Balancing Herbal Medicine and Functional Food for Prevention and Treatment of Cardiometabolic Diseases through Modulating Gut Microbiota

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It has become apparent that gut microbiota is closely associated with cardiometabolic diseases (CMDs), and alteration in microbiome compositions is also linked to the host environment. Next generation sequencing (NGS) has facilitated in-depth studies on the effects of herbal medicine and functional food on gut microbiota. Both herbal medicine and functional food contain fiber, polyphenols and polysaccharides, exerting prebiotics-like activities in the prevention and treatment of CMDs. The administrations of herbal medicine and functional food lead to increased the abundance of phylum Bacteroidetes, and genus Akkermansia, Bifidobacteria, Lactobacillus, Bacteroides and Prevotella, while reducing phylum Firmicutes and Firmicutes/Bacteroidetes ratio in gut. Both herbal medicine and functional food interact with gut microbiome and alter the microbial metabolites including short-chain fatty acids (SCFAs), bile acids (BAs) and lipopolysaccharides (LPS), which are now correlated with metabolic diseases such as type 2 diabetes (T2D), obesity and non-alcoholic fatty liver disease (NAFLD). In addition, trimethylamine (TMA)-N-oxide (TMAO) is recently linked to atherosclerosis (AS) and cardiovascular disease (CVD) risks. Moreover, gut-organs axes may serve as the potential strategy for treating CMDs with the intervention of herbal medicine and functional food. In summary, a balance between herbal medicine and functional food rich in fiber, polyphenols and polysaccharides plays a vital role in modulating gut microbiota (phylum Bacteroidetes, Firmicutes and Firmicutes/Bacteroidetes ratio, and genus Akkermansia, Bifidobacteria, Lactobacillus, Bacteroides and Prevotella) through SCFAs, BAs, LPS and TMAO signaling regarding CMDs. Targeting gut-organs axes may serve as a new therapeutic strategy for CMDs by herbal medicine and functional food in the future. This review aims to summarize the balance between herbal medicine and functional food utilized for the prevention and treatment of CMDs through modulating gut microbiota.

Keywords: herbal medicine, functional food, cardiovascular disease, metabolic disease, intestinal microbiota
INTRODUCTION

The Human Microbiome Project funded by National Institutes of Health (NIH) (Qin et al., 2010) and Metagenomics of the Human Intestinal Tract (MetaHIT) consortium funded by European Commission (Turnbaugh et al., 2007) have promoted better understanding of the functional properties and healthy composition of gut microbiota. Various microbial communities and their genes (the microbiome) are present in human body, influencing human health and diseases (Human Microbiome Project, 2012). The human gut microbiota contains a diverse array of microorganisms, including bacteria, archaea and fungi that colonize the surfaces of the gastrointestinal (GI) tract; bacteriophage are also in high abundance in GI tract (Savage, 1977). Six bacterial phyla dominate the gut microbiota of healthy adult subjects: Firmicutes, Proteobacteria, Bacteroidetes, Fusobacteria, Actinobacteria, and Verrucomicrobia. The intestine hosts >10^14 microorganisms with critical physiological roles, and the microbial compositions differ along the digestive tract (Aron-Wisniewsky and Clement, 2016). The large intestine, particularly the colon, harbors a complex and dynamic microbial ecosystem with high densities of living bacteria. These bacteria achieve concentrations of approximately 10^{11}–10^{12} cells/g of luminal contents (Simon and Gorbach, 1984; Guarner and Malagelada, 2003).

A multitude of literature supports the role of gut microbiota in the development and progression of cardiometabolic diseases (CMDs). CMDs have become a worldwide epidemic, with dramatically increasing prevalence of cardiovascular disease (CVD), obesity, type 2 diabetes (T2D), non-alcoholic fatty liver disease (NAFLD), atherosclerosis (AS), hypertension, and dyslipidemia (Hansen et al., 2015; Aron-Wisniewsky and Clement, 2016; Meyer and Bennett, 2016; Woting and Blaut, 2016; Micha et al., 2017). In the search for novel therapeutic leads, the association of gut microbiota and microbial metabolites with the development of CMDs holds the potential in future drug discovery (Koopen et al., 2016).

Disruption of microbial ecosystems during crucial developmental periods could affect body physiology or cause undesired negative effects. For instance, the overuse of antibiotics in early life is associated with obesity in both humans and rodents (Cho et al., 2012). Herbal medicine such as traditional Chinese medicine (TCM) can be used as an alternative strategy to modulate microbiota and for modern drug discovery. Moreover, certain food components provided benefits beyond basic nutrition, leading to the concept of functional food and nutraceuticals. Functional food offer benefits beyond basic nutrition when consumed regularly as part of a diet. Herbal medicine and functional food produce a large diversity of secondary metabolites which display a broad array of biological and pharmacological properties (Wink, 2015) and are widely accepted as high-efficiency and low toxicity “medicinal diets” which are capable of avoiding certain side-effects. In this review article, recently discovered mechanisms of herbal medicine and functional food are summarized and their contributions to prevention and treatment of CMDs through modulating microbiota are also outlined.

GUT MICROBIOTA IN CMDs

Gut Microbiota in Cardiovascular Diseases

In recent years, an increasing number of researchers begin to pay their attention to the mutual effects on intestinal flora and CVDs, resulting from the new findings of gut microbiota-derived metabolite trimethylamine (TMA)-N-oxide (TMAO). Gut microbiota has an intimate relationship with CVDs, including thrombosis, AS, myocardial infarction (MI) and stroke.

TMAO

TMAO was first identified as a contributor to CVD in a large clinical cohort of 1,876 subjects by Stanley L. Hazen team using an untargeted metabolomics platform (Wang et al., 2011). In a subsequent expansion study of 4,007 subjects undergoing elective coronary angiography indicated an association between elevated TMAO levels in plasma and increased risk for major adverse cardiovascular events (MACE) over a 3-year period in humans (Tang et al., 2013). Then, increasing clinical reports support an involvement of plasma TMAO levels in the etiology of various CVDs. For example, elevated plasma TMAO levels in patients predict a high atherosclerotic burden (Senthong et al., 2016a), long-term adverse event risk and incremental prognostic of peripheral artery disease (PAD) (Senthong et al., 2016b), higher long-term mortality risk of coronary artery disease (CAD) (Senthong et al., 2016c), and adverse clinical outcomes in heart failure (HF) (Tang et al., 2014, 2015b; Troseid et al., 2015). Higher TMAO levels provide clinical utility in risk stratification of acute coronary syndromes (ACS) (Li X. S. et al., 2017) showing a direct pro-thrombotic effect (Zhu et al., 2017), predict close association with poor prognosis of MI (Suzuki et al., 2017). A systematic review and meta-analysis reconfirmed elevated concentrations of TMAO and its precursor TMA were associated with increased risks of MACE (Heianza et al., 2017). Furthermore, gut microbiota played an obligatory role in the metabolism of TMA, eight species (Anaerococcus hydrogenalis, Clostridium asparagiforme, Clostridium hathewayi, Clostridium sporogenes, Escherichia fergussonii, Proteus penneri, Providencia stotleri, and Edwardsiella tarda) in two different phyla (Firmicutes and Proteobacteria) and six genera correlated with choline consumption and TMA accumulation were identified (Romano et al., 2015). Undoubtedly, TMAO had become a new biomarker in diagnosis of CVD.

The conclusions of cumulative reports on the meta-organismal metabolic pathway for TMAO production and
its possible mechanisms resulting in CVD are highlighted: (1) TMAO production: phosphatidylcholine (PC), choline, and L-carnitine, generating the precursor TMA by gut microbiota cleavage, were abundant in dietary foods such as red meat, shellfish, egg yolk and high-fat dairy products (Wang et al., 2011). Until now, either choline or L-carnitine as substrate, TMA is produced by two identified distinct microbial enzyme systems. Catalytic unit (cutC) and a regulatory polypeptide (cutD) are required for TMA production from choline (Craciun and Balskus, 2012; Craciun et al., 2014). The catalytic protein (CntA) and the regulatory protein (CntB) are involved in TMA production form L-carnitine (Zhu et al., 2014). (2) TMAO→TMAO: hepatic flavin monooxygenase 3 (FMO3) expression was up-regulated by bile acids (BAs) via nuclear receptor farnesoid X receptor (FXR) activation (Bennett et al., 2013). TMA was readily absorbed and traveled through the portal circulation to the liver and was oxidized into TMAO by FMO3 (Wang et al., 2011; Bennett et al., 2013). (3) TMAO induced or enhanced cell phenotypic changes: elevated plasma TMAO induced endothelial dysfunction via activating reactive oxygen species (ROS)/thioredoxin-interactive protein (TXNIP)/nod-like receptor family pyrin domain containing 3 (NLRP3) inflammasome (Sun X. et al., 2016) and impairing endothelial nitric oxide synthase (eNOS)-derived NO bioavailability (Hu et al., 2015; Li T. et al., 2017). In addition, TMAO accelerated vascular inflammation through mitogen-activated protein kinase (MAPK) and nuclear factor-κB (NF-κB) signaling (Seldin et al., 2016), reduced endothelial self-repair, and increased monocyte adhesion partly via the pathway of protein kinase C (PKC)/NF-κB/vascular cell adhesion molecule-1 (VCAM-1) activation (Ma et al., 2017). Moreover, TMAO contributed to macrophage cholesterol accumulation and foam cell formation (Wang et al., 2011). Furthermore, TMAO elevated platelet hyperreactivity, enhancing agonists-induced platelet activation through intracellular Ca$^{2+}$ mobilization (Zhu et al., 2016). These changes in cell phenotype contribute to atherosclerotic CVD. (4) TMAO promoted CAD in animal studies: TMAO accelerated AS by reversing cholesterol transport and altering bile acids (BAs) composition (Koeth et al., 2013), enhanced thrombosis formation by activating platelet (Zhu et al., 2016), exacerbated pressure overload−−induced heart failure by inducting adverse cardiac remodeling (Organ et al., 2016). Attention should be paid to the gender identity in the study of TMAO synthesis, since FMO3 expression is higher in females than males in both human and mouse (Bennett et al., 2013).

For further research, pharmacologic inhibition of TMAO production will be a potential therapeutic strategy to reduce CVD events by targeting microbial community, microbial enzyme and/or FMO3 expression. The mechanisms of TMAO pathway (PC, choline, L-carnitine→TMA→FMO3→TMAO) linking the specific microbiota to cardiovascular function is very important and need to be further elucidated. In addition to the new finding of TMAO, other microbial metabolites such as SCFAs (Marques et al., 2017), BAs (Mayerhofer et al., 2017), and LPS (Pastori et al., 2017) which are beneficial for CVD will not be discussed in details here.

**Gut Microbiota in Metabolic Diseases**

A considerable number of publications have reported correlations between gut microbiota and metabolic diseases (Moreno-Indias et al., 2014; Janssen and Kersten, 2015; Greenhill, 2016; Saad et al., 2016; Sonnenburg and Backhed, 2016; Woting and Blaut, 2016). Specific metabolic abnormalities such as pro-inflammatory states, insulin resistance, glucose intolerance, dyslipidemia, high blood pressure and NAFLD, which accompanies gut microbiota dysbiosis, often develop in obese people. Moreover, obesity and T2D are considered as a medical condition, which not only contributes to the risk of developing CVD and cancer, but also negatively affects longevity and quality of life. Here, we describe several crucial mechanisms (mainly about SCFAs, LPS and BAs) that contribute to understanding the correlation between gut microbiota and obesity/T2D.

**SCFAs**

The intestinal microbial fermentation and degradation of dietary nondigestible fiber and polysaccharides to SCFAs (acetate, propionate and butyrate) are regarded as potential metabolic targets to prevent obesity/T2D in glucose metabolism and insulin resistance. Besides, several mechanisms correlate with SCFAs affect body weight via energy intake and energy harvesting, and link with insulin sensitivity through inflammatory resoponse, lipid storage and adipose tissue function (Canfora et al., 2015). SCFAs, serving as energy substrates, directly inhibit histone deacetylases (HDACs) and activate G-protein-coupled receptors (GPCRs). Moreover, butyrate also has effect on epithelial barrier function by increasing mucus production and protein zonula occludens-1 (ZO)-1, occludin expression (Bordin et al., 2004; Peng et al., 2007). GPR41and GPR43 targets are of significance for SCFAs. Gut microbiota promotes adiposity and body weight via SCFAs receptor GPR41. The expression of peptide YY (or PYY), a key hormone involved in the elevation of intestinal transit rate and reduction in energy hearvest, is decreased in GPR41−/− mice (Samuel et al., 2008). On the contrary, SCFAs may prevent obesity via activation of GPR43. Normal diet GPR43−/− mice are obese, whereas HFD-fed GPR43+/+ mice remain lean. Insulin signaling in adipocytes and fat accumulation in white adipose tissue (WAT) are inhibited via acetate-medatied GPR43 (Kimura et al., 2013). These distinct differences remain to be analyzed in how the gut microbiota is modulated. Besides, GPCR43 activation by SCFAs promotes the release of glucagon-like peptide-1 (GLP-1) by intestinal enteroendocrine L cells, thereby leading to insulin release and stimulating glucose tolerance (Tolhurst et al., 2012). Furthermore, a recent paper reported that acetate contributes to GPR43-mediated intestinal IgA response to microbiota, leading to crucial role in intestinal homeostasis maintenance and intestines inflammation defenfence (Wu et al., 2016). Apparently, SCFAs-mediated GPCRs signaling in mice shows extensive effects on obesity/T2D, but the role of GPR41/43 signaling in humans remains to be established.

**LPS**

Endotoxin LPS is a major component of the gram-negative bacterial (such as *Escherichia coli*) outer membrane.
HFD-induced gut microbiota dysbiosis can alter gut permeability and then increase circulating LPS levels which promotes low-grade inflammation and insulin resistance and, ultimately, obesity and T2D in rodents and humans (Cani et al., 2007, 2008; Creely et al., 2007). In addition, Increased intestinal epithelial barrier permeability is due to increased endocannabinoid system tone (Muccioli et al., 2010) and tight junctions (ZO)-1, occludin and claudin-1 expression (Wang J. H. et al., 2014). LPS stimulates inflammatory response mainly by binding to CD14/Toll-like receptor 4 (TLR4) which is responsible for the recruitment and activation of MyD88 adaptor and NF-kB transcription factor, inducing the pro-inflammatory factors interleukin-6 (IL-6), interleukin-1β (IL-1β) and monocyte chemoattractant protein-1 (MCP-1) secretion (Hennessy et al., 2010), and therefore it triggers metabolic diseases (Robbins et al., 2014; Kang et al., 2016). Metabolic characteristics of obesity and T2D in mice were not initiated by injecting LPS when CD14/TLR4 receptor was genetically deleted, showing the significant contribution of LPS/CD14/TLR4 signaling (Shi et al., 2006; Cani et al., 2007, 2008; Poggi et al., 2007). Unexpectedly, insulin is more sensitive in TLR4−/− (Shi et al., 2006) mice, but less in TLR6−/− (Vijay-Kumar et al., 2010) mice with the modulator of gut microbiota than wild-type controls.

BAs

BAs are produced in the liver from cholesterol and metabolized in the gut by the intestinal microbiota (Midtvedt, 1974). Inversely, BAs can modulate gut microbial composition via innate immune genes activation in the small intestine (Wahlstrom et al., 2016). Cholic acid (CA) and chenodeoxycholic acid (CDCA) are the primary BAs produced in humans, whereas CA and muricholic acids (MCAs) are generated in rodents. Besides, mice also produce ursodeoxycholic acid (UDCA) as primary BAs (Sayin et al., 2013), whereas as a secondary BA in human (Ishizaki et al., 2005). The primary BAs are converted into secondary BAs by gut microbial modifications. BAs play multiple roles in the control of obesity/T2D related glucose and lipid metabolism, and energy homeostasis by activating the nuclear FXR and the cytoplasmic G protein-coupled membrane receptor 5 (TGR5) which regulate a large number metabolic pathways in the host (Thomas et al., 2008, 2009; Wahlstrom et al., 2016). On one hand, FXR is activated mainly by the CA and CDCA (Makishima et al., 1999; Parks et al., 1999; Wang et al., 1999), while TGR5 is stimulated mostly by LCA and DCA which are secondary BAs metabolized from CA and CDCA (Maruyama et al., 2002; Chen X. et al., 2011). On another, Ta/BMCA (primary BAs in mice) and UDCA inhibit FXR activation (Li et al., 2013; Sayin et al., 2013; Mueller et al., 2015). Furthermore, GLP-1 synthesis is inhibited by FXR activation (Trabelsi et al., 2015), while it is activated and secreted by TGR5 activation in colonic I cells (Thomas et al., 2009). GLP-1 signaling may be exploited into a new therapy for T2D with the help of gut microbiota (Claus, 2017; Grasset et al., 2017). Hepatic cholesterol 7a-hydroxylase (CYP7A1) is regulated by intestinal FXR with the contribution of a fibroblast growth factor15 (FGF15) activity (Inagaki et al., 2005). What’s more, recent study showed HFD-fed FXR−/− mice an obesity phenotype compared to the wild-type mice (Parsèus et al., 2016). Thus, targeting BAs, FXR, and/or TGR5 signaling with microbiota, may shed a new light on preventing or treating metabolic diseases. At present, our knowledge on the mutual effects between BAs and gut microbiota is still far from complete.

In recent studies, the gut metabolite TMAO is also found to have an intimate relationship with metabolic diseases such as T2D (Dambrova et al., 2016; Tang et al., 2016; Schugar et al., 2017), NAFLD (Chen Y. M. et al., 2016), chronic kidney disease (CKD) (Tang et al., 2015a; Xu K. Y. et al., 2017) and bariatric surgery (Troseid et al., 2016), along with the metabolic functions including insulin resistance (Oellgaard et al., 2017) and BAs metabolism (Wilson et al., 2016). With the rapid development in the field of intestinal microbiota, the gut metabolites like TMAO, SCFAs, LPS, and BAs with their signaling interplay between microbiota, have evolved as promising avenues for prevention and treatment of CMDs. Herbal medicine and functional food with the property of muti-ingredient, multi-target and muti-pathway action may serve as a prebiotic-like remediation (Laparra and Sanz, 2010; Xu J. et al., 2017). How might they work in CMDs by modulating gut microbiota are discussed below.

**HERBAL MEDICINE AND GUT MICROBIOTA**

The effectiveness of antibiotics in modern medicine has diminished somewhat due to the development of multi-drug resistant bacteria after using for more than 70 years. New classes of antimicrobial drugs are unlikely to become widely available any time soon (Laxminarayan et al., 2016). If and when they do, bacteria, viruses and other microbes will again evolve antimicrobial resistance (AMR) through variety of ways including horizontal gene transfer of mobile genetic elements (Carroll et al., 2014; Jorgensen et al., 2016). Experimental evidence, particularly rodent studies, showed convincingly that prebiotics, non-digestible, fermentable carbohydrates and fibers are capable of enhancing the growth of specific beneficial gut bacteria, thus reducing body weight, reversing insulin resistance and exerting anti-inflammatory effects (Bindels et al., 2015; Sonnenburg and Backhed, 2016). However, these effects have yet to be confirmed by intervention studies in human. Recent investigations support the idea of the involvement of intestinal bacteria in host metabolism and preventative therapeutic potential of prebiotic interventions for CMDs. Herbal medicine may therefore serve as a potential prebiotic remedy to treat CMDs and complications.

Several herbal medicine formulae, herals and nutraceuticals that contain fiber, polyphenol, polysaccharide and certain other substances have anti-obese, anti-diabetic and anti-atherosclerotic effects through the modulation of diverse gut microbiota. These herbal with their components have the potential to be a new source for CMD drugs discovery that target specifically the gut microbiota, as summarized in Tables 1–3. According to the early direct evidence in 187 T2D patients, a herbal formula Gegen Qinlian Decoction (GQD) including four herbs: Gegen (Radix Puerariae), Huangqin (Radix Scutellariae), Huanglian (Radix Angelicae Sinensis), Zhi Bai (Radix Notopterae Officinalis) and Xi Mu (Puidiocarpus Folia) was found to significantly reduce blood sugar levels and improve clinic efficacy. This study suggests that herbal medicine and gut microbiota, may shed a new light on preventing or treating metabolic diseases. At present, our knowledge on the mutual effects between BAs and gut microbiota is still far from complete.
## TABLE 1 | Herbal formulae and gut microbiota.

<table>
<thead>
<tr>
<th>Formulae</th>
<th>Herbs &amp; ingredients</th>
<th>Objects</th>
<th>Diseases</th>
<th>Physiological function related to gut microbiota</th>
<th>Gut microbiota</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gegen Qinlian Decoction (GQD)</td>
<td>Herbs: Radix Puerariae (Ge Gen), Radix Scutellariae (Huang Qin), Rhizoma Coptidis (Huang Lian), Honey-fried Licorice Root (Gan Cao), Ingredients: Bicalin, Puerarin, Berberine</td>
<td>187 T2D patients</td>
<td>T2D</td>
<td>① Enrich beneficial bacteria, ② Reduce blood glucose and glycated hemoglobin.</td>
<td>Increased: Faecalibacterium spp.</td>
<td>Xu et al., 2015</td>
</tr>
<tr>
<td>Sancai Lianmei Particle (SLP)</td>
<td>Herbs: Panax ginseng (Ren Shen), Rhizoma Atractylodis Macrocephalae (Bai Zhu), Coptis chinensis (Huang Lian)</td>
<td>60 T2D patients</td>
<td>T2D</td>
<td>Regulate intestinal flora of T2D and have similar function with acarbose.</td>
<td>N/A (Not Applicable)</td>
<td>Fang et al., 2016</td>
</tr>
<tr>
<td>Ginseng decoction</td>
<td>Herbs: Panax ginseng (Ren Shen), Ingredients: Ginseng polysaccharides, Ginsenosides</td>
<td>SD rat</td>
<td>Over-fatigue and acute cold stress model (OACS)</td>
<td>① Improve intestinal metabolism and absorption of certain ginsenosides, ② Reinstate the holistic gut microbiota.</td>
<td>Increased: Lactobacillus spp., Bacteroides spp.</td>
<td>Zhou et al., 2016</td>
</tr>
<tr>
<td>Daesio-tang (Korea)</td>
<td>Herbs: Bupleuri radix (Chai Hu), Finefiae rhizome (Ban Xia), Zingiberis rhizome (Gan Jiang), Scutellatae radix (Huang Qin), Paeoniae radix (Shao Yao), Zizyphus fructus (Da Zao), Ponciri fructus , Rheinundulati rhizome</td>
<td>C57BL/6 mice</td>
<td>Obesity</td>
<td>① Ameliorate body weight gain and body fat, ② Regulate adiponectin and leptin genes expression, ③ Exert an anti-diabetic effect by attenuating fasting glucose level and serum insulin level, ④ Reduce TC, TG and increase HDL, GPT and GOT levels and reduce fat droplets accumulation.</td>
<td>Increased: Bacteroidetes/Firmicutes ratio, Bacteroidetes, Lactobacillus, Akkermansia, Bifidobacterium. Decreased: Firmicutes.</td>
<td>Hussain et al., 2016</td>
</tr>
<tr>
<td>Yupingfeng polysaccharides</td>
<td>Herbs: Astragali radix (Huang Qi) Atractylodes macrocephala rhizome (Bai Zhu), Radix saposhnikoviae (Fang Feng), Ingredients: Yupingfeng polysaccharides</td>
<td>Weaning rex rabbits</td>
<td>Immune-related diseases</td>
<td>① Promote growth and immune activities, improve intestinal microbiota homeostasis and maintain intestinal barrier functionality and integrity. ③ Enhance IL-2, IL-4, IL-10, INF-γ, TNF-α, TLR2, TLR4 mRNA levels; improve IL-1, IL-2, IL-4, IL-6, IL-10, IL-12, TNF-α, INF-γ protein levels, and TLR2, TLR4 mRNA expressions.</td>
<td>Increased: Cellulolytic bacteria Decreased: Streptococcus spp., Enterococcus spp.</td>
<td>Sun H. et al., 2016</td>
</tr>
<tr>
<td>Qushi Huayu Decoction (QHD)</td>
<td>Herbs: Artemisia capillaries Thunb (Yin Chenhao), Gardenia jasminoides Ellis (Zhi Zi), Fallopia japonica (Hu Zhang), Curculio longa L. (Jiang Huang), Hypericum juponicum Thunb. (Tian Jhuang), Ingredients: Geniposide, chlorogenic acid.</td>
<td>SD rats</td>
<td>NAFLD</td>
<td>① Decrease serum LPS, hepatic lipid synthesis, and regulatory T cell inducing microbiota, ② Improve gut barrier function and hepatic anti-oxidative mechanism.</td>
<td>Increased: Fusobacteria, Lentsphaerenae, Virruncoccusla, Cyanobacteria, Deferribacteria, Proteobacteria, Bacteroidetes. Decreased: Firmicutes, Tenericutes, Actinobacteria.</td>
<td>Feng et al., 2017</td>
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<tr>
<td>Herbs</td>
<td>Ingredients</td>
<td>Objects</td>
<td>Diseases</td>
<td>Physiological function related to gut microbiota</td>
<td>Gut microbiota</td>
<td>References</td>
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<tr>
<td>Rehmannia glutinosa Libosch (Shu Dihuang)</td>
<td>N/A</td>
<td>Twenty 40-65 years old female middle-aged subjects with obesity</td>
<td>Obesity</td>
<td>Decrease waist circumference.</td>
<td>Increased: Actinobacteria, Bifidobacterium,</td>
<td>Han et al., 2015</td>
</tr>
<tr>
<td>Flos Lonicera (JinYinghua)</td>
<td>Polysaccharides, Organic acids, Saponins, Irido glycosides</td>
<td>SD rats</td>
<td>Obesity and metabolic endotoxemia</td>
<td>Decrease body weights, Decrease endotoxin, aspartate transaminase, HDL, triglyceride levels, Reduce lipid accumulation and alleviate urinary lactulose/mannitol ratio.</td>
<td>Increased: Akkermansia spp., Bifidobacterium/Firmicutes ratio.</td>
<td>Wang et al., 2014</td>
</tr>
<tr>
<td>Rhizoma Coptidis (Huang Lian)</td>
<td>Berberine</td>
<td>C57BL/6J mice</td>
<td>Obesity</td>
<td>Lower degradation of dietary polysaccharides, decrease potential calorie intake, increase Fiaf protein and its related gene expressions of mitochondrial energy metabolism.</td>
<td>Increased: Bacteroidetes/Firmicutes ratio, Decreased: Lactobacillus.</td>
<td>Xie et al., 2011</td>
</tr>
<tr>
<td>Lingonberry (Vaccinium vitis-idaea L.)</td>
<td>20% lingonberries</td>
<td>C57BL/6J mice</td>
<td>Obesity</td>
<td>Reverse endotoxemia and inflammation, Anti-obesity.</td>
<td>Increased: Akkermansia/Faecalibacterium ratio.</td>
<td>Heyman-Linden, et al., 2016</td>
</tr>
<tr>
<td>Herba Epimdi (Yin Yanghao)</td>
<td>Icarin, Epimedin A, B, C</td>
<td>SD rats</td>
<td>Osteoporosis</td>
<td>Enhance epimedium flavonoids absorption and antosteoporosis activity.</td>
<td>Decreased: Lactobacillus, Bacteroides, Parabacteroides.</td>
<td>Zhou et al., 2015</td>
</tr>
<tr>
<td>Gariaonia cambogia (Teng Huangguo)</td>
<td>Extract</td>
<td>C57BL/6J mice</td>
<td>Obesity</td>
<td>Alleviate weight gain and adiposity</td>
<td>Increased: Clostridium aminophilum.</td>
<td>Mei et al., 2015</td>
</tr>
<tr>
<td>Cassia obtusifolia L. (Jue Mingzi)</td>
<td>Anthraquinone</td>
<td>SD rats</td>
<td>NAFLD</td>
<td>Evaluate Lipid metabolism and gut microbiota diversity, Up-regulate FXR, CYP7A1, LDL-R mRNA and PPAR-α protein levels, down-regulate HMGCR, PPAR-γ and SREBP-1c expression.</td>
<td>Decreased: Oscillospira.</td>
<td></td>
</tr>
<tr>
<td>Radix ginseng rubra (Hong Shen) and Semen Coicis (Yi Yiren)</td>
<td>N/A</td>
<td>Wistar rat</td>
<td>Ulcerative colitis (UC)</td>
<td>Improve gut microbiota structure and relieve the ulcerative Colitis symptom.</td>
<td>Increased: Bifidobacterium, Lactobacillus.</td>
<td>Guo et al., 2015</td>
</tr>
<tr>
<td>Polygonatum kingianum (Dan Huangjing)</td>
<td>Polysaccharides, Saponins</td>
<td>SD rats</td>
<td>T2D</td>
<td>Reduce SCFAs production, Decrease LPS levels, Partial recover insulin secretion and fasting blood glucose levels.</td>
<td>Increased: Family Ruminococaceae, Genus Ruminococcus.</td>
<td>Yan et al., 2017</td>
</tr>
</tbody>
</table>

TABLE 2 | Herbs and gut microbiota.
<table>
<thead>
<tr>
<th>Phytochemicals Category</th>
<th>Objects</th>
<th>Diseases</th>
<th>Physiological function related to gut microbiota</th>
<th>Gut microbiota</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resveratrol Polyphenol 37 obese men and women</td>
<td>Obesity</td>
<td>Increase fat oxidation</td>
<td>Decreased: Bacteroidetes, Faecalibacterium</td>
<td>Most et al., 2017</td>
<td></td>
</tr>
<tr>
<td>Resveratrol Polyphenol (1) CS7BL/6J ApoE−/− mice</td>
<td>(1) AS</td>
<td>(1) AS-related</td>
<td>(1) Increase TMAO synthesis in liver → inhibit AS, Increase BSH activity → promote generation of unconjugated BAs, Decrease BA content → inhibit FXR-FGF15 axis → increase CYP7A1 expression → induce neosynthesis of hepatic BA → promote cholesterol homeostasis → attenuate AS</td>
<td>Most et al., 2017</td>
<td></td>
</tr>
<tr>
<td>(2) Kunming mice</td>
<td>(2) Obesity</td>
<td>(2) Obesity-related</td>
<td>(2) Decrease body and visceral adipose weights, and reduce lipid and blood glucose levels, Increase Fiaf gene expression, and decreases LPL, SCF1, PPAR-γ, ACC1, Fas mRNA expression correlation with fatty acids synthesis, lipogenesis and adipogenesis</td>
<td>Qiao et al., 2014; Chen M. L. et al., 2016</td>
<td></td>
</tr>
<tr>
<td>Berberine Alkaloid (1) Wistar rats</td>
<td>(1) Obesity, insulin resistance</td>
<td>(1) Inhibit obesity and insulin resistance development, Increase LPS-binding protein MCP-1, leptin levels, and decrease adiponecin level, Elevate SCFA levels in the intestine</td>
<td>Increased: Blautia, Allobaculum</td>
<td>Xie et al., 2011; Zhang et al., 2012a, 2015; Cao et al., 2016; Wang Y. et al., 2017</td>
<td></td>
</tr>
<tr>
<td>(2) Wistar rats</td>
<td>(2) Obesity</td>
<td>(2) Enrich bacteria produced by SCFA and reduce microbial diversity</td>
<td>Decreased: Allobaculum, Bacteroides, Blautia, Butyricoccus, Phascolarctobacterium</td>
<td>Decreased: Enterococcus faecalis.</td>
<td></td>
</tr>
<tr>
<td>(3) CS7BL/6J mice</td>
<td>(3) Obesity</td>
<td>(3) Decrease dietary polysaccharides degradation, lower the intake of potential calorie, and activate the expressions of Fiaf protein and related genes of mitochondrial energy metabolism</td>
<td>Increased: Bacteroidetes/Firmicutes ratio, Decreased: Bacteroidetes/Firmicutes ratio, Blatia, Allobaculum.</td>
<td>Xie et al., 2011; Zhang et al., 2012a, 2015; Cao et al., 2016; Wang Y. et al., 2017</td>
<td></td>
</tr>
<tr>
<td>(4) BALB/C Mice</td>
<td>(4) NAFLD</td>
<td>(4) Reduce body weight, and lipids, glucose, insulin level in serums. Improve transaminase activity and NAFLD activity score through down-regulated CD14, IL-1, IL-6, TNF-α.</td>
<td>Increased: Bacteroidetes/Firmicutes ratio, Decreased: Lactobacillus, Bacteroidetes/Firmicutes ratio, Blatia, Allobaculum.</td>
<td>Xie et al., 2011; Zhang et al., 2012a, 2015; Cao et al., 2016; Wang Y. et al., 2017</td>
<td></td>
</tr>
<tr>
<td>(5) SD rat</td>
<td>(5) Energy metabolism</td>
<td>(5) Promote butyrate production, Regulate energy metabolism by suppressing bacterial ATP production and nicotinamide adenine dinucleotide phosphate (NADPH) levels.</td>
<td>(4) Increased: Bacteroidetes/Firmicutes ratio, Blatia, Allobaculum.</td>
<td>Etxeberria et al., 2015a</td>
<td></td>
</tr>
<tr>
<td>Quercetin Polyphenol Wistar rats</td>
<td>Obesity</td>
<td>Prevent body weight gain and reduce serum insulin levels and insulin resistance.</td>
<td>Decreased: Firmicutes/Bacteroidetes ratio, Erysipelotrichaceae, Baciillus, Eubacteriumcylindroides</td>
<td>Etxeberria et al., 2015a</td>
<td>(Continued)</td>
</tr>
<tr>
<td>Phytochemicals</td>
<td>Category</td>
<td>Objects</td>
<td>Diseases</td>
<td>Physiological function related to gut microbiota</td>
<td>Gut microbiota</td>
</tr>
<tr>
<td>----------------</td>
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</tr>
<tr>
<td>Curcumin</td>
<td>Polyphenol</td>
<td>(1) 129/SvEv mice, germ-free Il10−/− mice</td>
<td>(1) Colitis and colon cancer</td>
<td>(1) Increase survival, decrease colon weight/length ratio, eliminate tumor burden.</td>
<td>(1) Increased: Lactobacillus, Lactobacillales, Bifidobacteriales, Erisipelotrichales, Coriobacteriales, Decreased: Obesitales, Firmicutes.</td>
</tr>
<tr>
<td>(2) LDLR−/− mice</td>
<td>(2) AS</td>
<td>(2) LDLR−/− mice</td>
<td>AS</td>
<td>Decrease LPS levels, Increase intestinal barrier function by restoring intestinal alkaline phosphatase activity and tight junction proteins ZO-1 and Claudin-1 expression, Reduce glucose intolerance and AS.</td>
<td>(2) N/A</td>
</tr>
<tr>
<td>Ophiopogon japonicas polysaccharide</td>
<td>Polysaccharide</td>
<td>C57BL/6J mice</td>
<td>Obesity</td>
<td>Improve gut microbiota diversity and promote proliferation.</td>
<td>Increased: Taiwan lactobacillus, Lactobacillus murinus</td>
</tr>
<tr>
<td>Pterostilbene</td>
<td>Polyphenol</td>
<td>Zucker (ts/ta) rats</td>
<td>Obesity</td>
<td>Improved metabolic function (insulin sensitivity) and Anti-obesity.</td>
<td>Increased: Akkermansia, Odoribacter, Verrucomicrobia, Decreased: Firmicutes.</td>
</tr>
<tr>
<td>Taurine</td>
<td>Amino acid</td>
<td>BALB/C mice</td>
<td>Neuroendocrine</td>
<td>Increase SCFA content in feces, decrease LPS content in serum. Functions</td>
<td>Decreased: Proteobacteria (especially Helicobacter)</td>
</tr>
</tbody>
</table>
showed the anti-T2D effect partly by enriching the amounts of specific beneficial bacteria Faecalibacterium spp. (Xu et al., 2015). Interestingly, both Rhizoma coptidis (as the major component of GQD) and berberine (as the main phytochemicals of Rhizoma coptidis) are confirmed to have an anti-obese effect by inhibiting the ratio of Firmicutes/Bacteroidetes, and lowering the growth of Lactobacillus (a classical type of Firmicutes) in HFD-fed mice feces. In addition, Rhizoma coptidis and berberine can reduce HFD-induced body weight and visceral adipose weights, and blood glucose and lipid levels in mice (Xie et al., 2011). What's more, berberine increases putative SCFA-producing bacteria, including Blautia, Allobaculum, Bacteroides, Blautia, Butyricoccus, and Phascolarctobacterium, possibly leading to anti-obese and anti-diabetic effects in the host (Zhang et al., 2012a, 2015). Rhizoma coptidis and berberine, also the main ingredients of GQD, may contribute to the significant resistance to metabolic disease by targeting intestinal microbiota, which need to be further confirmed in clinical trials. A recent study showed that berberine improved non-alcoholic steatohepatitis (NASH) by restoring Bifidobacteria and reducing Firmicutes/Bacteroidetes ratio (Cao et al., 2016). Another herbal formula Qushi Huayu Decoction (QHD), a mixture of five herbs (Artemisia capillaries Thumb, Gardenia jasminoides Ellis, Fallopia japonica, Curcuma longa L., and Hypericum japonicum Thumb.) and two active ingredients (geniposide and chlorogenic acid) reduces oxidative stress and inflammatory response in liver by inducing glutathione-generating enzymes, decreases lipid synthesis and elevates steatosis by inhibiting glucokinase expression, and ameliorates gut barrier function and alleviates liver inflammation by inducing Treg-producing bacteria. In these studies, 12 phyla of gut bacteria were altered, including increased Fusobacteria, Lentisphaerae, Verrucomicrobia, Cyanobacteria, Deferribacteres, Proteobacteria, and Bacteroidetes, as well as decreased Firmicutes, Tenericutes and Actinobacteria (Yang et al., 2017).

Resveratrol (RSV), a natural polyphenolic compound extracted from herbal medicine Rhizoma Polygani Cuspidati or functional food peanut, grape, and Fructus Mori, exerts antioxidant, anti-inflammatory (Walker et al., 2014), anti-tumor, cardioprotective, aging-delay, and anti-obesity effects (Baur and Sinclair, 2006; Zhang et al., 2012b). On one hand, RSV decreases TMAO levels and increases hepatic BA neosynthesis via increasing the genera Lactobacillus and Bifidobacterium, thus attenuating TMAO-induced AS in ApoE−/− mice. RSV-induced BA neosynthesis was partially mediated through the enterohepatic FXR-fibroblast growth factor 15 (FGF15) axis (Chen M. L. et al., 2016). On another, RSV increases the ratio of Bacteroidetes/Firmicutes and the growth of Lactobacillus and Bifidobacterium. It also reduces the growth of Enterococcus faecalis through fasting-induced adipose factor (Fiaf, a key gene expresses in the intestine and negatively regulated by intestinal flora) signaling, decelerating the development of obesity (Qiao et al., 2014). RSV is probably an unique and firstly reported natural product that mediates protection against both CVD and metabolic diseases via gut microbiota to date. In addition, quercetin, a key member of the polyphenol family, is discovered in numerous medicinal botanicals, including Ginkgo biloba, Hypericum perforatum, and Sambucus canadensis and also found in a variety of functional foods including apple, grape, berry, onion and tea (Li Y. et al., 2016). Intake of quercetin reduced body weight gain and attenuated serum insulin levels by reducing Firmicutes/Bacteroidetes ratio and inhibiting the growth of bacterial species Erysipelotrichaceae, Bacillus and Eubacterium cylindroides, which correlated with HFD-induced obesity (Etxeberria et al., 2015a). Moreover, it was shown in a recent study that curcumin, the major polyphenolic ingredient of an edible herb Curcuma longa L. improved intestinal barrier function by modulation of intracellular signaling, and organization of tight junctions, providing a mechanism that curcumin modulates chronic inflammatory diseases despite poor bioavailability (Wang J. et al., 2017). The details of some other herbal medicines, including formulae, herbs and phytochemicals reportedly to achieve their therapeutic effects for CMDs through gut microbiota modulation are summarized in Tables 1–3.

**FUNCTIONAL FOOD AND MICROBIOTA**

Functional food has the advantages of wide availability, ease of preparation and fewer adverse effects. They could be well suited for CMDs remedies due to their potential effects such as anti-inflammatory, antioxidants, antiestrogens, immunomodulatory, whereas purified active compounds are preferable as pharmaceutical drugs for the treatment of severe chronic symptoms (Martel et al., 2016; Meyer and Bennett, 2016). Epidemiological studies have identified associations between frequent consumption of fruits, vegetables, whole grains and teas, which are rich in fiber, polyphenol, and polysaccharide could reduce the risk of CMDs (Woodside et al., 2013; Klinder et al., 2016). These phytochemicals and their metabolic products may inhibit pathogenic bacteria while stimulating the growth of beneficial bacteria for CMDs (Laparra and Sanz, 2010).

Apples are among the most frequently consumed fruits to prevent obesity by modulating gut microbiota with their multiple components, including fiber, pectin (Jiang et al., 2016), procyanidins (Masumoto et al., 2016) and polysaccharides (Wang S. et al., 2017). Administration with apple procyanidins (a subclass of polyphenols) for 20 weeks was able to reduce obesity, decrease lipid metabolism related genes expression, lower LPS levels and gut permeability through decreasing the Firmicutes/Bacteroidetes ratio and increasing Akkermansia proportion (Masumoto et al., 2016). In addition, treatment with apple polysaccharide inhibited chronic inflammation, gut permeability, and SCFAs production, leading to lower abundance of Firmicutes and Fusobacteria, and higher Bacteroidetes and Lactobacillus in HFD-fed rats (Wang S. et al., 2017). Furthermore, the reciprocity between apple ingredients and the gut microbiota may benefit cardiovascular health (Koutsos et al., 2015). Unexpectedly, diet apple fiber and flavone were positively associated with Blautia, Lactobacillus, Bifidobacterium, and Faecalibacterium, showing great significance for the patients who suffer from systemic lupus erythematosus (SLE) (Cuervo
Kitai and Wang J. H. (2016) have demonstrated beneficial effects of functional foods on anti-inflammation, vascular function, and energy metabolism. The “medicine-food homology” concept has given a new meaning since the discovery of human-microbiota existing as a whole symbiotic ecosystem. The interplay between herbal medicine and food deriving from the same source has been realized since ancient times. In TCM, food is conceptualized not only as a remedy, but also are delicious food with rich nutrients. Besides, these components can also be converted by local microbiota to biologically active and bioavailable metabolites with systemic effects.

OVERLAPING EFFECTS BETWEEN HERBAL MEDICINE AND FUNCTIONAL FOOD ON GUT MICROBIOTA

Medicine and food deriving from the same source has been realized since ancient times. In TCM, food is conceptualized according to both nutritional and functional aspects, and can be used to treat illnesses. The “medicine-food homology” concept has given a new meaning since the discovery of human-microbiota existing as a whole symbiotic ecosystem. Interestingly, a series of overlapping characteristics through modulating gut microbiota for CMDs between herbal medicine and functional food are uncovered based on the description above (Tables 1–5): shared components, similar functions, common mechanisms, and same intestinal microbiota.

First and foremost, there is no absolute boundary between medicine and food. Some medicines are food whereas certain foods can be employed as medicine. Lonicera japonica Thunb., Cassia obtusifolia L., Semen Coicis, adlay, Zingiber officinale Roscoe (major ingredient: curcumin), and mulberry (main ingredient: RSV), are edible medicines, there are only dosage differences between edible and medicinal use. These herbs not only belong to medicine with valid efficacies for CMDs remedy, but also are delicious food with rich nutrients. Besides, some medicines have been developed into nutraceuticals, which contain important natural bioactive compounds that confer health-promoting and medical benefits to humans, such as Ganoderma lucidum, Herba Epimidi, Ophiopogon japonicas, Rehmannia glutinosa Libosch, Rheum rhabarbarum (major ingredient: rhein), and lingonberry, see Tables 1–3. Furthermore, many foods could serve as nutraceutical candidates, and some of those, such as pomegranate peel, bamboo shoot, grape (major ingredient: RSV), and laminarin have the potential to branch into medicines (Tables 4, 5).

Secondly, the components of fibers (e.g., bamboo shoot, nopal, and yellow pea), polyphenols (e.g., GQD, Flos Lonicera, adlay, apple, grape, orange, nopal and tea) and/or polysaccharides (e.g., Ginseng decoction, Yupingfeng, Ganoderma lucidum, Polygonatum kingianum, Ophiopogon japonicas, apple and barley) are shared in most herbs and foods, exerting prebiotics-like effects for CMDs, which can be seen in Tables 1–5. Moreover, polyphenol phytochemicals such as RSV and quercetin are present in both herbs and foods. These components are able to escape absorption in the upper gastrointestinal tract and reach the large intestine without breaking down. Thus, these components can also be converted by local microbiota to biologically active and bioavailable metabolites with systemic effects.

Thirdly, just as what we have introduced above, gut microbiota-derived metabolites such as SCFAs, LPS, and TMAO are the most likely microbial metabolites linking CMDs remedy to intestinal microbiota. Numerous herbs and foods are likely to prevent and treat CMDs through these mediators. Improved gut permeability and gut integrity in conjunction with the increased expression of ZO-1 and/or occludin-1 and/or claudin-1, resulted in reduction of circulating LPS levels and a series of inflammatory response, which are affected by herbs (Yupingfeng polysaccharides enhanced immunity, Sun H. et al., 2016). QHD was used in the treatment of NAFLD (Feng et al., 2017); Flos Lonicera ameliorated obesity (Wang J. H. et al., 2014); curcumin attenuated AS (Ghosh et al., 2014) and foods [apple derived polyphenols and polysaccharide prevented obesity, (Masumoto et al., 2016; Wang S. et al., 2017), nopal and capsaicin were used in combating obesity (Kang et al., 2017; Sanchez-Tapia et al., 2017)]. SCFAs production was shown to restore aberrant levels of gut hormones such as GLP-1, PYY, and the activation of GPR43. SCFAs production are also promoted by berberine in energy metabolism, insulin resistance and obesity (Xie et al., 2011; Zhang et al., 2015; Xu J. H. et al., 2017); elevated by apple polysaccharide in chronic inflammation, and enriched by oat in obesity treatment (Wang S. et al., 2017). In addition, Polygonatum kingianum and taurine intervene with both SCFAs and LPS levels in different CMDs (Yu et al., 2016; Yan et al., 2017). TMAO levels were inhibited via the reduction of TMA formation by RSV and then attenuate AS (Wang Z. et al., 2015; Chen M. L. et al., 2016). At the same time, RSV increased BAs deconjugation and fecal excretion by enhancing the activity of hydrolase activity, which displayed correlation with the lowered BA content in ilealby suppressing FXR-FGFI5 axis and promoting CYP7A1 expression (Chen M. L. et al., 2016). All of these interventions are along with the changed microbiota composition. An increasing number of metabolic pathway and potential mechanisms are studied on the mediators of SCFAs, LPS, BAs and TMAO. These studies provide a better understanding of how herbs and foods prevent or treat CMDs by gut microbiota. The cross-talk between these mediators and specific alteration of intestinal bacteria in host physiology, as well as the precise contributing elements in herbs and foods for CMDs remedy should be subjects for future studies.

Finally, previous work has established that genera Clostridium, Lactobacillus and Ruminococcus, as well as the butyrate producers...
<table>
<thead>
<tr>
<th>Functional Food</th>
<th>Ingredients</th>
<th>Objects</th>
<th>Diseases</th>
<th>Physiological function related to gut microbiota</th>
<th>Gut microbiota</th>
<th>References</th>
</tr>
</thead>
</table>
| Vegetable/fruit juice | Polyphenols, Oligosaccharides, Fer, Nitrates | Twenty adults | Obesity | 1. Alter the intestinal microbiota associated with weight loss,
2. Increase in vasodilator NO,
3. Decrease in lipid oxidation. | Increased: Bacteroidetes, Cyanobacteria,
Decreased: Firmicutes, Proteobacteria | Henninger et al., 2017 |
| Barley | β-Glucan | 30 volunteers | CVD | N/A | Increased: Bacteroidetes,
Decreased: Firmicutes, Prevotella,
Decreased: Firmicutes, Dorea. | Wang Y. et al., 2016 |
| Apple | (1) procyanidin, (2) pectin, (3) Polyphenols, (4) Polysaccharide | (1) C57BL/6J mice, (2) SD rat, (3) Systemic lupus erythematosus patients, (4) SD rat | Obesity | (1) Attenuate inflammatory effects and weight gain including gut permeability and lipopolysaccharide,
2. Decrease endogenous metabolites levels related with insulin resistance,
(2) Attenuate weight gain and serum total cholesterol level,
2. Improve intestinal alkalinephosphatase, claudin 1 expression, decrease TLR4 expression in ileal tissue, decrease inflammation (TNF-α) and metabolic endotoxemia.
(3) Attenuate inflammatory effects and weight gain,
2. Decrease endogenous metabolites levels related with insulin resistance,
(4) Microbial dysbiosis and chronic inflammation,
2. Attenuate gut permeability and chronic inflammation (decrease LBP, up-regulation of occludin, down-regulation TNF, MCP-1, CXCL-1, IL-1β)). | Increased: Akkermansia,
Decreased: Firmicutes/Bacteroidetes ratio. | Cuervo et al., 2015; Jiang et al., 2016; Masumoto et al., 2016; Wang S. et al., 2017 |
| Oranges | Polyphenols | 20 Systemic lupus erythematosus patients | N/A | N/A | Increased: Bifidobacterium. | Cuervo et al., 2015 |
| Grape | (1) Pomace, Polyphenols | (1) Lamb, (2) N/A, (2) C57BL/6J mice | (1) N/A, (2) Obesity | (1) Decrease oxidative stress-induced damage to lipids and proteins such as TBARS and CARB,
2. Decrease triglyceride and liver weight levels and reduce GPAT1 expression,
2. Reduce hepatic mRNA PPAR-γ2, SCD1, FABP4 and GPAT1 levels | Decreased: Enterobacteriaceae, Escherichia coli. | Baldwin et al., 2016; Kafantaris et al., 2016 |

(Continued)
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<thead>
<tr>
<th>Functional Food</th>
<th>Ingredients</th>
<th>Objects</th>
<th>Diseases</th>
<th>Physiological Function related to gut microbiota</th>
<th>Gut microbiota</th>
<th>References</th>
</tr>
</thead>
</table>
| Grape seed     | Proanthocyanidin | C57BL/6 mice | Obesity | 1. Decrease plasma inflammatory factors TNF-α, IL-6 and MCP-1 levels,  
2. Ameliorate macrophage infiltration,  
3. Reduce epididymal fat mass and improve insulin sensitivity. | Increased: Clostridium XIVa, Roseburia, Prevotella | Liu et al., 2017 |
| Agave salmiana | Saponin      | C57BL/6 mice | Obesity and hepatic steatosis | 1. Decrease fat mass and weight gain, Lower insulin, glucose, and LDL levels,  
2. Lower hepatic lipid levels and HOMA index, increase fatty acid oxidation related genes expression,  
3. Increase fatty acid oxidation, AMPK phosphorylation, white adipose tissue browning, mitochondrial activity and energy expenditure. | Increased: Akkermansia muciniphila | Leal-Diaz et al., 2016 |
| Cranberry      | Cranberry extract | C57BL/6J mice | Obesity | 1. Decrease liver weight and triglyceride accumulation involved in inflammation and blunted hepatic oxidative stress,  
2. Improve insulin tolerance, decrease glucose-induced hyperinsulinaemia,  
3. Lower intestinal triglyceride content and alleviate intestinal oxidative stress and inflammation. | Increased: Akkermansia | Anhe et al., 2015 |
| Bamboo shoot   | Fiber        | C57BL/6J mice | Obesity | Lose weight. | | Li et al., 2016 |
| Nopal          | Fiber, Polyphenols, Vitamin C | Wistar rat | Obesity | 1. Modify gut microbiota and increase intestinal occludin-1,  
2. Decrease in LPS, glucose insulinotropic peptide, glucose intolerance, lipogenesis, and metabolic inflexibility,  
3. Reduce hepatic steatosis and oxidative stress in adipose tissue and brain,  
4. Improve cognitive function. | Increased: Bacteroidetes | Sanchez-Tapia et al., 2017 |
| (1) Wheat      | (1) Enzyme-treated wheat bran | (1) C57BL/6J mice | (1) Obesity | 1. Decrease body weight and liver TGs, increase index of liver reactive oxygen species,  
2. Decrease liver antioxidants (glutathione and α-tocopherol) and liver carbohydrate metabolites (glucose); lower hepatic arachidonic acid; and increase liver and plasma 3-hydroxybutyrate. | Increased: Bacteroidetes, Butyricoccus, Faecalibacterium, Clostridium, Verrucomicrobia | Neyrinck et al., 2011; Kieffer et al., 2016 |
| (2) Wheat      | (2) Arabinosylan | (2) C57BL/6J mice | (2) Obesity | 1. Regulate host metabolic parameters; reduce body weight gain, fat mass development, inflammation (serum IL-6, MCP-1), cholesteroenaemia and insulin resistance, and increase gut junction proteins.  
2. Regulate host adipose tissue: reduce lipogenesis (Fatty acid synthase), fatty acid oxidation (carnitinepalmitoyl transferase-1), fatty acid uptake (lipoprotein lipase) and GPR-43 expression, and increase adipocyte area and nemonic acid. | increased: Bacteroides/Prevotella ratio, Bifidobacteria, Roseburia spp. | |
<table>
<thead>
<tr>
<th>Functional Food</th>
<th>Ingredients</th>
<th>Objects</th>
<th>Diseases</th>
<th>Physiological Function Related to Gut Microbiota</th>
<th>Gut Microbiota</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oat</td>
<td>N/A</td>
<td>SD rat</td>
<td>Obesity</td>
<td>1. Decrease body weight, epididymal fat accumulation, and serum inflammatory factor (TNF-α) levels and significantly regulate serum lipid levels, 2. Increase the total SCFA concentration in colonic digesta.</td>
<td>Increased: Bacteroidetes, Bacteroidetes/Firmicutes Ratio, Decreased: Firmicutes.</td>
<td>Dong et al., 2016</td>
</tr>
<tr>
<td>Tea Polyphenols</td>
<td>Polyphenols</td>
<td>C57BL/6 ApoE−/− mice</td>
<td>AS</td>
<td>Decrease the total cholesterol and low-density lipoprotein cholesterol, Decrease the plaque area/lumen area ratios.</td>
<td>Increased: Lactobacillus, Bifidobacteria. Increased: Lactobacillus, Bifidobacteria, Akkermansia, Roseburia spp., Prevotella, Bacteroides, Decreased: Firmicutes/Bacteroidetes ratio.</td>
<td>Liao et al., 2016</td>
</tr>
<tr>
<td>Green tea and isomalto-oligosaccharides</td>
<td>N/A</td>
<td>HFD-induced male Swiss albino mice</td>
<td>Obesity</td>
<td>Prevent leaky gut phenotype and LPS, pro-inflammatory cytokines (e.g., resistin, adiponectin, TNF-α, IL-1β, IL-6) increase</td>
<td>Increased: Lactobacillus, Bifidobacteria, Akkermansia, Roseburia spp., Prevotella, Bacteroides, Decreased: Firmicutes/Bacteroidetes ratio.</td>
<td>Singh et al., 2017</td>
</tr>
<tr>
<td>Yellow pea</td>
<td>Fiber</td>
<td>SD rat</td>
<td>Obesity</td>
<td>Lower final percent body fat.</td>
<td>Decreased: Firmicutes ratio.</td>
<td>Eslinger et al., 2014</td>
</tr>
<tr>
<td>Green tea, oolong tea, black tea</td>
<td>8 phenolic acids, 12 flavonols, 9 flavonols, 2 alkaloids, 1 amino acids</td>
<td>C57BL/6J mice</td>
<td>Obesity</td>
<td>Trend to lose weight.</td>
<td>Increased: Akotipes, Rikenella, Lachnospiraceae, Akkermansia, Bacteroides, Atibaculum, Parabacteroides. Increased: Lactobacillus spp.</td>
<td>Liu et al., 2016</td>
</tr>
<tr>
<td>Fuzhuan tea</td>
<td>N/A</td>
<td>Wistar rats</td>
<td>NAFLD</td>
<td>Reduce plasma leptin and prevent high saturated fat diet-induced inflammation.</td>
<td>Increased: Lactobacillus spp.</td>
<td>Foster et al., 2016</td>
</tr>
</tbody>
</table>

TABLE 4 | Continued
Table 5: Functional food phytochemicals and gut microbiota.

<table>
<thead>
<tr>
<th>Phytochemicals</th>
<th>Category</th>
<th>Objects</th>
<th>Diseases</th>
<th>Physiological function related to gut microbiota</th>
<th>Gut microbiota</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laminarin</td>
<td>Polysaccharide</td>
<td>BALB/c mice</td>
<td>Obesity</td>
<td>Reduce energy metabolism</td>
<td>Increased: Bacteroidetes (especially the genus Bacteroides), Decreased: Firmicutes.</td>
<td>Ko et al., 2014; Nguyen et al., 2016</td>
</tr>
<tr>
<td>Fucoidan</td>
<td>Polysaccharide</td>
<td>C57BL/6J mice</td>
<td>Intestinal dysbiosis</td>
<td>Reduce inflammatory response and antigen load, and decrease LPS-binding protein levels.</td>
<td>Increased: Lactobacillus, Ruminococcaceae, Decreased: Peptococcus.</td>
<td>Shang et al., 2016</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Alkaloid</td>
<td>C57BL/6J mice</td>
<td>Obesity</td>
<td>Change gut microbiota composition</td>
<td>Increased: Akkermansia, Decreased: Firmicutes/Bacteroidetes ratio.</td>
<td>Xu P. et al., 2017</td>
</tr>
<tr>
<td>Fructans</td>
<td>Polysaccharide</td>
<td>C57BL/6J mice</td>
<td>Obesity</td>
<td>Improve intestinal physiology and shift gut microbiota.</td>
<td>Increased: Actinobacteria, Verrucomicrobia (Akkermansia).</td>
<td>Liu J. P. et al., 2016</td>
</tr>
<tr>
<td>Capsaicin (Chili peppers)</td>
<td>Alkaloid</td>
<td>C57BL/6J mice</td>
<td>Obesity</td>
<td>Prevent HFD-induced gut barrier dysfunction by inhibiting cannabinoid receptor type 1 (CB1). Protect against HFD-induced obesity is transferable.</td>
<td>Increased: Ruminococcaceae, Lachnospiraceae.</td>
<td>Kang et al., 2017</td>
</tr>
<tr>
<td>3,3-dimethyl-1-butanol (DMB)</td>
<td>Choline analogue</td>
<td>C57BL/6J mice</td>
<td>AS</td>
<td>Reduce microbial trimethylamine formation and inhibit choline diet-enhanced AS.</td>
<td>N/A</td>
<td>Wang Q. et al., 2015</td>
</tr>
</tbody>
</table>

Eubacterium, Fecalibacterium and Roseburia are the important members of Firmicutes. Bacteroidetes including the genus Bacteroides, Prevotella and Xylanibacter are known to be efficient degraders of dietary fiber (Simpson and Campbell, 2015). Genus Bifidobacterium is a major member of Actinobacteria. Proteobacteria contains Escherichia and Desulfovibrio, whereas Verrucomicrobia includes only the mucus-degrading genus Akkermansia so far (Schröder and Backhed, 2016). Tables 1–5 show that the ratio of Firmicutes/Bacteroidetes is modulated in most herbal- and food-intervention studies for CVD as well as various metabolic diseases. For example, decreased ratio of Firmicutes/Bacteroidetes was observed in obesity after intervened by herbs [Daesihoo-tang (Hussain et al., 2016), Ganoderma lucidum (Chang C. J. et al., 2015), Flos Lonicera (Wang J. H. et al., 2014), Rhizoma coptidis (Xie et al., 2011), Resveratrol (Qiao et al., 2014), Berberine (Xie et al., 2011; Zhang et al., 2012a), Quercetin (Etzeberria et al., 2015b)] and foods [apple (Jiang et al., 2016; Masumoto et al., 2016), nopal (Sanchez-Tapia et al., 2017), wheat (Kieffer et al., 2016), Laminarin (Nguyen et al., 2016)], as well as in QHD (Feng et al., 2017) and berberine (Cao et al., 2016) for NAFLD (Feng et al., 2017), and barley for CVD (Wang Y. et al., 2016). All of these studies confirmed that increase in gut bacteria phylum Bacteroidetes, and inhibition of Firmicutes, and alteration of Firmicutes/Bacteroidetes ratio helped to treat CMDs including obesity (Ley et al., 2006; Sweeney and Morton, 2013), insulin resistance (Greenhill, 2015), NAFLD (Liu J. P. et al., 2016) and CVD (Marques et al., 2017). In addition, an increase in the Akkermansia population was found to be in favorable treatment for T2D (Shin et al., 2014), obesity (Everard et al., 2013), AS (Li J. et al., 2016) and some other metabolic syndromes (Roopchand et al., 2015). A recent study showed that fat mass development, insulin resistance and dyslipidemia were reduced by purified membrane protein from Akkermansia (Plovier et al., 2017). Interestingly, the abundance of Akkermansia was dramatically increased not only by Daesihoo-tang for T2D (Hussain et al., 2016) and agave salmiana for hepatic steatosis (Leal-Diaz et al., 2016), but also by Flos Lonicera (Wang J. H. et al., 2014), pterostilbene (Etzeberria et al., 2016), apple (Masumoto et al., 2016), grape (Baldwin et al., 2016), agave salmiana (Leal-Diaz et al., 2016), cranberry (Anhe et al., 2015), green tea (Liu Z. et al., 2016; Singh et al., 2017), melatonin (Xu P. et al., 2017) and capsaicin (Kang et al., 2017) for obesity. Moreover, various diseases such as obesity, diabetes and ballergies have been associated with lower numbers of Bifidobacterium at various stages of life (Arboleya et al., 2016). The therapeutic effects of RS for AS (Chen M. L. et al., 2016), berberine for NAFLD (Cao et al., 2016), and Rehmannia glutinosa Libosch (Han et al., 2015), Daesihoo-tang (Hussain et al., 2016), rhein (Wang et al., 2016), tea polyphenols (Singh et al., 2017), green tea (Singh et al., 2017) for obesity were associated with the elevated abundance of Bifidobacterium. What’s more, increased abundance of genus Lactobacillus, Bacteroides, and...
Prevotella which contribute to metabolic diseases and/or CVD, were also closely associated with digestion of herbs and foods, as shown in Tables 1-5. In summary, increasing the abundance of phylum Bacteroidetes, and genus Akkermansia, Bifidobacterium, Lactobacillus, Bacteroides, and Prevotella, while reducing phylum Firmicutes and Firmicutes/Bacteroides ratio may serve as the common characteristics for gut bacteria modulation of herbal medicine and functional food for CMDs. For future studies, the related gut microbiota species interplay with plants and mammalian hosts need to be further investigated.

**POTENTIAL EFFECTS OF HERBAL MEDICINE AND FUNCTIONAL FOOD ON GUT-ORGANS AXES**

Commensal gut bacteria impact the host health especially CMDs processes in multiple organs. Several new concepts are proposed in recent reviews focusing on the relationship between gut and organs, such as gut-heart axis (Buglioni and Burnett, 2013), gut-brain axis (De Clercq et al., 2017; Dinan and Cryan, 2017), gut-liver axis (Wiest et al., 2017), gut-kidney axis (Katagiri et al., 2013; Budden et al., 2017) and gut-liver-lung axis (Young et al., 2016). The gut is no longer viewed as just a digestive organ, it is also considered as a metabolic and immunomodulatory organ. The major components of fiber, polyphenols and polysaccharides are present in large quantities in both herbal medicine and functional food, which we have analyzed above. Besides, their muti-ingredient, muti-target and muti-pathway mode are well known and capable of meeting the complex system of the gut-organ interactions. Targeting the gut-organs axes may also be responsible for CMD treatment. The potential effects are implicated by some latest reports. For instance, a recently published study found that chronic prebiotic treatment indeed exhibited both antidepressant and anxiolytic effects, reduced stress-induced corticosterone release, and modified specific gene expression in the hippocampus and hypothalamus. These effects were exerted via increased cecal acetate and propionate and reduced isobutyrate concentrations. These findings provided clear evidence supporting therapeutic targeting of the gut microbiota for gut-brain axis disorders (Burokas et al., 2017). Another recent finding (Marques et al., 2017) illustrated how HFD and supplementation with acetate influenced gut-heart-kidney axis in a mouse hypertension and heart failure model. It was found that both fiber and acetate decreased gut dysbiosis, measured by the ratio of Firmicutes to Bacteroidetes, and increased the prevalence of Bacteroides acidificiens. Both HFD and acetate supplementation significantly reduced blood pressure, cardiac fibrosis, and left ventricular hypertrophy. Transcriptome analyses showed that the protective effects of high fiber and acetate were accompanied by the downregulation of cardiac and renal early growth response protein 1 (EGR1), a master cardiovascular regulator involved in cardiac hypertrophy, cardiorenal fibrosis, and inflammation. The upregulation of a network of genes involved in circadian rhythm in both tissues and downregulation of the renin-angiotensin system in the kidney and MAPK signaling in the heart presents an interesting example of gut-multi organs interactions that are simultaneously affected by diet via microbiota.

Although there are no reports on herbal medicine or functional food directly targeting gut-organs axes, more study should be carried out in the area to fully exploit the beneficial aspects of gut microbiota. Major components such as fiber and polysaccharide could be fermented and converted into SCFAs which has been shown to be beneficial on the treatment of CMDs. It is foreseeable that the influence of functional food and herbal medicine on the interactive and dynamic relationships between gut microbiota and essential organs will be elucidated in the future.

**CONCLUSIONS AND PERSPECTIVE**

The concept of “medicine-food homology” has evolved from its ancient origin and is given a new prospective with newly revealed role of gut microbiota of the host. Human diseases, particularly CMDs, not only could be treated by herbal derived medicine, but also could be prevented by medicinal food via co-inhabiting and influencing gut microbiota.

With the rapid advancement of sequencing technology and intense efforts by researchers, a significant understanding of host gut microbiota has been achieved (Xiao et al., 2017). It is also becoming apparent that herbal medicine and functional food may strongly influence gut microbiota associated with CMDs in humans ranging from obesity to T2D and CVD. Nevertheless, studies on the interaction between herbal derived bioactive compounds and gut microbes are still needed. Future investigation in the field may include, but not limited to the following directions: (1) disease-related and disease-specific microbiota and pathological mechanisms; (2) future research on herbal medicine and functional food should exploit molecular mechanisms and the relationship between microbiota and host behavior; (3) until now, most medicine and functional food research has focused on obesity and T2D rather than CVD, which deserves more careful studies and funding; (4) certain polyphenols (puerarin, paeoniflorin, baicalein, icariin, mangiferin, gallic acid, luteolin, cryptotanshinone, kaempferol, etc.) are similar to RSV and showed poor absorption into the bloodstream after oral administration, but they may have an impact on gut microbiota as well. In conclusion (Figure 1), herbal medicine and functional food with major ingredients including fiber, polyphenols and polysaccharides are inclined to increasing abundance of phylum Bacteroidetes, and genus Akkermansia, Bifidobacterium, Lactobacillus, Bacteroides, and Prevotella, while reducing phylum Firmicutes and Firmicutes/Bacteroides ratio to prevent or treat CMDs through SCFAs, BAs, LPS and TMAO signaling. The condition of health or disease in human is critically dependent on the balance between medicine/food by modulating gut microbiota. Human intake of herbal medicine and functional food can alter gut microbiota, and microbiome in turn can influence human health through microbial metabolites. The convergence between herbal medicine and functional food through microbiota reinforces the idea that CMDs are not
only treatable but also preventable by maintaining the balance between the two.

**AUTHOR CONTRIBUTIONS**

YZ conceived, designed, organized and revised the manuscript; ML conceived, designed, wrote and revised the manuscript; YW, GF, XW, and SX revised the manuscript and discussed interpretation.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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