and traditional Chinese medicine ameliorate type 2 diabetes by modulating gut microbiota

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ABSTRACT

Diabetes mellitus (DM) and its complications are major public health concerns which strongly influence the quality of humans' life. Modification of gut microbiota has been widely used for the management of diabetes. In this review, the relationship between diabetes and gut microbiota, as well as the effects of different dietary components and traditional Chinese medicine (TCM) on gut microflora are summarized. Dietary compounds and TCM possessing bioactive components (fiber and phytochemicals) first change the composition of gut microbiota (inhibiting pathogens and promoting the beneficial bacteria growth) and then influence the production of their metabolites, which would further modify the intestinal environment through inhibiting the production of detrimental compounds (such as lipopolysaccharide, hydrogen sulfide, indol, etc.). Importantly, metabolites (short chain fatty acids and other bioactive components) fermented/degraded by gut microbiota can target multiple pathways in intestine, liver, pancreas, etc., resulting in the improvement of gut health, glycemic control, lipids profile, insulin resistance and inflammation. Furthermore, understanding the interaction between different dietary components and gut microbiota, as well as underlying mechanisms would help design different diet formula for the management of diabetes. Further researches could focus on the combination of different dietary components for preventing and treating diabetes, based on the principle of "multiple components against multiple targets" from the perspective of gut microbiota.

KEYWORDS

Dietary component; type 2 diabetes; gut microbiota; dietary fiber; polyphenols; melatonin; traditional Chinese medicine

1. Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from the defects in insulin secretion and/or insulin action (American Diabetes Association 2003). Diabetes caused profound psychological and physical distress to patients and is related to several severe complications, which has obtained a major concern worldwide and is a leading cause of death in most countries (Nanditha et al. 2016; Zimmet et al. 2014). According to the statistics of the International Diabetes Federation, more than 450 million people (aged from 18 to 99) suffer from diabetes worldwide in 2017, representing 8.4% of the adult population, and this number is expected to increase to 629 million by 2045 (Cho et al. 2018).

DM can be classified into type 1 diabetes (T1D, destruction of β-cell leading to absolute insulin deficiency), type 2 diabetes (T2D, progressive loss of insulin secretion on the background of insulin resistance), gestational diabetes mellitus (GDM, diabetes diagnosed in the second or third trimester of pregnancy) and specific types of diabetes (such as monogenic diabetes syndromes, drug- or chemical-induced diabetes, etc.) (American Diabetes Association 2017). Among which T2D accounts for more than 90% of patients with diabetes (Chatterjee, Khunti, and Davies 2017). The epidemic of T2D is driven by multiple factors, including obesity, physical inactivity, energy-dense diets and genetic factors, etc., which may interact with each other and with the environment. Over the past few decades, humans' lifestyle around the world has changed greatly, a reduced physical activity level and increased animal food consumption and dietary fat intake are now more favorable (Choi et al. 2006; Franks and Poveda 2017; Imamura et al. 2015). Incidence of T2D was positively related to these unhealthy lifestyles, especially the unhealthy diet (diet rich in red meat, sugary desserts, fast foods, high-fat foods and refined grains, etc.), indicating that dietary factors plays a crucial role in the onset and progression of T2D (Hu, Satija, and Manson 2015; Pan et al. 2011; Zhao et al. 2018).

The human gut microbiota is a lush microbial ecosystem with about 10^{14} bacteria belonging to 1000 species, which is tenfold of human somatic and germ cells (Qin et al. 2010). The gut microbiota has evolutionarily co-developed with the host which provides the microbes a stable environment to exert their functions (such as digestion of complex dietary macronutrients, production of small molecules, and maintenance of the immune system). Emerging researches have

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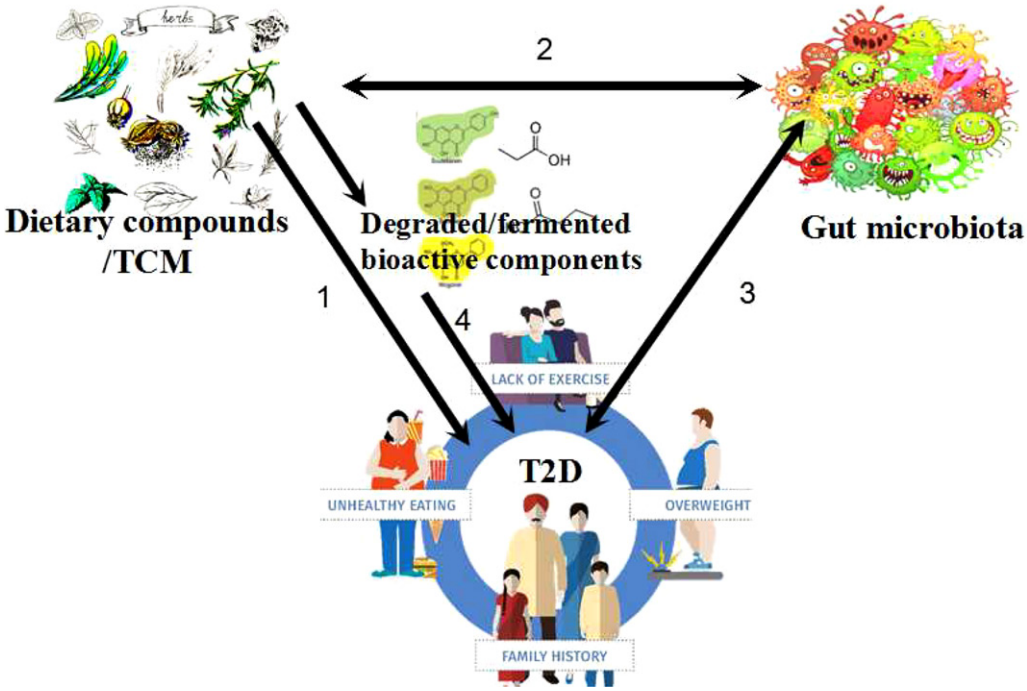

Figure 1. The triangle relationships between dietary compounds/TCM, gut microbiota and T2D. 1. Bioactive components (flavonoids, alkaloids, phenolic acids, etc.) presented in diet/TCM can directly improve T2D. 2. Intake of some dietary compounds (fiber, polyphenols, etc.) and TCM could improve the composition of gut microbiota, and gut microbiota fermented/degraded these materials to generated bioactive components. 3. Improved gut health by modification of gut microbiota related to ameliorating T2D. 4. The generated bioactive components by gut microbiota generally have greater absorption and bioactivity than their precursors, reaching the blood circulation to exert anti-diabetic effects.

demonstrated that perturbations of gut microbiota has the ability to influence the development of diabetes (Nicholson et al. 2012; Tai, Wong, and Wen 2015). Multiple host genetic and environmental factors (including host genome, age, sex, geographic location, pathological conditions, pharmacological treatments and daily diet) could shape the compositional and functional patterns of the gut microbiota (Nie, Luo, and Lin 2018). Among them, diet is one of the most important factors that determine composition of gut microbiota (diet changes could explain 57% of the total structural variation in gut microbiota) (Carmody et al. 2015; Zhang et al. 2010). The aim of this review is to illustrate the links (the triangle relationships, Figure 1) between T2D, dietary components/TCM, and gut microbiota, which may help design different diet formula for the management of T2D and/or its complications based on improvement of gut microbiota.

2. Gut microbiota and T2D

The mammalian intestine is populated by billions of bacteria which mainly belong to the phyla of *Firmicutes* (Gram-positive, 60–65%), *Bacteroidetes* (Gram-negative, 20–25%), *Proteobacteria* (Gram-negative, 5–10%) and *Actinobacteria* (Gram-positive, 3%) (Rosenbaum, Knight, and Leibel 2015). Gut microbiota is involved in host metabolism, immune and inflammation because of its role in the performance of related functions. Aberrant gut microbiota composition was found in the onset and progression of T2D, but the results were varied among different studies because different factors (such as ethnic and dietary habit, geographical location, disease status, as well as different sequencing techniques used) all play part in low reproducibility of the results from genomics. Nonetheless, Patients with T2D exhibited a moderate intestinal dysbiosis characterized especially by reduced abundance of butyrate-producing bacteria (*Clostridiales* sp. SS3/4, *Faecalibacterium prausnitzii*, *Eubacterium rectale*, *Roseburia intestinalis*, etc.), and the increased concentrations of certain *Lactobacillus* species and some opportunistic pathogens, such as *Desulfovibrio* sp. and *Clostridium* (Qin et al. 2012; Sato et al. 2014). Furthermore, the ratio of the major phyla *Firmicutes*/*Bacteroidetes* in patients with T2D was also varied in different studies (Sircana et al. 2018).

Akkermansia muciniphila is a mucin-degrading bacterium residing in the intestinal mucus layer. The Gram-negative bacterium constitutes 3–5% of the gut's microbiota and its abundance are inversely correlated with the overweight and diabetes (Tilg and Moschen 2014). Although *Akkermansia* was found enriched in fecal samples of Chinese T2D patients (Qin, et al. 2012), a number of studies have recently demonstrated that *Akkermansia* might play a key role in the integrity of the mucous layer and has the potential to improve inflammation, glucose tolerance, dyslipidaemia, insulin resistance and offer protection against the development of T2D (Roshanravan et al. 2017; Zhang et al. 2013). This discrepancy may be a result of differences in study design, methodology, and population characteristics such as ethnicity, age and dietary pattern. In addition, results from animal studies found that the increase of *Akkermansia* (direct administration or induced by metformin treatment) could prevent obesity, insulin resistance, and improve glucose homeostasis (Everard et al. 2013; Org et al. 2015; Shin et al. 2014), indicating that the modulation of the *Akkermansia* may have beneficial effects on T2D.

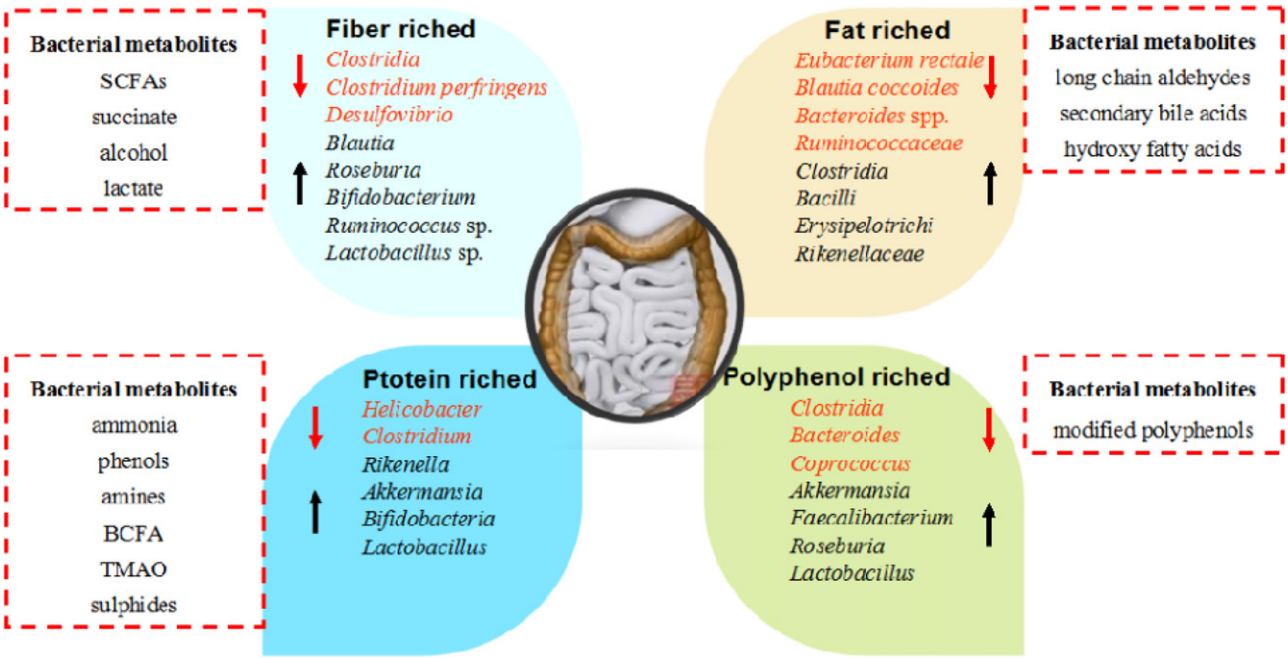

Figure 2. Interaction between diet and gut microbiota.

3. Interaction between diet and gut microbiota

The interaction between gut microbiota and diet had been underestimated until the past decade. Recently numerous studies demonstrated that dietary changes result in substantial and rapid changes in the make-up of the gut microbiota (David et al. 2014; Wen and Duffy 2017; Wu et al. 2011). Microbial enterotypes were closely related to a certain dietary habits for a long period (Lin et al. 2013; Ou et al. 2013). Wu et al. (2011) found that high *Bacteroides* associated with high protein and animal fat intake and high *Prevotella* with complex carbohydrate intake. Although the detectable change of microbiome composition occurred within 24 h of initiating a high-fat/low-fiber or low-fat/high-fiber diet (a controlled-feeding study of 10 subjects), the enterotype remained stable during the 10-day study, indicating that the manipulation of the gut microflora via diet should be long term. In another study, enrichment of *Bacteroidetes* and depletion of *Firmicutes* were found in rural African children (diet rich in fiber), while *Enterobacteriaceae* (*Shigella and Escherichia*) were significantly enriched in European children. Particularly, the genus of *Prevotella* and *Xylanibacter* (contained a set of bacterial genes for cellulose and xylan hydrolysis) were uniquely enriched in rural African children (De Filippo et al. 2010).

Compared with long-term food patterns, dramatic short-term consumption of diets can promote shifts in the microbiota if diets are exclusively composed of animal or plant based foods, and diets rich in fiber increased the abundance of fiber degrading bacteria (*Roseburia*, *Eubacterium rectale*, and *Ruminococcus bromii*) (David et al. 2014). A recent study found that the level of *Prevotella* was increased with the supplementation of barley kernel-based bread (BKB, 3 days) while decreased by white wheat flour bread intake, and BKB consumption improved glucose metabolism in healthy individuals is in association with enrichment of *Prevotella copri* and increased capacity to ferment complex polysaccharides (Kovatcheva-Datchary et al. 2015). Trial of time courses also found a relatively fast alteration in the microbiota following a shift in diet with fiber supplementation (3–4 days, but reverse equally rapidly) (Arora and Bäckhed 2016; Walker et al. 2011).

The host and its gut microbiota coproduce a large number of small molecule metabolites during the metabolism of food and xenobiotics, and many of these metabolites play critical roles in shuttling information between host cells and the host's microbial symbionts (Nicholson et al. 2012). Bacterial metabolites synthesized by gut microbiota are different from its host enzyme metabolites. A large number of dietary compounds were degraded by the gut bacterial community, some of the transformation would selectively enhance the bioactivity of its products. Gut microbiota is particularly enriched in genes encoding enzymes essential for metabolizing several macronutrients (especially dietary polysaccharides), which in turn influences the composition and gene expression of the gut microbiota (Arora and Bäckhed 2016). For example, microbiomes from herbivores were enriched in enzymes that map to biosynthetic reactions for many amino acids and hydrolysis of plant polysaccharides, while the microbiome of carnivores is specially enriched in enzymes that degrade proteins as an energy source (Muegge et al. 2011). Thus, diet drives gut microbiota composition and metabolism, making microbes a link between diet and different physiological states via their capacity to generate microbial metabolites depending on dietary intake (Figure 2) (Banhos Danneskiold-Samsøe et al. 2018; Kashtanova et al. 2016; Senghor et al. 2018).

4. Dietary intervention in T2D

Experimental and clinical studies have shown that targeting gut microbiota might be an effective strategy to prevent and

Table1. Dietary fiber attenuates diabetes by modulation of gut microbiota.

Fibers	Subjects	Indexes for pathological improvement	Gut microbiota-targeted therapy[a]	Therapeutic mechanisms	Reference
Polysaccharide from seeds of *Plantago asiatica* L. (arabinoxylan)	Type 2 diabetic rats	FBG, insulin sensitive, lipids profile, antioxidant capacity	*Alistipes obesi* (↓), *Bacteroides ovatus* (↑), *Bacteroides vulgates* (↑), *Lactobacillus fermentum* (↑), *Prevotella loescheii* (↑)	Increased SCFAs regulate glucose, lipids metabolism and insulin resistance	(Nie et al. 2017)
Pumpkin polysaccharide	Type 2 diabetic rats	FBG, insulin resistance, lipids profile	*Bacteroidetes* (↑), *Prevotella* (↑), *Deltaproteobacteria* (↑), *Oscillospira* (↑), *Veillonellaceae* (↑), *Phascolarctobacterium* (↑), *Sutterella* (↑), *Bilophila* (↑)	Promotion of SCFAs-producing bacterial	(Liu et al. 2018)
Polysaccharide from *Physalis alkekengi var. francheti*	Type 2 diabetic mice	FBG, ALT, AST	*Lactobacillus* (↑), *Clostridium butyricum* (↑), *Bacteroides* (↑), *Enterobacter* (↓)	Amelioration of liver injury by modulation of protein expressions	(Zhao et al. 2017)
Strict vegetarian diet (42 g fiber/day)	Patients with T2D	FBG, HbA1c, lipids profile, BMI, fecal lipocalin-2, total SCFA, acetate, propionate, butyrate	*Firmicutes*/*Bacteroidetes* (↓), *Enterobacteriaceae* (↓), *Bacteroides fragilis* (↑), *Clostridium* (↑)	Fibre intake reduces gut inflammation by changing the gut microbiota	(Kim et al. 2013)
Fiber rich diet (arabinoxylan, β-glucan, cellulose, resistant starch, oligosaccharides, and etc.)	Patients with T2D	FBG, body weight, lipids profile	*Bifidobacterium pseudocatenulatum* (↑), *Faecalibacterium prausnitzii* (↑), *Eubacterium rectal* (↑), *Clostridium leptum* (↑), and etc.	Increased abundance of SCFA-producing bacteria, increased SCFAs promote production of GLP1, PYY and insulin to exert glycemic control	(Zhao et al. 2018)
Inulin	Type 2 diabetic rats	FBG, body weight, lipids profile, insulin resistance	*Bacteroidetes* (↑), *Lactobacillus* (↑), *Lachnospiraceae* (↑), *Phascolarctobacterium* (↑), *Bacteroides* (↑), *Firmicutes* (↓), *Desulfovibrio* (↓), Firmicutes/Bacteroidetes (↓)	Increased serum GLP-1 to reduce IL-6 secretion and suppress hepatic gluconeogenesis, and then improved insulin tolerance	(Zhang et al. 2018)
oligofructose	Type 2 diabetic rats	Body weight, plasma endotoxin, IL-1α, IL-6	*Bifidobacterium* spp. (↑), *Enterobacteriaceae* (↓)	Modulated gut microbiota contributes to improvement of endotoxaemia and inflammation in diabetes	(Cani et al. 2007)
Galacto-oligosaccharides	Patients with T2D	No significant improvement of clinical parameters was found	*Firmicutes* (↓), *Lachnospiraceae* (↓), *Erysipelotrichaceae* (↓), *Porphyromonadaceae* (↓), *Actinobacteria* (↑), *Bifidobacteriaceae* (↑)	Although glycemic control was not found, GOS can ameliorate dysbiosis in patients with diabetes	(Gonai et al. 2017)
Xylo-oligosaccharide	Prediabetic adults	Tend to reduce OGTT 2-h insulin levels	*Blautia hydrogenotrophica* (↑), *Enterorhabdus* (↓), *Slackia* (↓), *Howardella* (↓), *Clostridia* (↓), *Streptococcaceae* (↓), *Subdoligranulum* (↓)	Reversed changes in the gut microbiota during the development of diabetes	(Yang et al. 2015)

[a]Compared with model group.

manage T2D. A number of studies found that the intake of dietary components (fiber, polyphenols, herbal components, etc.) was associated with the improvement of T2D, which may be related to improved gut health and fermented/degraded microbial metabolites.

4.1. Dietary fiber

Dietary fiber is defined as non-digestible carbohydrates (with 3 or more monomeric units) presented inherently in plants, and also includes isolated or synthetic fibers with physiological benefits for human health (Food and Drug Administration, HHS 2016). A number of prospective cohort studies have shown that persons with a relatively high intake of dietary fiber were inversely associated with the risk of diabetes compared with a low intake (Alessa et al. 2015; Chiu et al. 2018; InterAct Consortium 2015). Majority of dietary fiber belongs to prebiotics with anti-digestion and anti-absorption capacity, which basically retains intact passing through the upper gastrointestinal tract and is mainly fermented by colonic microbiota, selectively stimulating the growth and activity of one or more potential beneficial bacteria in the colon (Flesch, Poziomyck, and Damin 2014; Kim, Keogh, and Clifton 2018). Human gut microbiota were reported to encode four types of

carbohydrate-active enzymes, including glycoside hydrolases, polysaccharide lyases, glycosyltransferases and carbohydrate esterases, based on their functional roles (El et al. 2013). These enzymes synergistically degrade crude, untreated plant biomass, and the generated low molecular weight metabolites (degradation products) may exert anti-diabetic effects in T2D. In addition, dietary fiber can act in the small intestine in three main physical forms: as soluble polymer chains in solution, as insoluble macromolecular assemblies, and as swollen, hydrated, sponge-like networks (Eastwood and Morris 1992). Consequently, fiber intake directly improves postprandial glucose and insulin response by both slowing sugar absorption and causing a bulking effect in the stomach, and the added satiety results in the reduction of energy intake (Chambers, McCrickerd, and Yeomans 2015; Howarth, Saltzman, and Roberts 2001). So dietary fiber may exert anti-diabetic effects based on their gastrointestinal functions. Table 1 provides some examples of different dietary fiber, which could attenuate diabetes by modulating gut microbiota.

4.1.1. Polysaccharides

Administration of polysaccharides was found to be associated with the shift of gut microbiota in diabetic animals (Nie et al. 2017; Wang et al. 2016) and improved metabolic markers and insulin sensitivity in diabetic patients (Zhao et al. 2018). More recently, it was found that the intake of polysaccharide from *Plantago asiatica* L. increased the levels of colon *Bacteroides ovatus*, *Bacteroides vulgates*, *Lactobacillus fermentum* and *Prevotella loescheii*, and decreased the level of *Alistipes obesi* (a species isolated from the feces of a morbidly obese individual) in diabetic rats. The concentrations of fecal SCFAs and serum insulin sensitivity were also significantly increased simultaneously (Nie et al. 2017). Similarly, treatment of *Maydis stigma* polysaccharide was also found to restore the intestinal microflora balance in type 2 diabetic rats (especially enriched the number of *Lactobacillus* and *Bacteroides*) (Wang et al. 2016). Yan et al. (2017) found that oral administration of polysaccharide from *Polygonatum kingianum* (PSPK) prevented the increase of FBG and decreased portal vein endotoxin LPS in type 2 diabetic rats. PSPK treatment changed the composition of gut microbiota by decreasing the abundances of *Bacteroidetes* and *Proteobacteria*, and increasing that of *Firmicutes* in phylum level, and enriched the number of *Ruminococcaceae* family and *Ruminococcus* genus simultaneously. Pumpkin polysaccharide alleviated T2D by improving the insulin tolerance, serum glucose and lipids profile, which also enriched large SCFA-producing species, such as *Bacteroidetes*, *Prevotella*, *Deltaproteobacteria*, *Oscillospira*, *Veillonellaceae*, *Phascolarctobacterium*, *Sutterella*, and *Bilophila* (Liu et al. 2018).

A few clinical trials reported anti-diabetic effects of polysaccharide based on the improvement of gut microbiota. Patients with T2D are characterized by reduced SCFAs and its related producing bacteria. A new randomized controlled trial found that the supplementation with dietary fiber (rich in polysaccharide) increased the abundance of SCFA-producing bacteria, which in turn normalized the levels of HbA1c via an increase in the production of glucagon-like peptide- 1 (GLP-1) in patients with T2D (Zhao et al. 2018). The high-fiber diet increased the abundance of 15 strains that belong to phyla of *Firmicutes*, *Actinobacteria* and *Proteobacteria*. The 15 positive responders harbored genes for acetate and butyrate production. Especially the *Bifidobacterium pseudocatenulatum* strain C95 was found to be negatively associated with the obesity-related parameters (body weight, body fat, FBG, insulin resistance, etc.) and increase the production of cecum acetate. Furthermore, the promotion of these positive responders diminished the producers of metabolically detrimental compounds (indole and hydrogen sulfide), resulting in the healthier gut ecosystem. These results suggested that, treatment with polysaccharide could alleviate T2D by its regulation role on the gut microbiota.

4.1.2. Oligosaccharides

Short-chain non-digestible dietary fiber (fructo-oligosaccharides, galacto-oligosaccharides, xylo-oligosaccharides, raffinose, etc.) are the quintessential prebiotics and the targeted bacterial groups are typically *Bifidobacterium* and *Lactobacillus*. Compared with polysaccharides with high molecular weight, oligosaccharides fermentation may particularly sustain *Bifidobacterium* growth and promote the SCFAs production (such as xylo-oligosaccharide and xylo-polysaccharide, rhamnogalacturonan I polysaccharide and its galactose-rich oligosaccharides) (Ho et al. 2018; Khodaei et al. 2016). Chitosan oligosaccharides (COS) can improve insulin resistance and glucose metabolism in diabetic mice, as well as reverse the dysbiosis of gut microbiota by promoting *Akkermansia* and suppressing *Helicobacter* (Zheng et al. 2018). Gobinath et al. (2010) found that both of fructo-oligosaccharides and xylo-oligosaccharides exerted favorable influences in diabetic rats by improving body weight, antioxidant capacity and reducing hyperglycemia and cholesterol, and both oligosaccharides increased *Bifidobacteria* and *Lactobacilli* population in the cecum. Cani et al. (2007) examined the prebiotics effects of the oligofructose in diabetic mice. The results suggested that treatment with oligofructose increased the abundance of *Bifidobacterium* spp. and decreased the number of *Enterobacteriaceae*. And *Bifidobacterium* spp. was also found to be significantly and positively correlated with glucose tolerance, glucose-induced insulin secretion and inflammatory tone (decrease of endotoxaemia, plasma and adipose tissue proinflammatory cytokines). Inulin (one type of non-digestible oligosaccharides) treatment also increased the abundance of *Lactobacillus* and SCFA-producing bacteria (*Lachnospiraceae*, *Phascolarctobacterium*, and *Bacteroides*), and decreased the number of LPS-producing bacteria (*Desulfovibrio*) in type 2 diabetic rats (Zhang et al. 2018).

However, improvement of glycemic control and insulin sensitivity by oligosaccharides seems to be very limited in clinical trials (Kim et al. 2018; Pedersen et al. 2016; Yang et al. 2015). Although treatment with galacto-oligosaccharides for 4 weeks (10 g/d) did not improve glucose tolerance

in patients with T2D, the aberrant microbiota composition was ameliorated to some extent. *Firmicutes* was decreased and *Actinobacteria* was increased in phylum level, *Lachnospiraceae, Erysipelotrichaceae* and *Porphyromonadaceae* were decreased and *Bifidobacteriaceae* was increased greatly at family level (Gonai et al. 2017). In another pilot study, xylo-oligosaccharide (XOS) treatment significantly decreased the abundance of *Howardella*, *Enterorhabdus*, and *Slackia* in prediabetic adults (these bacteria were increased in prediabetic adults compared with healthy adults), and increased the abundance of *Blautia hydrogenotrophica*. In addition, intake of XOS also exhibited the inhibitory effect on some opportunistic pathogens, including *Clostridia*, *Streptococcaceae*, and *Subdoligranulum*, suggesting that XOS can potentially reduce the risk of T2D by promoting the optimal gut microbiota profile (Yang et al. 2015). Another study also found that the administration of galacto-oligosaccharide increased the abundance of *Bifidobacteria* in patients with T2D (Pedersen et al. 2016). The limited effects of oligosaccharides on glycemic control and insulin secretion in clinical researches may be due to the low dose, small sample size and the short duration of the supplementation. Significant associations between changes in gut microbiota and clinical parameters have been commonly observed, indicating the potential anti-diabetic effects of oligosaccharides in T2D.

4.2. Anti-T2D mechanism of fiber

In post-industrial society, the increased consumption of processed carbohydrates with inadequate consumption of dietary fiber has been recognized as a major risk factor for diabetes. Aberrant gut microbiota related to development of diabetes were involved in energy metabolism, inflammation, innate immune system, and the bowel function of the intestinal barrier (Hu, Nie, and Xie 2018). Fiber ingestion increased abundance of some species, such as *Roseburia*, *Eubacterium rectale*, *Ruminococcus bromii*, *Prevotella*, *Bacteroides* and *Bifidobacterium*, etc., and decreased the number of some gram-negative bacteria, such as *Desulfovibrio* and *Enterobacteriaceae* (LPS-producing bacteria, LPS can lead to inflammation and insulin resistance by stimulation of Toll-like receptor 4) (David et al. 2014; Kovatcheva-Datchary et al. 2015; Zhang et al. 2018). These changes by dietary fiber intervention constructed a healthier gut ecosystem through the production of SCFAs to lower gut luminal pH, the inhibition of pathogenic or detrimental gut bacteria (through competitive exclusion effects), the reduction of LPS and metabolically detrimental compounds (indole and hydrogen sulfide, etc.) (Duncan et al. 2009; Walter and Ley 2011; Zhao et al. 2018). Importantly, the SCFAs can bind to the G-protein-coupled receptor and induce the expression of the enteroendocrine hormone PYY and GLP-1 in gut epithelial L-cells. Release of PYY and GLP-1 has been demonstrated to be essential for pancreatic function and insulin secretion, as well as appetite regulation (Fava 2014; Schroeder and Bäckhed 2016). In addition, SCFAs were associated with the improvement of thermogenesis, energy expenditure and insulin release, glucose tolerance and calorie intake, suggesting a link between SCFAs and glucose homeostasis (Koh et al. 2016). However, although increased acetate level led to activation of the parasympathetic nervous system for the secretion of the glucose-stimulated insulin, but hunger hormone (ghrelin) also increased simultaneously and thus facilitated food intake, promoting obesity (Perry et al. 2016). Therefore, the dominant mechanism (nervous system or gut hormones) mediated by SCFAs in humans should be further investigated. Studies showing that the SCFAs fermented from dietary fiber ameliorated T2D by targeting inflammation, cell proliferation and differentiation, insulin resistance, lipid deposition and β-cell function have been well summarized before (Hu et al. 2018; Koh et al. 2016; Mraz and Haluzik 2014), and therefore are not included in this review.

SCFAs (butyrate and propionate) targeting intestinal gluconeogenesis (IGN) may be another potential mechanism for management of T2D. Compared with the hepatic gluconeogenesis, induction of IGN results in reduction in food intake, weight gain and hepatic glucose output, and the improvement of glucose homeostasis by IGN may be associated with low risk of T2D (Kim et al. 2018). The intestine contributes around 20–25% of total endogenous glucose in the fasted state (Mithieux 2014). Glucose produced by the intestine is sent to the portal vein, and periportal neural system in the portal vein walls is able to sense glucose and sends a signal to the brain to modulate energy and glucose homeostasis (Mithieux 2014). Propionate can be used as a substrate of IGN and activates IGN gene (free fatty acid receptor FFAR3) expression via a gut-brain neural circuit. Butyrate also stimulates the gene expression of IGN directly in the enterocyte mucosa via an intracellular increase of cAMP (Goncalves 2014). Consequently, SCFAs may exert anti-obesity and anti-diabetic effects via the induction of IGN.

4.3. Polyphenols

Dietary polyphenols are natural compounds occurring in plant-based foods, including fruits, vegetables, cereals, whole grains, nuts, tea, coffee and wine (Pérez-Jiménez et al. 2010). Beneficial effects of dietary polyphenols on the human body have been evaluated in numerous studies. In fact, majority of polyphenols (90–95%) were found to pass through the small intestine without being absorbed, these compounds persist into the colon and metabolized by gut microbiota (such as demethylation, dehydroxylation, decarboxylation, etc.). Evidence is emerging that the modulation of dietary polyphenols on colonic microbial population composition or activity, resulted in generation of smaller metabolites such as phenolic acids to increase its biological activities (Cardona et al. 2013; Dueñas et al. 2015).

Results from animal studies (Liu et al. 2017; Park et al. 2016) and clinical trials (Cao et al. 2018; Lee et al. 2016; Tresserra-Rimbau et al. 2016) indicated that dietary polyphenols and polyphenol-rich foods might reduce the risk of T2D and/or its complications. The main anti-diabetic

mechanisms of dietary polyphenols including protection of pancreatic β-cell against hyperglycemia-induced oxidative stress, inhibition of the activities of various enzymes (such as α-amylases, α-glucosidases and pancreatic lipase), promotion of β-cell proliferation and survival, and inhibition of advanced glycation end products formation had been reviewed previously (Ramachandran and Xu 2015; Xiao and Hogger 2015). Focusing on the modification of gut microbiota, polyphenols can exert prebiotic-like effects to improve intestinal health by stimulating the growth of beneficial bacteria and inhibiting the pathogenic bacteria simultaneously (Dueñas et al. 2015; Rasines-Perea and Teissedre 2017). Only a few studies have examined the impact of dietary polyphenols on gut microbiota in diabetes. Zhao et al. (2017) found that *Lessonia nigrescens* ethanolic extract (LNE, rich in phenolics and flavonoids) had better glycemic control on type 2 diabetic mice. More importantly, LNE treatment significantly increased the abundance of *Bacteroidetes* and decreased *Firmicutes* population in intestine. Specifically, it could selectively enrich the abundance of beneficial bacteria (*Barnesiella*), as well as reduce the number of *Clostridium* and *Alistipes*. A recent study found that anti-diabetic effect by polyphenols were associated with the changes of gut microbiota and markers of gut barrier (Van Hul et al. 2018). Administration of cinnamon bark extract (CBE, rich in oligomeric proanthocyanidins) and grape pomace extract (GPE, mixture of polyphenols including anthocyanins, hydroxycinnamic acids, flavanols and flavanol glycosides) improved fat mass gain, adipose tissue inflammation, impaired glucose tolerance and insulin resistance. Additionally, GPE reduced the levels of *Desulfovibrionaceae*, *Streptococcaceae*, *Clostridium sensu stricto* and *Lactococcus*, while increasing the abundance of *Prevotellaceae*, *Erysipelotrichaceae Allobaculum* and *Roseburia*. And the modified gut microbiota may be responsible for the improved gut barrier function. In addition, polyphenols (such as tea and berry polyphenols) including epigallocatechin gallate, epicatechin gallate, epigallocatechin, gallocatechin, epicatechin and catechin, inhibited the growth of many pathogens, such as *staphylococcus*, *salmonella*, *E. coli*, *Clostridium perfringens* and certain gram-negative *Bacteroides* spp, which may result in the improvement of gut microecology in T2D (Dudachodak et al. 2015; Puupponen-Pimiä et al. 2005).

4.4. Melatonin

Melatonin (N-acetyl-5-methoxy tryptamine) is a natural molecule widely present in animals, plants, bacteria, fungi, and eukaryotic protists. In mammals, melatonin is an indolaminergic hormone synthesized mainly by the pineal gland situated in the brain, from the metabolism of tryptophan via serotonin after two enzymatic transformations that acetylate and replace the hydroxyl group by methoxy (Gomes Domingos, Hermsdorff, and Bressan 2017). Melatonin is known as a hormone with strong antioxidant activity, which could ameliorate diabetes by improvement of low-grade inflammation, insulin secretion and action, β-cell dysfunction, oxidative stress and glucose homeostasis, resulting in regulation of glycemic control and improvement of lipids profile (Agil et al. 2013; Agil et al. 2012).

Recent compelling investigations have demonstrated that melatonin could influence composition and abundance of some gut microbiota. Administration of melatonin protects against diet-induced obesity, which improved insulin resistance and reduced body weight, liver steatosis, and low-grade inflammation (Xu et al. 2017). More interestingly, the richness and diversity of gut microbiota were notably decreased by melatonin, but melatonin supplementation reversed 14 OTUs (including *Ruminococcaceae*, *Desulfovibrionaceae*, *Bacteroides*, *Porphyromonadaceae*, *Helicobacteraceae* and *Christensenellaceae*) to the same configuration than those present in the normal chow diet group (high fat diet feeding altered 69 OTU), and melatonin also increased the abundance of *Akkermansia* (Xu et al. 2017). Another study found that melatonin treatment increased ratio of *Firmicutes*/*Bacteroidetes* (Zhu et al. 2018). The increased ratio of *Firmicutes*/*Bacteroidetes* was positively correlated with weight gain and negatively correlated with glucose concentration (Larsen et al. 2010). Therefore, the decreased body weight and increased glucose in T2D may be ameliorated by increasing the ratio of *Firmicutes*/*Bacteroidetes* through melatonin. Although these results presented strong association between melatonin and gut microbiota, the exact involvement of gut microbiota in the regulatory functions of melatonin in intestinal physiology needs to be further explored.

5. Traditional Chinese medicine

Traditional Chinese medicine (TCM), generally also known as botanical medicine or phytomedicine, is an important scientific and technological resource with therapeutic or other human health benefits. Generally, the use of TCM herbal formula (FuFang in Chinese) is fundamental and includes several medicinal herbs (Liu et al. 2015). Consequently, TCM is a rich source of carbohydrates and non-carbohydrate bioactive compounds. The carbohydrates (particularly polysaccharides and oligosaccharides) are a kind of widely distributed chemicals in TCM. Many well-known TCMs, such as, *Dendrobium officinale*, *Plantago asiatica* L., *Cyclocarya paliurus* are enriched with carbohydrates. Most of these carbohydrates are indigestible by the human body, and their pharmacological effects, such as anti-diabetic, hypoglycemic, anti-inflammatory effects, may be related to their gastrointestinal function. The non-carbohydrate chemicals (particularly triterpene glycosides, flavonoids, isoflavones, iridoid glycosides, alkaloids, and tannins, etc.) are another kind of bioactive compounds in TCM. However, the bioavailability of these chemicals is generally very low due to their high hydrogen-bonding capacity, high molecular flexibility, and poor lipophilicity (Liu et al. 2013). Fortunately, multiple gut microbiota are involved in the biotransformation (glycoside hydrolase, oxidation, reduction and isomerization, etc.) of these non-carbohydrate components, which increase the efficiency of intestinal

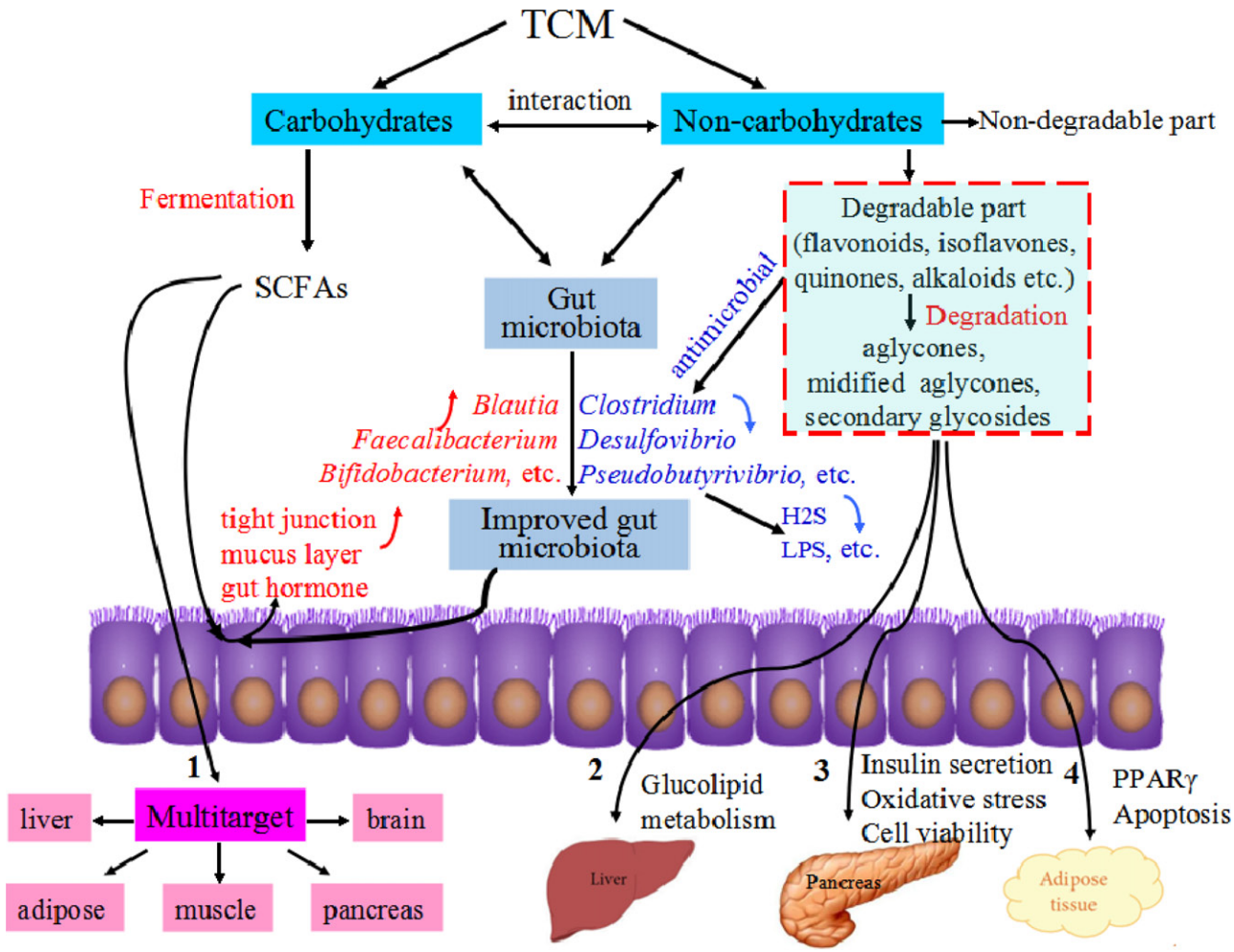

Figure 3. Multitarget effects of TCM on T2D. Fermentation/degradation of carbohydrates and non-carbohydrates related to improvement of gut microbiota and increase of its metabolites (SCFAs, secondary glycosides, aglycones and/or its derivatives). SCFAs and the modified gut microbiota could ameliorate T2D by the enhancement of tight junction expression, mucus layer fortification and gut hormone secretion, etc. 1). SCFAs can reach the blood circulation to exert anti-diabetic effects on the human body, acting in the multi organ such as brain (appetite, ↓), liver (lipid accumulation, ↓; insulin sensitivity, ↑), white adipocytes (lipid accumulation, ↓; inflammation, ↓; insulin sensitivity, ↑), muscle (insulin sensitivity, ↑) and pancreas (β-cell apoptosis, ↓; insulin secretion, ↑) (Martel et al. 2017). 2). Phytochemicals related to the improvement of liver function. Berberine inhibits gluconeogenesis and lipogenesis in liver by reducing expressions of transcription factors including forkhead transcription factor O1 (FoxO1), sterol regulatory element-binding protein 1c (SREBP1) and carbohydrate responsive element-binding protein (ChREBP) (Xia et al. 2011). 3). Phytochemicals related to the improvement of pancreas function. Urolithins (degraded metabolites from ellagic acid by gut microbiota) stimulates the secretion of insulin; Berberine induces β-Cell proliferation, increases cell viability, and ameliorates β-Cell injury through TLR4-independent JNK/NF-κB pathway; Flavonoids (such as apigenin, quercetin and luteolin) also have antioxidant effects to protect pancreatic β-Cells from reactive oxygen species (Cros et al. 2015; Kim et al. 2007; Wang 2014). 4). Phytochemicals related to the improvement of adipocyte function (inhibition of lipid accumulation and enhancement of insulin sensitive). Epigallocatechin gallate and resveratrol are related to the inhibition of adipogenesis and induction of apoptosis in adipocytes; Honokiol and curcumin increased secretion of adiponectin by activation of peroxisome proliferator-activated receptor γ (PPARγ) (Wang et al. 2014; Yang et al. 2008).

absorption and thereby improving its bioavailability (Laparra et al. 2010).

Numerous researches on TCM management of T2D and its complications have been published. Patients with pre-diabetes are willing to choose TCM because it has the minimum side effects compared with anti-diabetic drugs at this stage. Administration of TCM has beneficial effects on enhancing insulin sensitivity, protecting β-cells, simulating insulin secretion, correcting glucose and lipid metabolism disorders, improving the immune system, and modulating the structure of the gut microbiota in T2D (Nie et al. 2018; Pang et al. 2017; Pang et al. 2015; Xu et al. 2015). *Rhizoma coptidis* (containing the active component berberine) is mostly used to clear heat, purge sthenic fire, and eliminate toxic materials, and it had been also recorded in Qianjin Yaofang (a great book of prescriptions, which was written by Sun Simiao in Tang Dynasty) for treating polydipsia. And many TCMs herbal formula used for treating T2D contain *Rhizoma coptidis* or berberine.

In a recent clinical trial, a TCM (named AMC) herbal formula composed of 8 herbs (*Rhizoma Anemarrhenae*, *Momordica charantia*, *Coptis chinensis*, *Salvia miltiorrhiza*, *red yeast rice*, *Aloe vera*, *Schisandra chinensis* and dried ginger) was used to treat T2D (Tong et al. 2018). Both metformin and AMC treatment significantly alleviated hyperglycemia and hyperlipidemia, and shifted structure of gut microbiota, but only AMC significantly improved HOMA-IR and triglyceride levels in patients with T2D. Metformin and AMC significantly increased abundance of *Blautia* (SCFA-producing bacteria), *Megamonas* and *Klebsiella* at genus level, but AMC intake specifically enriched *Faecalibacterium*, *Roseburia*, *Gemmiger* and

Coprococcus (*Faecalibacterium* and *Roseburia* are two genera containing butyrate-producing bacteria), and which was found to be related to the improvement of glucose and lipid homeostasis (Tong et al.,2018). A double-blinded, placebo-controlled clinical trial found that Gegen Qinlian Decoction (GQD, a traditional Chinese herbal formula) can modulate the structure of gut microbiota in patients with T2D (Xu et al. 2015). GQD is composed of four herbs (*Radix Puerariae*, *Radix Scutellariae*, *Rhizoma Coptidis* and honey-fried *Licorice Root*) that are rich in baicalin, puerarin and berberine. Administration of GQD significantly improved glycemic control and gut microbiota in T2D patients. *Faecalibacterium*, *Gemmiger*, *Bifidobacterium* and *Lachnospiracea_incertae_sedis* were significantly increased by high-dose GQD treatment, whereas *Alistipes* (associated with irritable bowel syndrome), *Parabacteroides* and *Pseudobutyrivibrio* were significantly decreased. More importantly, the significantly increased *Faecalibacterium prausnitzii* was negatively correlated with FBG, HbA1c and 2-h postprandial blood glucose levels and positively correlated with homeostasis model assessment of β-cell function (Xu et al. 2015). Another clinical trial showed anti-diabetic effects of berberine (patients were administered 300 mg berberine three times daily, 0.5 h after each major meal for 8 weeks) may be related to the modulation of *Bifidobacterium* species (Chen, Lu, and Li 2016). Abundance of *Bifidobacterium*, *Bifidobacterium longum*, *Bifidobacterium breve* and *Bifidobacterium adolescentis* were significantly increased, and *Bifidobacterium infantis* was significantly decreased after berberine treatment compared with before treatment, and *Bifidobacterium, B. longum* and *B. infantis* showed significant negative correlations with TNF-α and LPS levels (Chen et al. 2016).

In animal studies, TCM such as Qijian mixture, Xiexin Tang and ZiBuPiYin recipe were also found to be able to regulate gut microbiota in T2D (Gao et al. 2018; Gu et al. 2017; Wei et al. 2018). Qijian mixture (composed of *Astragalus membranaceus*, *Ramulus euonymi*, *Coptis chinensis* and *Pueraria lobata*, rich in active compounds including formononetin, calycosin, and puerarin) treatment effectively alleviated T2D and increased abundance of *Senegalimassilia*, *Clostridium sensu strict*_1 and *Bacteroides* in genus level, and *Porphyromonadaceae* and *Bacteroidaceae* in family level (Gao et al. 2018). Wei et al. (2018) found that Xiexin Tang (composed of *Rhei rhizome*, *Scutellaria radix* and *Coptidis rhizome*) ameliorated insulin resistance and T2D by the enhancement of epithelial barrier function and improvement of gut permeability and inflammation. The improved intestinal function was closely related to the shifts of gut microbiota, such as the notable increase of *Alloprevotella*, *Barnesiella*, [*Eubacterium*] *Ventriosum group*, *Lachnospiraceae* UCG-001, *Papillibacter* and *Prevotellaceae* NK3B31 in type 2 diabetic rats (majority of these flora are SCFAs-producing and anti-inflammatory bacteria). However, the abundance of *Blautia* was significantly decreased by XXT treatment. *Blautia* is an acetic acid-producing bacteria and was found to be related to the improvement of T2D in one clinical trial (Tong et al. 2018), and the decrease of *Blautia* by XXT in this study might be attributed to the organism competing for the same substrates or the differences in strain-specific functions.

5.1. Multitarget effects of TCM on T2D

TCM used to treat T2D generally belong to herbal medicine. Components present in TCM can be divided into carbohydrates and non-carbohydrates (flavonoids, triterpene glycosides, alkaloids, ellagitannins, condensed tannins, lignans, quinines, etc.), both of them can influence the composition and activity of gut microbiota in host (Xu, Chen, and Li 2017). Anti-diabetic effects of TCM from the perspective of gut microbiota may be related to inhibition, promotion and synergism (Figure 3).

1. **Inhibition:** Increase of pathogenic bacteria is an important risk factor in T2D, the released toxins (such as toxin α, β, ε and ι from *Clostridium perfringens*, cytotoxic necrotizing factor 1 and hemolysin from *E. coli*) and enzymes (urease and neuraminidases) exacerbated host tissue damage and influence host signaling pathways, including inflammatory responses, host cell survival, and cytoskeletal dynamics (Petit, Gibert, and Popoff 1999; Wiles, Kulesus, and Mulvey 2008). Various compounds (emodin, saponins, berberine, etc.) extracted from TCM (*Rhubarb*, *G.pentaphyllum*, *Rhizoma coptidis, Panax ginseng,* etc) have been reported to inhibit intestinal epithelial cell adherence, intracellular invasion, and enteric colonization of certain potential or opportunistic pathogens (Xu et al. 2017). Especially the inhibiting effects of some TCM on LPS-producing bacteria led to the improvement of inflammation (inhibit inflammatory cytokines, such as TNF-α, IL-1, and IL-6), gut barrier integrity (promote expression of ZO-1, occluding, and Cb-1), and dysbiosis of gut microbiota (Pan and Kong 2018).
2. **Promotion:** Generally, the promotion effects (prebiotics effects) of TCM are related to fermentation/degradation of carbohydrates and non-carbohydrates (glycoside, alkaloids, isoflavones, flavonoids, quinines, etc.) (Zhou et al. 2016). For the fermentation of carbohydrates, the modified gut microbiota and increased SCFAs improved gut health by modification of tight junction expression, mucus layer fortification and gut hormone secretion, etc. SCFAs can enter the blood circulation to exert anti-diabetic effects on the human body, and SCFAs generally act in the multi organs, such as brain, liver, white adipocytes, etc (Martel et al. 2017). Compared with SCFAs fermented from carbohydrates, non-carbohydrates and its degraded metabolites can also help ameliorate T2D (Figure 3). These components transformed by certain gut microbiota into secondary metabolites (secondary glycosides, aglycones and/or its derivatives) generally have greater absorption and bioactivity than their precursors (Chen et al. 2016; Nie et al. 2017). For instance, baicalein can be hydrolyzed from baicalin by gut microbiota (baicalin is poorly absorbed in gut), and

then activates hepatic AMPKa2 pathway to improve high fat-induced oxidative and metabolic disturbances in liver (Pu et al. 2012). Berberine can be converted into dihydroberberine by nitroreductases of the gut microbiota (dihydroberberine has an intestinal absorption rate 5-fold higher than that of berberine). And dihydroberberine can be oxidized back to berberine in intestine tissues, entering blood circulation to exert anti-diabetic effects by targeting β-cell proliferation and AMPK pathway, etc. (Pang et al. 2015; Feng et al. 2015). It should be mentioned that the different prebiotic effects of those components in TCM were based on their unique or common characteristic (molecular weight, chemical structures, viscosity, etc.), and the bioactive compounds in the herbal formula should be identified to understand molecular mechanism for treating T2D.

3. **Synergism:** Compared with the treatment with single component in T2D, TCM formula conform to the principle "multiple components against multiple targets" proposed recently. The synergistic effects of TCM included effect-enhancing and toxicity-reducing (Wang et al. 2008; Xu et al. 2017). For the effect-enhancing, the mixed bioactive components present in TCM could synergistically exert multitarget effects, such as improvement of β-cell function, hormones secretion, free radicals scavenging and microcirculation simultaneously (Li et al. 2004; Martel et al. 2017). For example, berberine can be converted into dihydroberberine by gut microbiota in intestine and then entered blood circulation to exert anti-diabetic effects. Intake of berberine also increased the abundance of *Blautia* and *Allobaculum* (SCFA-producing bacteria), which further facilitated the fermentation of dietary carbohydrates and promoted the production of SCFAs to mitigate diabetes (Zhang et al. 2012). Sennoside A in rhubarb extract also significantly accelerated metabolic activity in intestinal bacteria in comparison with sennoside A alone, and the increased metabolic activity was related to 8-O-β-D-glucopyranoside that co-occurred in rhubarb extracts (Takayama et al. 2012). For the toxicity-reducing, usage of TCM formula may alleviate host and gut metabolism impairment caused by some toxic components. Some components present in TCM (such as realgar and *Aconitum carmichaelii*) could exert toxic effect when used alone, while other components (such as *Indigo naturalis*, *Salvia miltiorrhiza*, *G. uralensis* root and rhizome, etc.) can be co-administrated for toxicity reduction and pharmacological effect improvement (Wang et al. 2008; Zhang et al. 2013). Collectively, these results indicated that TCM may exert multiple health-promoting effects synergistically rather than individually.

6. Targeting *Akkermansia*

Akkermansia (reported to have effects on obesity, T2D, and gut inflammation) has recently been proposed as a new biomarker of intestinal health. It is a key bacteria at the mucosal interface between the lumen and host cells due to its ability to degrade mucin (Derrien, Belzer, and de Vos 2017). Some dietary fibers and polyphenols (particularly cranberries and grapes polyphenol that contained a high level of proanthocyanidins) were found to positively regulate *Akkermansia* (Anhê et al. 2015; Anhê et al. 2016; Everard et al. 2011). A grape extract rich in polyphenols was found to increase the abundance of *Akkermansia* and decrease the ratio of *Firmicutes/Bacterioidetes* in obese mice, and the modified gut microbiota resulted in lower intestinal and systemic inflammation, and improved metabolic outcomes (Roopchand et al. 2015). Oligofructose was also found to increase the abundance of *Akkermansia* in obese and diabetic mice, and the increased *Akkermansia* was strongly and positively correlated with the L-cell number (GLP-1 and GLP-2 are produced by enteroendocrine L cells) (Everard et al. 2011). Therefore, the increase of the abundance of *Akkermansia* in the intestine by dietary components may be another strategy to alleviate T2D and provide the metabolic benefits to the host.

Compromised barrier function is the basis for metabolic syndrome. The colonic mucus layer is a dynamic and chemically complex barrier composed largely of mucin-2 glycoprotein (Muc2, secreted by goblet cells), which separates bacteria from the colon epithelia (Johansson, Sjövall, and Hansson 2013). On the one hand, supplementation of some dietary components (such as some polyphenols) may increase the expression of mucin 2 mRNA in the proximal colon, which results in the increase of mucus secretion thus creating a favorable environment for *Akkermansia* to grow. On the other hand, the increased mucin-degrading bacterium stimulated mucin production by host, resulting in the fortification of the integrity of the epithelial cell layer (Anhê et al. 2016). Additionally, *Akkermansia*-derived extracellular vesicles could also improve gut permeability through the regulation of tight junctions by AMPK pathway (Chelakkot et al. 2018). However, it should also be mentioned that overabundance of *Akkermansia* is not always associated with host benefits. Under the conditions of chronic or intermittent dietary fiber deficiency, gut microbiota (*A. muciniphila, B. caccae, B. ovatus, and E. rectale*) can utilize host-secreted mucus glycoproteins as a nutrient source. The unhealthy diet (fiber deficiency) led to proliferation of mucus-degrading bacteria and microbiota-mediated degradation of the colonic mucus layer, promoted greater epithelial access and lethal colitis by the mucosal pathogen (*Citrobacter rodentium*) (Desai et al. 2016).

As mentioned above, this prompted us to hypothesize that there is a dynamic balance between colonic mucus layer and abundance of *Akkermansia*. The increased *Akkermansia* plays a key role in the development of an impenetrable mucus layer and improvement of metabolic syndrome when "nutrients" (such as some dietary fibers, polyphenols and polyunsaturated fatty acids) were administered in adequate amounts. However, increased *Akkermansia* may destroy colonic mucus barrier if the "nutrients" are deficient (Figure 4). Collectively, targeting *Akkermansia* to improve metabolic syndrome may be an effective strategy in T2D.

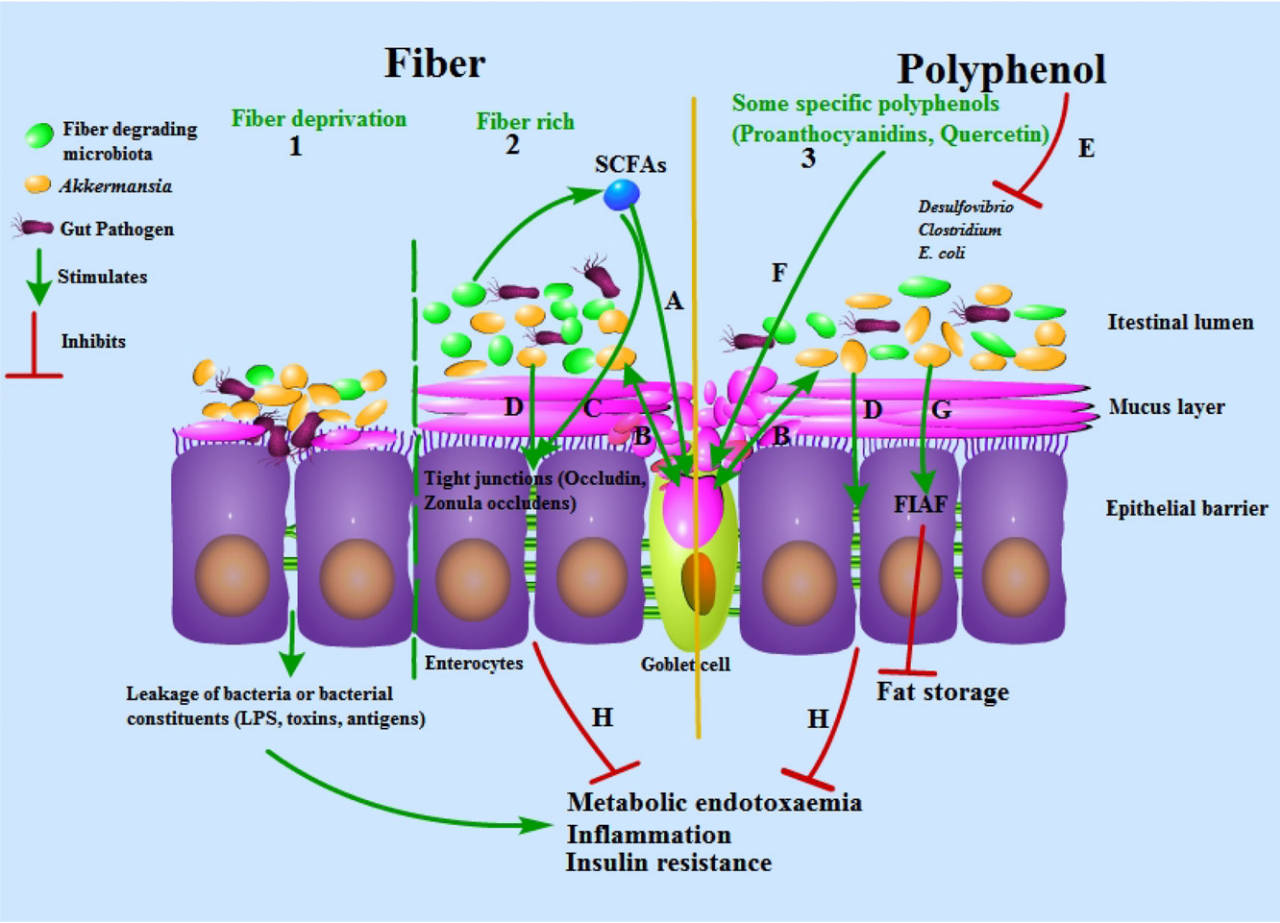

Figure 4. Targeting *Akkermansia* to improve metabolic syndrome in T2D. 1) Fiber deficiency promotes the increase of *Akkermansia* to degrade mucus glycoproteins as alternative energy source, which results in the reduced mucus layer thickness that favors microbiota encroachment. Fiber deficiency also enriched some LPS-producing bacteria, and the increased LPS related to inhibition of the expression of epithelial tight junction, leading to leakage of bacteria or bacterial constituents. These changes eventually leading to inflammation, insulin resistance and metabolic endotoxaemia. 2) Dietary fiber increase the abundance of fiber-degrading microbiota, promoting the production of SCFAs. A: SCFAs promote the express of mucin 2 mRNA, and results in the increase of mucus secretion, and thereby creating a favorable environment for *Akkermansia* to thrive. B: *Akkermansia* also degrades mucins to generate SCFAs, which in turn acts on goblet cells to stimulate mucus secretion, results in fortification of the integrity and thickness of the mucus layer. C and D: SCFAs and *Akkermansia*-derived extracellular vesicles could regulate the expression of epithelial tight junction. H: These improvement decrease the leakage of bacteria, LPS, toxins, etc., which related to improvement of inflammation, insulin resistance and metabolic endotoxaemia. 3) E: Polyphenols inhibits the growth of many pathogens (*Clostridium*, *Desulfovibrio,* etc.) to improve healthier gut microecology. F: Some specific polyphenols promote the express of mucin 2 mRNA, and results in the increase of mucus secretion. G: *Akkermansia* may increase the production of fast-induced adipose factor (FIAF) in intestine, and the FIAF can inhibit fat storage in the host.

7. Targeting multiple pathways

Dietary compounds and TCM contain bioactive compounds that affect the composition and abundance of gut microbiota and its metabolites, which would target multiple physiological pathways involved in insulin sensitivity, lipid accumulation, energy regulation, inflammation, etc. By targeting multiple pathways, combinations of different bioactive agents derived from diet and TCM may have the synergistic effects for management of T2D. For instance, polysaccharide could reduce energy intake and lipid accumulation by the increase of satiety and inhibition of dietary fat absorption, whereas bioactive phytochemicals (such as catechins, berberine, resveratrol) might have anti-diabetic effects by the improvement of β-cell injury and proliferation, gluconeogenesis, lipogenesis and insulin sensitive, etc (Chambers et al. 2015; Martel et al. 2017). In addition, a combination of some bioactive agents may enhance the effectiveness than individual treatments. A combination of resveratrol and quercetin remarkably inhibited intracellular lipid accumulation compared with individual treatments (7.3 and 4.3 fold, respectively) (Yang et al. 2008). Similarly, treatment with a combination of epigallocatechin-gallate and resveratrol for 3 days significantly increased fasting and postprandial energy expenditure in healthy overweight individuals (Most et al. 2014). But it is worth noting that the combination may lead to a decrease of bioactivity sometimes. For example, a combination of trans-resveratrol with quercetin scarcely modified high fat diet-induced gut dysbiosis (quercetin can effectively improve such gut dysbiosis) (Etxeberria et al. 2015). Collectively, a combination of different bioactive compounds from daily diet or herbal plant (TCM) can synergize to exert anti-diabetic effects by targeting multiple pathways, which would be an effective strategy that needs further investigation.

8. Conclusions

Many factors can induce diabetes, including unhealthy eating habits, reduced physical activity and hereditary

disposition. Gut microbiota has gained growing attention as a novel factor in the management of diabetes. Modulation of gut microbiota by dietary components and TCM to improve T2D has been reported to be a safe and effective strategy in clinical trial. This article summarized some important and effective dietary components and TCM that ameliorate T2D by modulating the gut microbiota. The use of these materials (dietary fiber, polyphenols, melatonin and TCM) could be a promising and important approach in controlling T2D, as they could attenuate diabetes by different mechanisms, including gut barrier function, anti-microbial, anti-inflammation, gut hormone related glycemic control and insulin secretion, etc. Furthermore, the potential mechanisms related to the interaction between different dietary components/TCM and gut microbiota was summarized, which could help design the different diet formula for treating T2D and/or its complications. However, there is still a far way to go in illuminating the anti-diabetic mechanisms of these bioactive compounds. Due to the diversity and complexity of gut microbiota and the complex microbiota-diet interactions present in host, individualized treatment strategies are prone to apply. In addition, the bioactivities of these dietary components and TCM that are influenced by different processing procedures (herbal medicine extracted by water or ethanol, matrix effects present in different types of food) should not be ignored. In conclusion, the improvement of diabetes and metabolic homeostasis using "ideal diet" is the optimal goal in the future.

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