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Polysaccharides from TCM herbs exhibit potent anti-obesity effect by mediating the community structure of gut microbiota

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High-calorie food intake and unhealthy lifestyle have considerably raised the incidence of obesity. The gut microbiota is associated with metabolic disorders which promote excessive accumulation of fat, elicit host systemic, low-grade chronic inflammation, and insulin resistance. These features make gut microbiota a promising target for the prevention and intervention of obesity. Herbal polysaccharides in TCM are uneasy to digest by the host, but can be decomposed and utilized by the intestinal flora as the carbon source to mediate bacterial composition. In this review, we are describing the therapeutic effect of polysaccharides on the imbalanced structure of gut microbiota and its metabolites, and discuss the research progress that has been made to unravel the underlying mechanism by which polysaccharides of TCM inhibit the onset and development of obesity.

1. Introduction

High-caloric diet and sedentary lifestyle have promoted the prevalence of obesity and the associated metabolic disorders to pose a major threat to people's health and life qualities. A 25-year follow-up study of 195 countries reported that the number of obese children and adults had reached 107.7 million and 603.7 million, respectively, in 2015, and that the incidence of obesity in more than 70 countries had doubled since 1980, claiming 4 million death tolls and eliciting 120 million cases of disabilities (Zhang and Wang 2017). Worse still, the enormous social and economic burden caused by obesity is aggravated by the comorbidities, including stroke, diabetes mellitus, cardiovascular diseases, and cancer.

The continuous development of biomedical technology in recent years has gradually advanced the understanding of the intestinal flora. Study results have shown that the intestinal flora is closely related to the onset and development of obesity, and that intestinal flora disorders can elicit chronic persistent low-degree inflammatory response, dysregulated lipid metabolism, and aberrant secretion of intestinal hormones (Xu et al. 2017). Bioactive polysaccharides, as effective components, could be extracted from TCM drugs by applying a variety of modern techniques, including water bath extraction, acid-base extraction, enzymolysis extraction, microwave-assisted extraction, ultrasonic-assisted extraction, ultra-high pressure extraction, ultrasonic microwave-assisted extraction, microwave-assisted enzymatic extraction and ultrasonic-assisted enzymatic extraction. The separation and purification of polysaccharides from TCM manifest the general removal of impurities, and the subsequent fractional purification by using precipitation, gel chromatography, anion exchange chromatography, macro-porous resin column chromatography, ultrafiltration and so forth. Mainly composed of glucose, rhamnose, mannose, galactose, xylose, arabinose, ribose, fructose, sucrose, fucose and other monosaccharides (Cheng et al. 2017; Zhou et al. 2019), the polysaccharides of TCM exhibit a variety of pharmacological effects, such as immune regulation, antibacterial, anti-viral, and anti-tumor effects, and lower hypoglycemia and lipids (Yang et al. 2016). However, the

insolubility and low degradability of polysaccharides make it hard for them to be digested and absorbed by the gastrointestinal tract, and hence compromising their bioavailability.

Of note, the intestinal flora can metabolize polysaccharides to produce metabolites with various bioavailability, bioactivity, and toxicity, as opposed to the precursors (Deehan et al. 2020). Meanwhile, polysaccharides in TCM function to reshape the composition of intestinal flora to restore the pathological disorders (Chooi et al. 2019). In this study, we shed light on the association between obesity and intestinal flora by reviewing the latest studies, discuss the research progress that has been made on the capacity of polysaccharides to regulate the community structure of gut microbiota.

2. Intestinal flora and obesity

Ley et al. (2005) proposed the relationship between intestinal flora and obesity for the first time in 2005. The investigators found that obese mice had notably higher numbers of *Firmicutes* and a markedly lower number of *Bacteroidetes* in their intestines than the healthy mice. Consistently, another study on the intestinal microecological changes showed that the relative abundance of *Firmicutes* in the intestinal flora of European children was significantly higher than that of African children, while the relative abundance of *Bacteroidetes* was significantly lower. Considering that obesity is much more prevalent among European children than the African children due to nutritional structure and other factors, it was hypothesized that the community structure of intestinal flora is associated with obesity.

The subsequent studies that delve into the relationship between intestinal flora and its metabolites and obesity indicated that gut microbiota is implicated in a vast variety of biological activities and functions.

(1) Intestinal flora increases the absorption of intestinal monosaccharides and short-chain fatty acids (SCFAs), thereby promoting the accumulation of fat in liver tissues (Zhi et al. 2019);

- (2) Intestinal flora can elevate intestinal permeability, allowing for the passage of a large amount of LPS to enter the body and triggering inflammatory response (Tabatabaei-Malazy et al. 2010);
- (3) Intestinal flora regulates the release of appetite-related hormones and signal factors to enhance appetite (Tavakkoly et al. 2010);
- (4) Intestinal flora can secrete trimethylamine-lyase (TMA-lyase) to cleave food-borne choline to produce trimethylamine, which is further oxidized in the liver to produce trimethylamine-n-oxide (TMAO). TMAO could induce liver inflammation, promote the occurrence and development of obesity (Ramdas et al. 2015);
- (5) Intestinal flora regulates the expression of host genes and promotes the synthesis of triacylglycerol to inhibit the oxidation of fatty acids, causing energy imbalance and obesity (Moreno-Indias et al. 2014);
- (6) Intestinal flora acts on endocrine cells to stimulate the release of intestinal peptide hormones and thereby slowing down (Turnbaugh et al. 2006);
- (7) The imbalanced structure of intestinal flora can lead to a lowered content of choline and higher concentration of toxic amines, thereby facilitating fat accumulation (Ley et al. 2005);
- (8) Intestinal flora mediates bile acid metabolism and regulates FXR /TGR5 signaling pathway to promote the occurrence of obesity in an indirect manner (Heimann et al. 2015);
- (9) Intestinal flora affects signal transmission in the gut-brain axis (GBA) to regulate the absorptive and secretory capacities of intestinal epithelial cells, and to mediate food intake and energy metabolism (Chimerel et al. 2014).

In a nutshell, a bulk of experimental study results indicates that the intestinal flora plays a critically important role in the synthesis and accumulation of fat in the host.

3. Polysaccharides in TCM regulates the structure of intestinal flora

As the carbon source of intestinal microbial fermentation, polysaccharides fuel microbial growth, regulate intestinal flora through their metabolites, and impact intestinal micro-ecological diversity as prebiotics in the host (Levy et al. 2017). Moreover, intestinal microorganisms degrade polysaccharides into a variety of active metabolites (Cheng et al. 2017), including monosaccharides, oligosaccharides, organic acids (such as ethanol, lactic acid and succinic acid), and short-chain fatty acids (such as acetic acid, propionic acid and butyric acid). The *in vivo* degradation of polysaccharides is related to molecular weight, monosaccharide composition, connection mode, degree of polymerization, spatial structure, solubility and adaptability of intestinal flora to polysaccharides. Recent studies focused on clarifying the effects of polysaccharides on the diversity and composition of intestinal flora by identifying the specific and functional bacteria, so as to establish the association between polysaccharides, gut microbiota and metabolic diseases.

4. Polysaccharides of TCM affect the proportion and abundance of intestinal microorganisms

Ley et al. (2006) found that obese people had high abundances of *Firmicutes* and *Bacteroidetes* in their intestinal tracts than lean people, and that after receiving weight control through low-calorie diet, higher abundance of *Bacteroides* and lower abundance of *Firmicutes* were observed in their intestines. It was shown that oligofructose can effectively improve the number of *Firmicutes* and *Bacteroidetes* in the intestinal tract of obese mice, thereby elevating the richness of *Bifidobacterium* and *Lactobacillus* (Everard et al. 2011; Cani et al. 2009). Yang Kai et al. (2020) studied the effect of oligosaccharides, which were extracted from broken and unbroken *Ganoderma lucidum* spore powder, on the intestinal flora, and the results suggested that both sources of oligosaccharides increased the richness of beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus*, which promote the secretion of short-chain fatty acids (SCFAs) and stimulate intestinal peristalsis. Moreover, Zhang et al.

(2019) determined that soybean oligosaccharides, xylo-oligosaccharides, isomalt and galactose oligosaccharides function to increase the quantities of *Bifidobacteria* and *Lactobacillus*. He et al. (2016) analyzed the effect of *Astragalus* polysaccharides (APS) treatment on obesity, and reported that APS exhibits pronounced inhibitory effect on the development of obesity in mice by restoring intestinal flora disorder. The conclusion was substantiated by increased abundance of *Bacteroidetes* and *Firmicutes*. Additionally, the anti-obese effect of APS has been validated in high-fat feeding mice which underwent intestinal flora transplantation.

5. Polysaccharides of TCM improve intestinal barrier function

Obesity-induced intestinal dysfunction is mainly characterized by intestinal flora disturbance and increased intestinal permeability. Intestinal flora contributes to intestinal barrier integrity by preventing harmful substances, such as bacteria and toxins, from entering the blood circulatory system through intestinal mucosa (Rokhsafat et al. 2016; Raybould 2012). Studies have found that a high-fat diet could lead to increased endotoxin levels, obesity-associated inflammation and improved insulin resistance in mice. As the membrane constitute of gram-negative cells, lipopolysaccharides (LPS) will be released after the death of bacteria. LPS is known as the best-studied TLR (Toll-like receptor) and can be recognized by TLR4 and MD-2 (Zhang et al. 2020). TLRs are the key components that affect insulin signaling pathways and the production of inflammatory cytokines. The binding of LPS to TLRs would lead to improved insulin resistance and the excessive release of inflammatory cytokines.

Moreover, LPS produced by the intestinal flora enters the intestinal epithelial cells through the tight junctions (TJs) barrier of small intestinal membrane, forming chylomicrons with triglycerides and cholesterol, which enters the lymph circulation and finally the blood circulation system. The binding of LPS to lipopolysaccharide receptor CD14 promotes the release of proinflammatory cytokines, thereby inducing low-grade inflammation and obesity. Thusly, the elevated blood concentration of LPS in obese mice is most attributable to the compromised intestinal permeability (Morris et al. 2016). Studies have shown that arabinoxan can significantly up-regulate the mRNA levels of occludin and ZO-1 in the small intestine of obese mice, improving the intestinal barrier integrity and lowering the blood concentration of LPS to inhibit the symptoms of obesity (Hobden et al. 2015). The mechanism that underlies the reparatory effect of polysaccharides on damaged *in vivo* intestinal barrier is shown in Fig. 1.

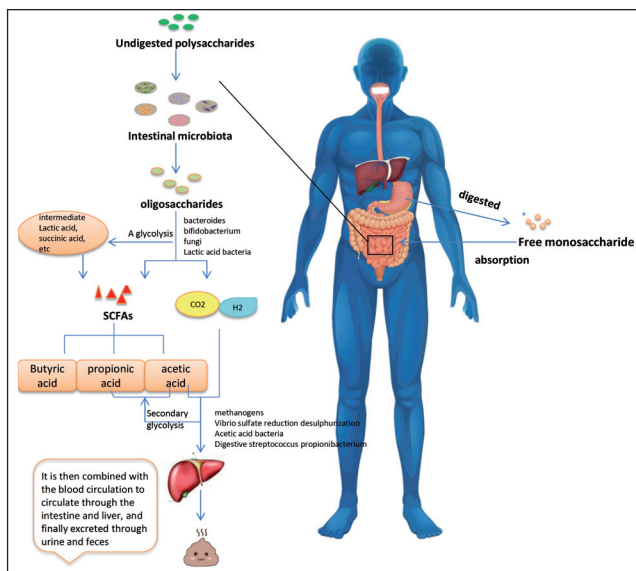


Fig. 1: The relationship between polysaccharide digestion and absorption and intestinal flora

6. Study on butyrate-producing bacteria based on polysaccharides of TCM

Butyrate-producing bacteria constitute a functional group with high abundance and prominent functionality in the human intestinal flora, rather than a coherent phylogenetic group (Lous and Flint 2009; Lous et al. 2010). Butyrate-producing bacteria belong to the phylum *Firmicutes*, yet various butyrate-producing-bacteria manifests different substrate. For instance, some butyrate-producing bacteria rely on nitrogen sources to synthesize protein, whereas others rely on carbon sources. Meanwhile, the utilization efficiency of different butyrate-producing bacteria on different sources of nitrogen and carbon varies enormously, and hence the different Chinese herbal medicines. Thus, polysaccharides from different Chinese herbal drugs exhibit various performances on various butyrate-producing bacteria (Lin and Shu 2020). The intestinal flora serves as the bridge for bioactive polysaccharides in herbal medicine to exhibit biological effects on the human body by decomposing polysaccharides into SCAFs and carbon dioxide (CO₂), which participate in energy metabolism and immune response. Conversely, herbal polysaccharides could also impact the abundance of species of intestinal flora to intervene the progression of obesity by sustaining the growth of beneficial bacteria and thwarting the proliferation of harmful bacteria, thereby modulating the balanced structure of bacterial communities (Goodell et al. 2012).

Recent research found that a supplement of several Chinese herbal polysaccharides can affect the richness of butyrate-producing bacteria and the concentration of butyrate (Yang et al. 2010). Sun et al. (2019) proved that *Pachyacria* effectively increased the taxon richness of butyrate-producing bacteria in the cecum of mice, thereby upregulating the concentration of intestinal butyric acid and improving intestinal mucosa integrity.

7. Polysaccharides of TCM regulate the bi-directional gut-brain axis

As a bidirectional communication system between the central nervous system (CNS) and the gut tract, gut-brain axis effectively regulates appetite, food intake, and net energy balance (NEB) by mediating hormone levels and the nervous system (Van et al. 2017; Westfall et al. 2017). Specifically, the transmission of neural and hormonal signals in gastrointestinal tract to the brain after the intake of food is mediated by the afferent nerve fibers (such as vagus nerve) of the autonomic nervous system. After the information from the intestine is projected to the solitary tract nucleus (NTS) by the nerve fibers, it is then assigned to hypothalamic arcuate nucleus (ARC) neurons, thereby regulating energy balance, appetite and food intake (Torres et al. 2017). Analogously, after the small intestine absorbs sufficient nutrients, such as amino acids, fatty acids, and glucose, the I cells and L cells in the intestine will secrete cholecystokinin (CCK) and glucagon-like peptide-1 (GLP-1) and peptide-YY, thereby providing feedback to the central nervous system to suppress appetite, lower the secretion of gastric acid, and delay gastric emptying (Lai et al. 2015; Narayanaswami

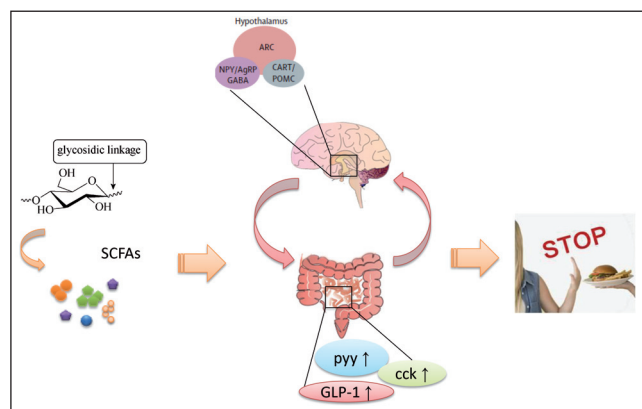


Fig. 2: polysaccharide regulation of the intestinal brain axis affecting appetite

and Dvoskin 2017). In addition, GLP-1 also exhibits a suppressive effect on the secretion of glucagon and a stimulative effect on insulin (Tharakan et al. 2011).

SCFAs produced by intestinal microorganisms to metabolize polysaccharides can upregulate the levels of appetite-related hormones and signaling factors, thereby reduce obesity symptoms (Christiansen et al. 2018). A previous study found that Guar bean gum significantly thwarts appetite by increasing the percentage of L cells in the colon and elevating GIP-1 levels in the blood, and that *Rehmannia* polysaccharide induced the secretion of GLP-1 to the normal level to restore energy metabolism and stimulate insulin secretion, thereby exhibiting therapeutic effect on obesity (Arshad et al. 2016). The mechanism by which polysaccharides in TCM regulate the gut-brain axis is illustrated in Fig. 2.

8. Polysaccharides of TCM regulate the intestinal flora in a synergistic manner with other essential components

The complicated interactions between intestinal flora and medications are mainly manifested in two forms: synergy and antagonism. For instance, a synergistic effect is revealed in the promotion of the growth of prebiotics by polysaccharide components, which in turn regulate the structural balance of the intestinal flora. Conversely, the competition between enzymes to lower the metabolism ability of the intestinal flora shows an antagonistic effect. The polysaccharides of TCM, as a source of prebiotic, can selectively stimulate the proliferation of specific probiotic subgroups, thereby effecting favorable changes in the community structure of the intestinal flora to enhance the metabolism and absorption of multi-component bioactive organisms in TCM.

Li et al. (2018) found that ginseng polysaccharide can significantly alleviate the syndrome of type-2 diabetes induced by streptozotocin and high-fat diet, as evidenced by the most satisfactorily downregulated level of FBG (fasting blood sugar), owing to the synergistic effect of ginseng polysaccharide and ginseng saponin. Further studies have found that such a synergistic effect is most attributable to the restoration of intestinal flora balance of the diabetic patients induced by elevated blood concentration of deglycosylated metabolites. Zhou et al. (2018) observed the manifestly superior therapeutic effect of white ginseng to red ginseng on obesity, and determined that such disparity lies in the enriched contents of saponins, polysaccharides and oligosaccharides in white ginseng, which are much more likely to interact with intestinal flora to reverse the imbalanced flora in the intestine. The restored intestinal flora can affect the metabolism of bile acid and short-chain fatty acid, thereby reducing the levels of IL-1 and interferon in the serum to serve the purpose of weight loss.

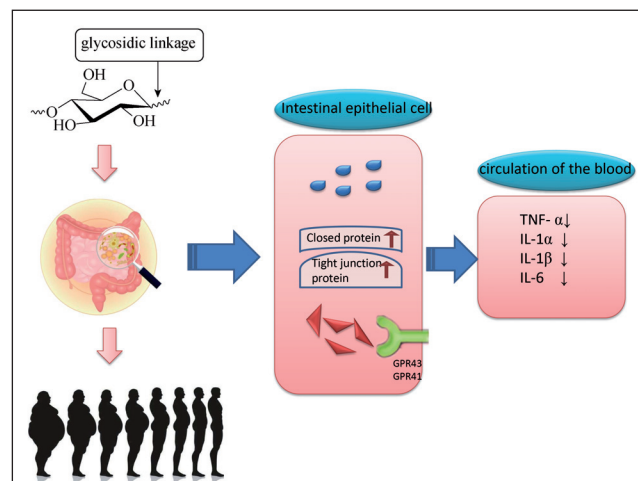


Fig. 3: Chinese traditional medicine polysaccharide can inhibit obesity by improving intestinal shielding

9. Mechanism of intestinal flora degradation of polysaccharides from TCM

Polysaccharides can be decomposed by intestinal microorganisms to regulate lipid metabolism and oxidative stress (Zhang et al. 2006). However, most of the polysaccharides cannot be digested directly by the human body after oral administration, owing to the lack of digestive enzymes that are encoded in the human genome (Gu and Shu 2019). In contrast, the gut microbes can encode a variety of carbohydrate-active enzymes (CAZymes), including glycoside hydrolase, polysaccharide lyase, carbohydrate esterase and glycosyltransferase (Lombard et al. 2013). The presence of various types and quantities of CAZyme enables the intestinal flora to digest the carbohydrates in TCM via specific signaling pathways, thereby fermenting a variety of TCM and metabolizing polysaccharides in an efficient manner (Terrapon et al. 2014; Cao et al. 2014). The relationship between the digestion and fermentation of polysaccharides in intestinal flora and their biological activity is shown in Fig. 3.

10. The metabolite SCFA of polysaccharides from TCM

Polysaccharides of TCM regulate the progression of obesity through the metabolites produced by fermentation of intestinal flora, among which SCFA is the essential mechanism that connects polysaccharide with intestinal flora. The concentration and proportion of SCFAs in the human system are closely related to obesity, diabetes and other metabolic syndromes (Bruning et al. 2020). SCFAs represent the main metabolites of polysaccharide, with abundant contents of acetic acid (40~100 mmol/kg), propionic acid (15~40 mmol/kg) and butyric acid (10~30 mmol/kg) (Zheng 2013).

A previous study found that while short chain fatty acids promote the system to obtain energy, they also increase energy consumption and stimulate the production of satiety hormone (Frost et al. 2014). Acetic acid and propionic acid can improve the lipid buffering capacity of adipose tissue by reducing the decomposition of intracellular fat while inducing the generation of fat, and potentially suppress the secretion of adipose tissue-derived pro-inflammatory cytokines and chemokines (Hansen et al. 2017).

Acetic acid can inhibit the oxidation of local fat via AMPK-dependent mechanism or by changing the oxidative status of muscle fibers, thereby improving the capacity of consuming lipids and carbohydrates (Torres et al. 2017). Butyric acid functions to prevent obesity, liver steatosis and insulin resistance induced by unhealthy diet (Mattace et al. 2013) by promoting energy consumption and strengthening mitochondrial function. Notably, butyric acid is not toxic to mice (Gao et al. 2009).

Butyric acid stimulates the production of intestinal hormones to reduce food intake without causing low count of phages (Lin et al. 2012). Bamboo radish polysaccharides (Jin 2017) could significantly regulate the structure of intestinal bacteria and promote the metabolism of the intestinal flora to produce SCFAs, which proves beneficial to human health and are effective to thwart obesity induced by high-fat diet in mice. Longan polysaccharides enriched the intestinal flora of mice and enhanced the immune function of the host under stressful conditions by promoting the abundances of *Bifidobacteria*, *Bacillus* and arabinoxylanase, as well as the concentrations of succinic acid, acetic acid, propionic acid and butyric acid. Xu et al. (2019) used *Orilla* polysaccharides as the sole carbon source in the co-culturing with intestinal flora, and observed that the taxon richness of intestinal flora was significantly increased. The results demonstrate that *Orilla* polysaccharides can improve microbial diversity by promoting the proliferation of probiotics and inhibiting pathogen proliferation. In addition, it was found that the total amount of short-chain fatty acids in the medium was increased significantly. Among these SCFCs, butyrate could ameliorate the symptom of obesity via the the induction of mitochondrial function to promote energy consumption and reduce the accumulation of fat.

11. Research status of the prevention and treatment of obesity by polysaccharides of TCM based on intestinal microorganisms

An increasing number of natural products have been found to alleviate obesity and restore lipid metabolism by regulating the community structure of intestinal flora. Polysaccharides are widely found in a variety of natural products, and exhibit extensive pharmacological effects, among which immune regulation, glycolipid and energy metabolism are manifestly related to the regulation of the intestinal flora (Yang et al. 2016; Zhou et al. 2016).

Chang et al. (2015) found that *Ganoderma lucidum* polysaccharides significantly alleviate the symptom of obesity in mice fed with high-fat diet by altering the intestinal flora structure (Chang et al. 2015). Polysaccharide MDG-1 from *Ophiopogon japonicus* exhibited a potent ameliorative effect on the intestinal bacteria disorder of diet-induced obese mice, which is manifested by the increased concentration of probiotics in the gut, such as *Lactobacillus taiwanensis* and *Lactobacillus murinus* (Xu et al. 2011). Moreover, the insulin resistance reducing effect of polysaccharide MDG-1 is attributable to the downregulation of the intestinal abundance of *Escherichia coli* and *Streptococcus* and the stimulated proliferation of *Bifidobacterium* in diabetic mice (Shi et al. 2015). The experimental intake of bamboo-shavings polysaccharide (BSP) increased the intestinal microbial diversity, elevated the read number of annotated operational taxonomic unit (OTU) of intestinal microorganisms, and reversed the increasing *Firmicutes/Bacteroidetes* (F/B) ratio in high-fat-diet (HFD) mice. In addition, BSP increased the abundance of certain beneficial microbes (such as *Akkermansia muciniphila* and *Lactobacillus*) related to obesity in the gut, and diminished the excessive proliferation of harmful microbes (such as *Enterobacter* and *Desulfovibrio*) (Jin 2017).

Astragalus polysaccharide (APS) constitutes the major bioactive components of TCM *Astragalus*. Research found that APS could effectively reduce the relative abundance of proteobacteria caused by high-fat diet, thereby alleviating the symptom of obesity (He et al. 2016). The research status of herbal polysaccharides as the protective regulators of intestinal microbiota in the treatment of obesity is summarized in the Table, along with pharmaceutical data of these TCM polysaccharides.

The in-depth exploration into the specific mechanisms of TCM polysaccharides interfere with the metabolic syndrome by modulating the community structure of gut microbiota is of great significance for the development of Chinese herbal medicine, and the prevention and intervention of metabolic disorders.

12. Discussion

The altered community structures of intestinal flora, such as the lower *Bacteroides/Firmicutes* (B/F) ratio and the decorated concentration of butyrate-producing bacteria, are closely related to the onset and progression of obesity. The disordered intestinal microbiota could induce multiple molecular and pathological mechanisms, such as chronic inflammation and metabolic endotoxemia, by implicating in the synthesis of SCFAs, LPS, adipokines and bile acids to trigger excessive apoptosis of pancreatic β cells, compromises insulin sensitivity, and ultimately leading obesity.

It has been widely shown that Traditional Chinese Medicine polysaccharides exhibit protective functions on the intestinal flora via a variety of underlying mechanisms. For instance, herbal polysaccharides alleviate the damage of the intestinal mucosa and safeguard the integrity of the intestinal barrier; stimulate the proliferation of beneficial bacteria whereas inhibit the proliferation of harmful bacteria to maintain a balanced structure of intestinal flora.

Moreover, polysaccharides can upregulate the expression of carbohydrate activity enzyme (CAZymes) genes to induce the production of short-chain fatty acids and to suppress metabolic endotoxins, thwart the secretion of pro-inflammatory cytokines, and elevate the expression of tight junction (TJ) proteins, such as ZO-1, claudin-1 and occludin.

Table: Anti-obesity effects of TCM polysaccharides via modulating the composition and abundance of intestinal microorganisms

Traditional Chinese medicine polysaccharides	Experimental model	Dose	Prevention and treatment of obesity	Intestinal flora
<i>Astragalus</i> polysaccharides, APS (Li et al. 2019)	HFD+C57BL/6J mice	20 g, 40 g, 80 g/kg (4 weeks)	Inhibit the formation of obesity, reduce liver steatosis, reduce liver TG, improve insulin sensitivity, and restore intestinal flora disorders	<i>Bacteroidetes</i> , <i>Firmicutes</i> ↑; <i>Proteobacteria</i> ↓
<i>Artemisia sphaerocephala</i> Krasch polysaccharide (ASKP) (Li et al. 2019)	HFD+Kunming mice	200 mg, 400 mg, 800 mg/kg (8 weeks)	Reduce obesity, improve dyslipidemia and metabolic endotoxemia.	<i>Proteobacteria</i> , AF12, <i>Helicobacter</i> ↓
Seaweed polysaccharide (Duan 2018)	HFD+BALB/c mice	----	Reduced fat accumulation in liver and adipose tissue, improved body composition, reduced malondialdehyde, cholesterol and triglyceride contents in serum and liver, and increased serum HDL levels	<i>Firmicutes</i> ↓ <i>Bacteroidetes</i> ↑
Bamboo-shaving polysaccharides, BSP (Lu 2017)	HFD+C57BL mice	200 mg, 400 mg/kg (8 weeks)	Inhibiting excessive weight gain, enhancing insulin sensitivity, inhibiting obesity-related chronic systemic inflammation, and improving intestinal flora structure	The ratio of <i>Firmicutes</i> abundance (F/B) to <i>Bacteroidetes</i> caused by high-fat diet was reversed.
<i>P. odoratum</i> polysaccharides (POPs) (Wang et al. 2018)	HFD+SD rat	400 mg/kg (4 weeks)	Weight loss, fat accumulation, epididymal fat cell size, triglyceride and total cholesterol content. Increased expression of short chain fatty acids (SCFA) upregulated genes involved in adipocyte differentiation (Pparg, Cebpa, Cebpb) and genes involved in adipocyte differentiation (Ppara, Atgl), and down-regulated genes involved in lipid synthesis	<i>Clostridium</i> , <i>Enterococcus</i> , <i>Symbacteriae</i> , <i>Lactococcus</i> and <i>Sutterella</i> ↓
<i>Ganoderma lucidum</i> polysaccharide, WEGL (Chang et al. 2015)	HFD+C57BL/6J mice	200 mg, 400 mg, 800 mg/kg (8 weeks)	Maintains the integrity of the intestinal barrier and reduces metabolic endotoxemia and insulin resistance	<i>Aerococcus</i> , <i>Ruminococcus</i> , <i>Corynebacterium</i> and <i>Proteus</i> ↓ <i>Blautia</i> , <i>Dehalobacterium</i> , <i>Parabacteroides</i> and <i>Bacteroides</i> ↑
Dwarf lilyturf polysaccharide, MDG-1 (Shi et al. 2015)	HFD+C57BL/6J mice	75 mg, 150 mg, 300 mg/kg (6 weeks)	Increase the number of intestinal probiotics in mice, improve the diversity of intestinal flora, and promote the proliferation of intestinal probiotics	<i>Lactobacillus taiwanensis</i> and <i>Lactobacillus murinus</i> ↑
<i>Polygonatum kingianum</i> Coll. et Hemsl, PF (Wang 2017)	HFD+SD rat	120 mg, 240 mg, 480 mg/kg (4 weeks)	Regulate the key OTUs abundance of intestinal microbes, enhance insulin sensitivity and reduce lipid accumulation;	<i>Firmicutes</i> and <i>Bacteroidetes</i> ↓ <i>Proteobacteria</i> ↓
Mulberry polysaccharide, MFP (Wang 2017)	db/db mice	200 mg, 500 mg, 800 mg/kg (8 weeks)	Reduce the content of free fatty acids, triglycerides and cholesterol, increase the level of high-density lipoprotein, and reduce oxidative stress	<i>Bacteroides</i> ↑ <i>Firmicutes</i> , <i>Proteobacteria</i> , <i>Actinobacteria</i> ↓
<i>Ophiocordyceps sinensis</i> (Wu et al. 2019)	HFD+C57BL/6J mice	20 mg·kg ⁻¹ (8 weeks)	Increase the expression of thermogenic protein markers in adipose tissue, intestinal integrity, reduce intestinal and systemic inflammation, and improve insulin sensitivity and lipid metabolism	<i>Parabacteroides goldsteinii</i> ↑
Sea cucumber polysaccharide sulfate (SCSP) (Zhu et al. 2018)	HFD+BALB/c mice	300 mg/kg (8 weeks)	Reduced fat accumulation, insulin resistance, lipid levels, and systemic inflammation; The ratio of <i>Firmicutes</i> / <i>Bacteroidetes</i> was reversed. Enriched SCFA to generate flora	<i>Akkermansia</i> ↑ Endotoxin-bearing <i>Proteobacteria</i> ↓ Improved the concentration of SCFA and intestinal tissue index
<i>Smallanthus sonchifolius</i> (Wu et al. 2012; Zhu et al. 2017)	Whole-body mouse obesity model in Kunming	200 mg·kg ⁻¹ (4 weeks)	Improved blood lipid levels; inhibits the liver damage caused by cholesterol	<i>Bifidobacterium</i> ↑ Lactic acid bacteria ↑ <i>E. coli</i> ↓
<i>Polygonum multiflorum</i> polysaccharides PS (Bi 2018)	HFD+SD mice	228 mg·kg (12 weeks)	TC and TG were decreased. HDL-C, LA, LPL and HL were increased. Liver weight ratio, heart weight ratio and kidney weight ratio were reduced	<i>Firmicutes</i> / <i>Bacteroidetes</i> ↓
Chicory polysaccharide (Sun et al. 2014)	HFD+SD mice	33.3 g·kg ⁻¹ ·d ⁻¹ (1 week)	Intervention by <i>Bifidobacterium</i> and opportunistic pathogens altered the balance of intestinal flora; Triglyceride levels go down	<i>Bifidobacterium</i> ↑ <i>E. coli</i> ↓
<i>Dendrobium officinale</i> Kimura et Migo, <i>D. officinale</i> polysaccharide (Jia 2016)	Whole-body mouse obesity model in Kunming	0.075 g/ml (2 weeks)	Reduce the levels of TC, TG and LDL-C in serum, improve the lipid metabolism in vivo, and reduce the inflammatory response caused by abnormal lipid metabolism in arteries and vessels	<i>Bifidobacterium</i> , <i>Lactobacillus</i> , <i>Clostridium perfringens</i> ↑ <i>Enterococcus</i> , <i>Enterobacter</i> ↓

The extant therapies for obesity prove little effective, due to individual differences and the unclear definition of pathology. It was presumed that the small-molecular components in TCM contribute the most to the efficacy of the medicine, while the polysaccharides in TCM are of negligible efficacy, owing to larger molecular weight and low absorption after oral administration. In recent years, technological advancement and the enrichment of modern pharmacological methods shed light on the interaction between polysaccharides in TCM and gut microbiota, revealing the anti-obese effect of polysaccharides in TCM by regulating the structure of gut microbiota and gut mucosal immunity, and mediating the metabolites.

The pharmacological effect of polysaccharides of TCM based on the alteration of intestinal flora is yet to be elucidated at the micro-ecological level. Therefore, the application of functional metagenomics to the study the community structure of intestinal flora is a future trend.

The development of high-throughput sequencing (HTS) and metabolomics provides technical support for studying the interaction between polysaccharides and intestinal flora. The application

of 16S rDNA, 18S rDNA and ITS can simultaneously detect species with various abundances in the samples, hence achieving the comprehensive study of community structure of intestinal microbes and functional analysis (Tang and Xie 2020).

Most of the previous researches on the therapeutic effect of polysaccharides focus on analyzing taxon abundance and community structure of the gut microbiota, yet neglect the specific functions of the genes expressed by the flora. The future research should make effort to unravel the function of the bacteria. Metagenomics has shown unique advantages in revealing the community structure and metabolic capacity of bacterial communities. Liu et al. (2019) applied metagenomic technique to discover a large number of gene clusters that are related to polysaccharide degradation and cellobiose utilization pathways in the intestinal flora of termite. Armstrong et al. (2018) studied the functional synergy of fecal flora and reported new polysaccharide utilization loci in the fecal microbiome of *Castor canadensis* by using metagenomic techniques.

Based on the latest literature, we discussed the interaction between obesity, gut microbiota, and TCM polysaccharides, and revealed

the molecular mechanism by which TCM polysaccharides exhibit anti-obesity effect and modulate community structure of gut microbiota. The information summarized in this review will be helpful to select the polysaccharides with huge potential for therapeutical purpose or as dietary supplements. This study provides a promising direction for the treatment of obesity and other metabolic diseases. Funding sources: This work was jointly supported by grants from the University Nursing Program for Young Scholars with Creative Talents in Heilongjiang Province (Grant No. UNPYSCT-2016207), Research Project of Harbin Science and Technology Innovation Talents (Grant No. 2017RAQXJ214)(RC2017QN003037), the Selective Financial Aid for Returnees from Overseas Studies in Heilongjiang Province (Start-up Category) (Grant No. 2018QD0011)(2018383), Outstanding Innovative Talents Project of Heilongjiang University of Traditional Chinese Medicine – Young Academic Leaders Project (Grant No. 2018RCD12)(201877), Post doctoral research start up project in Heilongjiang Province-LBH-Q19183), the Outstanding youth of project by Natural Science Foundation of Heilongjiang Province of China (YQ2020H030), The work was also supported by the Outstanding youth of project by Natural Science Foundation of Heilongjiang Province of China (Grant No. YQ2019H028).

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