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-Wisnewsky 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-Wisnewsky 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 value 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 fergusonii, Proteus penneri, Providencia retgeri, 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:

- **TMA 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). **TMA → 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). **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 Ca²⁺ mobilization (Zhu et al., 2016). These changes in cell phenotype contribute to atherosclerotic CVD. **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 inducing 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 functions are 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 responce, 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-mediatied GPR43 (Kimura et al., 2013). These distinct differences remain to be analyzed in how the gut microbiota is modulated. Besides, GPR43 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 denfence (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 L cells (Thomas et al., 2009). GLP-1 signaling may be exploited into a new therapy for T2D with the help of gut microbiota (Clauw, 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 (Parséus 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, muti-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; Jørgensen 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, herbas 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 herbs 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

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| Formulae                        | Herbs & ingredients                                                                 | Objects     | Diseases | Physiological function related to gut microbiota                                                                 | Gut microbiota                                      | References       |
|--------------------------------|-------------------------------------------------------------------------------------|-------------|----------|---------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|------------------|
| Gegen Qinlian Decoction (GQD)  | **Herbs:** Radix Puerariae (Ge Gen), Radix Scutellariae (Huang Qin), Rhizoma Coptidis (Huang Lian), Honey-fried Licorice Root (Gan Cao); **Ingredients:** Baccalin, Puerarin, Berberine | 187 T2D patients | T2D      | 1. Enrich beneficial bacteria, 2. Reduce blood glucose and glycated hemoglobin.                                | Increased: Faecalibacterium spp.                   | Xu et al., 2015   |
| Sancai Lianmei Particle (SLP)  | **Herbs:** Panax ginseng (Ren Shen), Rhizoma Atractylodis Macrocephalae (Bai Zhu), Coptis chinensis (Huang Lian) | 60 T2D patients | T2D      | Regulate intestinal flora of T2D and have similar function with acarbose.                                      | N/A (Not Applicable)                                | Fang et al., 2016 |
| Ginseng decoction              | **Herbs:** Panax ginseng (Ren Shen); **Ingredients:** Ginseng polysaccharides, Ginsenosides | SD rat      | Over-fatigue and acute cold stress model (OACS) | 1. Improve intestinal metabolism and absorption of certain ginsenosides, 2. Reinstate the holistic gut microbiota. | Increased: Lactobacillus spp., Bacteroides spp. | Zhou et al., 2016 |
| Daesih-tang (Korea)             | **Herbs:** Bupleuri radix (Chai Hu), Pinelliae rhizome (Ban Xia), Zingiberis rhizome (Gan Jiang), Scutellariae radix (Huang Qin), Paeoniae radix (Shao Yao), Zizyphu sfructus (Da Zao), Ponciri fructus, Rheum undulati rhizome | C57BL/6 mice | Obesity | 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. | Increased: Bacteroidetes/Firmicutes ratio, Bacteroides, Lactobacillus, Akkermansia, Blifodibacterium, Decreased: Firmicutes. | Hussain et al., 2016 |
| Yupingfeng polysaccharides     | **Herbs:** Astragali radix (Huang Qi), Atractylodes macrocephala rhizome (Bai Zhu), Radix saposhnikoviae (Fang Feng); **Ingredients:** Yupingfeng polysaccharides | Weaning rex rabbits | Immune-related diseases | Increased: Cellulolytic bacteria, Decreased: Streptococcus spp., Enterococcus spp. | Increased: Cellulolytic bacteria | Sun H. et al., 2016 |
| Qushi Huayu Decoction (QHD)     | **Herbs:** Artemisia capillaries Thumb (Yin Qhenshao), Gardenia jasminoides Ellis (Zhi Zi), Fallopia japonica (Hu Zhang), Curcuma longa L. (Jiang Huang), Hypericum junicum Thom. (Tian Jhuang); **Ingredients:** Geniposide, chlorogenic acid. | SD rats | NAFLD | 1. Decrease serum LPS, hepatic lipid synthesis, and regulatory T cell inducing microbiota, 2. Improve gut barrier function and hepatic anti-oxidative mechanism. | Increased: Fusobacteria, Lentisphaerae, Verrucomicrobia, Cyanobacteria, Defibrribacteria, Proteobacteria, Bacteroidetes, Decreased: Firmicutes, Tenericutes, Actinobacteria, | Feng et al., 2017 |
### TABLE 2 | Herbs and gut microbiota.

| Herbs                                      | Ingredients                                      | Objects                                      | Diseases                                    | Physiological function related to gut microbiota                                                                 | Gut microbiota                                                                 | References |
|--------------------------------------------|--------------------------------------------------|----------------------------------------------|---------------------------------------------|------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|------------|
| Rehmannia glutinosa Libosch (Shu Dihuang)  | N/A                                              | Twenty 40–65 years old female middle-aged subjects with obesity | Obesity                                     | Decrease waist circumference.                                                                                 | Increase: Actinobacteria, Bifidobacterium, Firmicutes, Blautia.             | Han et al., 2015 |
| Ganoderma lucidum (Ling Zhi)               | Polysaccharides                                  | C57BL/6NQ1Btw mice                          | Obesity                                     | Reverse HFD-induced gut dysbiosis, Anti-obesity.                                                                 | Decreased: Firmicutes/Firmicutes, Blautia.                                   | Chang C. J., et al., 2015 |
| Flos Lonicera (JinYinghua)                 | Polysaccharides                                  | SD rats                                      | Obesity and metabolic endotoxemia           | Reduce body weights, Lower endotoxin, aspartate transaminase, HDL, triglyceride levels.                          | Decreased: Firmicutes/Bacteroidetes ratio, Proteobacteria.                 | Wang et al., 2014  |
| Rhizoma Coptidis (Huang Lian)              | Barberry                                         | C57BL/6J mice                                | Obesity                                     | Lower degradation of dietary polysaccharides, decrease potential calorie intake, increase Fiaf protein and its related gene expressions of mitochondrial energy metabolism. | Increased: Bacteroidetes/Firmicutes ratio, Decreased: Lactobacillus.        | Xie et al., 2011 |
| Lingonberry (Vaccinium vitis-idaea L.)     | 20% lingonberries                                | C57BL/6J mice                                | Obesity                                     | Reduce endotoxemia and inflammation, Anti-obesity.                                                               | Increased: Akkermansia/Faecalibacterium ratio.                              | Heyman-Linden et al., 2016 |
| Herba Epimdi (Yin Yanghuo)                 | Icarin, Epimedin A, B, C                        | SD rats                                      | Osteoporosis                                | Enhance epimedium flavonoids absorption and antosteoporosis activity.                                           | N/A                                                                          | Zhou et al., 2015 |
| Garonia cambogia (Teng Huangguo)           | Extract                                          | C57BL/6J mice                                | Obesity                                     | Alleviate weight gain and adiposity                                                                             | Decreased: Lactobacillus, Bacteroides, Parabacteroides, Xylophilus.        | Mei et al., 2015 |
| Cassia obtusifolia L. (Jue Mingzl)         | Anthraquinone                                    | SD rats                                      | NAFLD                                       | Evaluate lipid metabolism and gut microbiota diversity, Up-regulate FNR, CYP7A1, LDL-R mRNA and PPAR-α protein levels, down-regulate HMGR, PPAR-γ and SREBP-1c expression. | Increased: Oscillospira.                                                   | Guo et al., 2015 |
| Radix ginsang rubra (Hong Sheng and Semen Coicis (Yi Yiren) | N/A                                              | Wistar rat                                   | Ulcerative colitis (UC)                     | Improve gut microbiota structure and relieve the ulcerative colitis symptom.                                  | Increased: Bifidobacterium, Lactobacillus.                                  | Guo et al., 2015 |
| Polygonatum kingianum (Dan Huangjing)      | Polysaccharides, Saponins                        | SD rats                                      | T2D                                         | Reduce SCFAs production, Decrease LPS level, Partial recover insulin secretion and fasting blood glucose levels. | Increased: Family Ruminococcaceae, Genus Ruminococcus.                     | Yan et al., 2017 |
| Adlay                                       | Polyphenol extract                               | Wistar rats                                  | High cholesterol-related disease            | Ameliorate and LDL cholesterol restore HDL cholesterol.                                                        | Decreased: Erysipelotrichales, Clostridia.                                  | Wang Q. et al., 2015 |
TABLE 3 | Herbal phytochemicals and gut microbiota.

| Phytochemicals | Category | Objects | Diseases | Physiological function related to gut microbiota | Gut microbiota | References |
|----------------|----------|---------|----------|-----------------------------------------------|---------------|------------|
| Resveratrol and epigallocatechin-3-gallate | Polyphenol | 37 obese men and women | Obesity | Increase fat oxidation | Decreased: Bacteroidetes, Faecalibacterium Prausnitzii. | Most et al., 2017 |
| Resveratrol | Polyphenol | (1) C57BL/6J ApoE−/− mice | (1) AS | (1) AS-related  
1. Reduce TMAO production → decrease TMAO synthesis in liver → inhibit AS,  
2. Increase BSH activity → promote generation of unconjugated BAs,  
3. Decrease BA content → inhibit FXR-FGF15 axis → increase CYP7A1 expression → induce neosynthesis of hepatic BA → promote cholesterol homeostasis → attenuate AS. | (1) Increased: Lactobacillus, Bifidobacterium. | Qiao et al., 2014; Chen M. L. et al., 2016 |
| Berberine | Alkaloid | (1) Wistar rats | (1) Obesity, insulin resistance | (1) AS-related  
1. Inhibit obesity and insulin resistance development,  
2. Increase LPS-binding protein MCP-1, leptin levels, and decrease adiponectin level,  
3. Elevate SCFA levels in the intestine. | (2) Increased: Bacteroidetes/Firmicutes ratio, Lactobacillus, Bifidobacterium. | Xie et al., 2011; Zhang et al., 2012a, 2015; Cao et al., 2016; Wang Y. et al., 2017 |
| Berberine | Alkaloid | (2) Wistar rats | (2) Obesity | (2) Obesity-related  
1. Decrease body and visceral adipose weights, and reduce lipid and blood glucose levels,  
2. Increase Fiaf gene expression, and decreases LPL, SCD1, FFA, PPAR-γ, ACC1, Fas mRNA expression correlation with fatty acids synthesis, lipogenesis and adipogenesis. | Decreased: Enterococcus faecalis. | |
| Berberine | Alkaloid | (3) C57BL/6J mice | (3) Obesity | (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. | (3) Increased: Bacteroidetes/Firmicutes ratio, Decreased: Lactobacillus, Bacteroidetes/Firmicutes ratio, Bifidobacteria. | |
| Quercetin | Polyphenol | Wistar rats | Obesity | Prevent body weight gain and reduce serum insulin levels and insulin resistance. | Decreased: Erysipelotrichaceae, Bacillus, Eubacterium cylindroides. | Etxeberria et al., 2015a |
| Quercetin | Polyphenol | BALB/C mice | NAFLD | (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. | (4) Increased: Bacteroidetes/Firmicutes ratio, Bifidobacteria. | |
| Quercetin | Polyphenol | SD rat | Energy metabolism | (5) Promote butyrate production,  
(5) Energy metabolism  
1. Reducing blood lipid and glucose level,  
2. Regulate energy metabolism by suppressing bacterial ATP production and nicotinamide adenine dinucleotide phosphate (NADH) levels. | (5) Increased: Enterobacter, Escherichia–Shigella. | |
(Continued)
| Phytochemicals Category | Objects | Diseases | Physiological function related to gut microbiota | Gut microbiota | References |
|-------------------------|---------|----------|------------------------------------------------|--------------|-----------|
| Curcumin Polyphenol     | (1) 129/SvEv mice, germ-free $\text{IL10}^{-/-}$ mice | (1) Colitis and colon cancer | (1) Increase survival, decrease colon weight/length ratio, eliminate tumor burden. | (1) Increased: Lactobacillus, Lactobacillales, Bifidobacteriales, Erysipelotrichales, Coriobacteriales, | Ghosh et al., 2014; McTadden et al., 2015 |
|                        | (2) LDLR$^{-/-}$ mice | (2) AS | (2) 1. Decrease LPS levels, 2. Increase intestinal barrier function by restoring intestinal alkaline phosphatase activity and tight junction proteins ZO-1 and Claudin-1 expression, 3. Reduce glucose intolerance and AS. | Decreased: Obesibacteriales, Firmicutes. | (2) N/A |
| Ophiopogon japonicas polysaccharide | CS7BL/6J mice | Obesity | Improve gut microbiota diversity and promote proliferation. | Increased: Taiwan lactobacillus, Lactobacillus murinus | Shi et al., 2015 |
| Pterostilbene Polyphenol | Zucker (ts/ts) rats | Obesity | Improved metabolic function (insulin sensitivity) and Anti-obesity. | Increased: Akkermansia, Odoribacter, Verrucomicrobia, | Etxeberria et al., 2016 |
| Rhein Polyphenol | CS7BL/6J | Obesity | 1. Reduce body weight and improve glucose tolerance, 2. Inhibit macrophage accumulation, anti-neuroinflammation and improve BDNF expression. | Increased: Bifidobacterium spp, Lactobacillus spp. | Wang et al., 2016 |
| Taurine Amino acid | BALB/C mice | Neuroendocrine | Increase SCFA content in feces, decrease LPS content in serum. | Decreased: Proteobacteria (especially Helicobacter) | Yu et al., 2016 |
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 Thunb, Gardenia jasminoides Ellis, Fallopia japonica, Curcuma longa L., and Hypericum japonicum Thunb.*) 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 Polygoni 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, herbas 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 thereby 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 *Fusobacterium* 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 et al., 2017).
et al., 2015; Table 4). As another example, ingestion of laminarin, a kind of polysaccharides extracted from Laminaria japonica, by HFD-fed mice significantly increased genus Bacteroides and decreased Firmicutes, with elevated energy metabolism (Nguyen et al., 2016; Table 5). Besides, 3,3-dimethyl-1-butanol (DMB), the structural analog of choline detected in some functional food such as balsamic vinegars, red wines, and olive oils (Kitai and Tang, 2017), is an inhibitor of TMA formation through inhibition of microbial TMA lyases. Therefore, it inhibited choline diet-promoted macrophage foam cell formation and atherosclerotic lesion development without altering the circulating cholesterol levels (Wang Z. et al., 2015).

Moreover, vegetables (e.g., bamboo shoot), whole grains (e.g., wheat, barley and oat), and teas (e.g., green tea, oolong tea, black tea and fuzhuan tea), exert positive effects on CMDs through modulating gut microbiota (Table 4). Numerous instances are detailed in Tables 4, 5. Although, intervention studies conducted both in animals and humans have demonstrated beneficial effects of functional foods on anti-inflammation, vascular function, and energy metabolism, the apparent association with altered gut microbiota is still lacking.

OVERLAPPING 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): (1) shared components, (2) similar functions, (3) common mechanisms, and (4) 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 herbals 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 herbals 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, Bas, 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 herbals (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 herbals 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 herbals 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 4 | Functional food and gut microbiota.

| Functional Food | Ingredients | Objects | Diseases | Physiological function related to gut microbiota | Gut microbiota | References |
|----------------|-------------|---------|----------|-------------------------------------------------|----------------|------------|
| Vegetable/fruit juice | Polyphenols, Oligosaccharides, Rbr, 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. | Henning et al., 2017 |
| Barley | β-Glucan | 30 volunteers | CVD | N/A | Increased: Bacteroidetes, Decreased: Firmicutes, Dorea. | Wang Y. et al., 2016 |
| Apple | (1) procyanidin | (1) C57BL/6J mice | (1) Obesity | 1. Attenuate inflammatory effects and weight gain including gut permeability and lipopolysaccharide, 2. Decrease endogenous metabolites levels related with insulin resistance. | Increased: Akkermansia, Decreased: Firmicutes/Bacteroidetes ratio. | Quevlo et al., 2015; Jiang et al., 2016; Masumoto et al., 2016; Wang S. et al., 2017 |
| | (2) pectin | (2) SD rat | (2) Obesity | (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. | Increased: Akkermansia, Decreased: Firmicutes. | (2) Increased: Bifidobacterium. |
| | Polyphenols | (3) Systemic lupus erythematosus patients | (3) Systemic lupus erythematosus | (3) N/A | Increased: Akkermansia muciniphila, Allobaculum, Decreased: Desulfbacte spp. | Cuervo et al., 2015; Jiang et al., 2016; Masumoto et al., 2016; Wang S. et al., 2017 |
| Oranges | Polyphenols | 20 Systemic lupus erythematosus patients | Systemic lupus erythematosus | N/A | Increased: Lactobacillus. | Quevlo et al., 2015 |
| Grape | (1) Pomace, Polyphenols | (1) Lamb | (1) N/A | (1) Decrease oxidative stress-induced damage to lipids and proteins such as TBARS and CARB. | Decreased: Enterobacteriaceae, Escherichia coli. | Baldwin et al., 2016; Kafantas et al., 2016 |
| | (2) N/A | (2) C57BL/6J mice | (2) Obesity | (2) 1. Decrease triglyceride and liver weight levels and reduce GPAT1 expression, 2. Reduce hepatic mRNA PPAR-γ2, SCD1, FABP4 and GPAT1 levels | Increased: Akkermansia muciniphila, Allobaculum, Decreased: Desulfbacte spp. | |

(Continued)
| Functional Food | Ingredients                                                                 | Objects         | Diseases                        | Physiological Function related to gut microbiota                                                                                   | Gut microbiota                         | References          |
|----------------|------------------------------------------------------------------------------|-----------------|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|---------------------|
| 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) Reduced epididymal fat mass and improve insulin sensitivity. | Increased: Clostridium XVa, Roseburia, Prevotella | Liu et al., 2017    |
|                |                                                                              |                 |                                 | (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 |
| Agave salmiana | Saponin                                                                      | C57BL/6 mice    | Obesity and hepatic steatosis   | (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    |
| Cranberry      | Cranberry extract                                                            | C57BL/6J mice   | Obesity                         | Lose weight.                                                                                                                   | Increased: Bacteroidetes,              | Li et al., 2016      |
|                | Fiber                                                                        | Wistar rat      | Obesity                         | Modify gut microbiota and increase intestinal occludin-1, Decrease in LPS, glucose insulinotropic peptide, glucose intolerance, lipogenesis, and metabolic flexibility, Reduce hepatic steatosis and oxidative stress in adipose tissue and brain, Improve cognitive function. | Increased: Verrucomicrobia,            | Sanchez-Tapia et al., 2017 |
| Nopal          | Fiber, Polyphenols, Vitamin C                                                | Wistar rat      | Obesity                         | Decrease body weight and liver TGs, increase index of liver reactive oxygen species. Decrease liver antioxidants (glutathione and α-tocopherol) and liver carbohydrate metabolites (glucose); lower hepatic arachidonic acid; and increase liver and plasma β-hydroxybutyrate. | Increased: Firmicutes,                | Neyrinck et al., 2011; Kieffer et al., 2016 |
|                | (1) Enzyme-treated wheat bran                                                | C57BL/6J mice   | Obesity                         | (1) Decrease body weight and liver TGs, increase index of liver reactive oxygen species. Decrease liver antioxidants (glutathione and α-tocopherol) and liver carbohydrate metabolites (glucose); lower hepatic arachidonic acid; and increase liver and plasma β-hydroxybutyrate. | (2) Increased: Bacteroidetes/ Firmicutes, Prevotella, Bifidobacteria, Roseburia spp. |                    |
|                | (2) Arabinoxylan                                                             | C57BL/6J mice   | Obesity                         | Regulate host metabolic parameters: reduce body weight gain, fat mass development, inflammation (serum IL-6, MCP-1), cholesterolemia and insulin resistance, and increase gut junction proteins. 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 erunic acid. | (Continued)                            |                    |

(Continued)
| Functional Food | Ingredients | Objects | Diseases | Physiological Function Related to Gut Microbiota | Gut Microbiota | References |
|----------------|-------------|---------|----------|------------------------------------------------|---------------|------------|
| Oat            | N/A         | SD rat  | Obesity  | Decrease body weight, epididymal fat accumulation, and serum inflammatory factor (TNF-α) levels and significantly regulate serum lipid levels, Increase the total SCFA concentration in colonic digesta. | Bacteroidetes, Bacteroidetes/Firmicutes Ratio, | Dong et al., 2016 |
| Tea Polyphenols| Polyphenols  | C57BL/6 ApoE−/− mice | AS       | Decrease the cholesterol and low-density lipoprotein cholesterol, Decrease the plaque area/lumen area ratios. | Bifidobacteria. | Liao et al., 2016 |
| Green tea and isomaltoligosaccharides | N/A | HFD-induced male Swiss albino mice | Obesity | Prevent leaky gut phenotype and LPS, pro-inflammatory cytokines (e.g., resistin, adiponectin, TNF-α, IL-1β, IL-6) increase | Bifidobacteria, Lactobacillus, Akkermansia, Roseburia spp., Prevotella/Bacteroides, | Singh et al., 2017 |
| Yellow pea     | Fiber       | SD rat  | Obesity  | Lower final percent body fat. | Firmicutes/Bacteroidetes ratio. | Eslinger et al., 2014 |
| Green tea, oolong tea, black tea | 8 phenolic acids, 12 flavonoids, 9 flavonols, 2 alkaloids, 1 amino acids | C57BL/6J mice | Obesity | Trend to lose weight. | Alistipes, Rikenella, Lachnospiraceae, Akkermansia, Bacteroides, Atoaculum, Parabacteroides. | Liu et al., 2016 |
| Fuzhuan tea    | N/A         | Wistar rats | NAFLD   | Reduce plasma leptin and prevent high saturated fat diet-induced inflammation. | Lactobacillus spp. | Foster et al., 2016 |
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 (Scheper 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 [Daesih-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 NASH (Feng et al., 2017), and barley for CVD (Wang et al., 2017). 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 Daesih-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), Daesih-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

| Phytochemicals | Category | Objects | Diseases | Physiological function related to gut microbiota | Gut microbiota | References |
|----------------|----------|---------|----------|---------------------------------------------|----------------|------------|
| Laminarin      | Polysaccharide | BALB/c mice | Obesity | Reduce energy metabolism | Increased: Bacteroidetes (especially the genus Bacteroides), Decreased: Firmicutes. | Ko et al., 2014; Nguyen et al., 2016 |
| Fucoidan       | Polysaccharide | C57BL/6J mice | Intestinal dysbiosis | Reduce inflammatory response and antigen load, and decrease LPS-binding protein levels. | Increased: Lactobacillus, Ruminococcaceae, Decreased: Peptococcus. | Shang et al., 2016 |
| Melatonine     | Alkaloid   | C57BL/6J mice | Obesity | Change gut microbiota composition | Increased: Akkermansia, Decreased: Firmicutes/Bacteroidetes ratio. | Xu P. et al., 2017 |
| Fructans       | Polysaccharide | C57BL/6J mice | Obesity | Improve intestinal physiology and shift gut microbiota. | Increased: Actinobacteria, Verrucomicrobia (Akkermansia). | Liu J. P. et al., 2016 |
| Capsaicin (Chili peppers) | Alkaloid | C57BL/6J mice | Obesity | 1) Prevent HFD-induced gut barrier dysfunction by inhibiting cannabinoid receptor type 1 (CB1). 2) Protect against HFD-induced obesity that is transferable. | Increased: Ruminococcaceae, Lachnospiracea. | Kang et al., 2017 |
| 3,3-dimethyl-1-butanol (DMB) | Choline analogue | C57BL/6J mice | AS | Reduce microbial trimethylamine formation and inhibit choline diet-enhanced AS. | N/A | Wang Q. et al., 2015 |

**TABLE 5 | Functional food phytochemicals and gut microbiota.**
Prevotella} which contribute to metabolic diseases and/or CVD, were also closely associated with digestion of herbals 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 functionial 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 acidifaciens. 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, baikaline, 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/Bacteroidetes 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...
The potentially shared biological processes and underlying mechanisms of herbal medicine and functional food for CMDs through modulating microbiota.

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**REFERENCES**

Anhe, F. F., Roy, D., Pilon, G., Dudonne, S., Matamoros, S., Varin, T. V., et al. (2015). A polyphenol-rich cranberry extract protects from diet-induced obesity, insulin resistance and intestinal inflammation in association with increased Akkermansia spp. population in the gut microbiota of mice. Gut 64, 872–883. doi: 10.1136/gutjnl-2014-307142

Arboleya, S., Watkins, C., Stanton, C., and Ross, R. P. (2016). Gut Bifidobacteria Populations in Human Health and Aging. *Front. Microbiol.* 7:1204. doi: 10.3389/fmicb.2016.01204

Arón-Wisnewsky, J., and Clement, K. (2016). The gut microbiome, diet, and links to cardiometabolic and chronic disorders. *Nat. Rev. Nephrol.* 12, 169–181. doi: 10.1038/nrneph.2015.191

Baldwin, J., Collins, B., Wolf, P. G., Martinez, K., Shen, W., Chuang, C. C., et al. (2016). Table grape consumption reduces adiposity and markers of hepatic lipogenesis and alters gut microbiota in butter fat-fed mice. *J. Nutr. Biochem.* 27, 123–135. doi: 10.1016/j.jnutbio.2015.08.027

Baur, J. A., and Sinclair, D. A. (2006). Therapeutic potential of resveratrol: *the in vivo* evidence. *Nat. Rev. Drug Discov.* 5, 493–506. doi: 10.1038/nrd2060

Bennett, B. J., de Aguiar Vallim, T. Q., Wang, Z., Shih, D. M., Meng, Y., Gregory, J., et al. (2013). Trimethylamine-N-oxide, a metabolite associated with atherosclerosis, exhibits complex genetic and dietary regulation. *Cell Metab.* 17, 49–60. doi: 10.1016/j.cmet.2012.12.011

Bindels, L. B., Delzenne, N. M., Cani, P. D., and Chabo, C. (2010). The gut microbiota and cardiovascular disease. *J. Endotoxin Res.* 16, 453–464. doi: 10.1177/0968926210369906

Bindels, L. B., Delzenne, N. M., Cani, P. D., and Chabo, C. (2010). The gut microbiota and cardiovascular disease. *J. Endotoxin Res.* 16, 453–464. doi: 10.1177/0968926210369906

Bordón, M., D’Atri, F., Guilmot, L., and Citi, S. (2004). Histone deacetylase inhibitors up-regulate the expression of tight junction proteins. *Mol. Cancer Res.* 2, 692–701.
Budden, K. F., Gellaty, S. L., Wood, D. L., Cooper, M. A., Morrison, M., Hugenholtz, P., et al. (2017). Emerging pathogenic links between microbiota and the gut-lung axis. *Nat. Rev. Microbiol.* 15, 55–63. doi: 10.1038/nrmicro.2016.142

Bugioni, A., and Burnett, J. C. Jr. (2013). A gut-hearth connection in cardiometabolic regulation. *Nat. Med.* 19, 534–536. doi: 10.1038/nm.3196

Burokas, A., Arboleya, S., Moloney, R. D., Peterson, V. L., Murphy, K., Clarke, G., et al. (2017). Targeting the Microbiota-Gut-Axis: prebiotics have anxiolytic and antidepressant-like effects and reverse the impact of chronic stress in mice. *Biol Psychiatry.* 82, 472–487. doi: 10.1016/j.biopsych.2016.12.031

Canfora, E. E., Jocken, J. W., and Blaak, E. E. (2015). Short-chain fatty acids in control of body weight and insulin sensitivity. *Nat. Rev. Endocrinol.* 11, 577–591. doi: 10.1038/nrendo.2015.128

Cani, P. D., Amar, J., Iglesias, M. A., Poppe, M., Knauf, C., Bastelica, D., et al. (2007). Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes.* 56, 1761–1772. doi: 10.2337/db06-1491

Cao, Y., Pan, Q., Cai, W., Shen, F., Chen, G. Y., Xu, L. M., et al. (2016). Modulation of gut microbiota by berberine improves steatohepatitis in high-fat diet-fed BALB/C mice. *Arch. Iran. Med.* 19, 197–203.

Carroll, S. P., Jorgensen, P. S., Kinnison, M. T., Bergstrom, C. T., Denison, R. F., Gluckman, P. D., et al. (2014). Applying evolutionary biology to address global challenges. *Science.* 346:1245993. doi: 10.1126/science.1245993

Chang, C. J., Lin, C. S., Lu, C. C., Martel, J., Ko, Y. F., Ojcius, D. M., et al. (2013). Pterostilbene-induced changes in gut microbiota: new insights in the pathophysiology of metabolic syndrome. *Psychosom Med.* 79, 874–879. doi: 10.1097/PSY.0000000000000495

Danin, T. G., and Cryan, J. F. (2017). Gut-brain axis in 2016: brain-gut-microbiota axis - mood, metabolism and behaviour. *Nat. Rev. Gastroenterol. Hepatol.* 14, 69–70. doi: 10.1038/nrgastro.2016.200

Dong, J. L., Zhu, Y. Y., Ma, Y. L., Xiang, Q. S., Shen, R. L., and Liu, Y. Q. (2016). Oat products modulate the gut microbiota and produce anti-obesity effects in osteoporosis rats. *J. Funct. Foods.* 25, 408–420. doi: 10.1016/j.jff.2016.06.025

Elingger, A., Lill, L. K., and Reimer, R. A. (2014). Yellow pea fiber improves glycemia and reduces *Cladostepum leptum* in diet-induced obese rats. *Nutr. Res.* 34, 714–722. doi: 10.1016/j.nutres.2014.07.016

Etneverria, U., Arias, N., Boque, N., Macarulla, M. T., Portillo, M. P., Martínez, J. A., et al. (2015a). Reshaping faecal gut microbiota composition by the intake of trans-resveratrol and quercetin in high-fat sucrose diet-fed rats. *J. Nutr. Biochem.* 26, 651–660. doi: 10.1016/j.jnutbio.2015.01.002

Etneverria, U., Arias, N., Boque, N., Romo-Hualde, A., Macarulla, M. T., Portillo, M. P., et al. (2013b). Metabolic faecal fingerprinting of trans-resveratrol and quercetin following a high-fat sucrose dietary model using liquid chromatography coupled to high-resolution mass spectrometry. *Food Funct.* 6, 2758–2767. doi: 10.1039/C5FO00473J

Etneverria, U., Hijona, E., Aguirre, L., Milagro, F. I., Bujanda, L., Rimondo, A. M., et al. (2016). Pterostilbene-induced changes in gut microbiota composition in relation to obesity. *Nat. Nutr. Food Res.* 61:1500996. doi: 10.1002/nmfr.201500996

Everard, A., Belzer, C., Geurts, L., Ouerwerker, J. P., Druart, C., Bindels, I. B., et al. (2013). Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity. *Proc. Natl. Acad. Sci. U.S.A.* 110, 9066–9071. doi: 10.1073/pnas.1219451110

Fang, W., Wei, C., Dong, Y., Tang, X., and Zu, Y. (2016). The effect on gut microbiota structure of primarily diagnosed type 2 diabetes patients intervened by sancal liannei parameter and acarbose: a randomized controlled trial. *J. Clin. Trails.* 6:270. doi: 10.2167/8070.10000270

Feng, Q., Liu, W., Baker, S. S., Li, H., Chen, C., Liu, Q., et al. (2017). Multi-targeting therapeutic mechanisms of the Chinese herbal medicine QHD in the treatment of non-alcoholic fatty liver disease. *Oncotarget.* 8, 27820–27838. doi: 10.18632/oncotarget.15482

Foster, M. T., Gentile, C. L., Cox-York, K., Wei, K., Wang, D., Estrada, A. L., et al. (2016). Fuzhuan tea consumption imparts hepatoprotective effects and alters intestinal microbiota in high saturated fat diet-fed rats. *Mol. Nutr. Food Res.* 60, 1213–1220. doi: 10.1002/mnfr.201500654

Ghosh, S. S., Bie, J. H., Wang, J., and Ghosh, S. (2014). Oral Supplementation with Non-Absorbable Antibiotics or Curcumin Attenuates Western Diet-Induced Atherosclerosis and Glucose Intolerance in LDLR/-: Mouse - Role of Intestinal Permeability and Macrophage Activation. *PLoS ONE* 9:0108577. doi: 10.1371/journal.pone.0108577

Grasset, E., Puel, A., Championnet, J., Collet, X., Christensen, J. E., Terce, F., et al. (2017). A Specific Gut Microbiota Dysbiosis of Type 2 Diabetic Mice Induces GLP-1 Resistance through an Enteric NO-Dependent and Gut-Axis Mechanism. *Cell Metab.* 26:278. doi: 10.1016/j.cmet.2017.04.013

Greenhill, C. (2015). Gut microbiota: firmicutes and bacteroides involved in insulin resistance by mediating levels of glucagon-like peptide 1. *Nat. Rev. Endocrinol.* 11:254. doi: 10.1038/nrendo.2015.40

Greenhill, C. (2016). Metabolism: intestinal microbiota affects host physiology. *Nat. Rev. Endocrinol.* 13:64. doi: 10.1038/nrendo.2016.207

Guarner, F., and Malagelada, J. R. (2003). *Gut flora in health and disease.*

Guo, M., Ding, S., Zhao, C., Gu, X., He, X., Huang, K., et al. (2015). Red Ginseng and Semen Coicis can improve the structure of gut microbiota and relieve the symptoms of ulcerative colitis. *J. Ethnopharmacol.* 167, 345–351.

Hansen, T. H., Gobel, R. J., Hansen, T., and Pedersen, O. (2015). Gut microbiota and intestinal permeability: a review of intestinal permeability and macrophage activation. *PLoS ONE* 6:19076. doi: 10.18632/oncotarget.15482

Hevia, A., Yma, M., Wanson, J. E., Rezode, K. M., and Qi, L. (2017). Gut microbiota metabolites and risk of major adverse cardiovascular disease events and death: a systematic review and meta-analysis of prospective studies. *J. Am. Heart Assoc.* 6:000497. doi: 10.1161/JAHA.116.000497
Kitai, T., and Tang, W. H. W. (2017). The role and impact of gut microbiota in cardiovascular disease. Rev. Esp. Cardiol. (Engl. Ed). 70, 799–800. doi: 10.1016/j.rec.2017.04.003

Klinder, A., Shen, Q., Heppel, S., Lovegrove, J. A., Rowland, I., and Tuohy, K. M. (2016). Impact of increasing fruit and vegetables and flavonoid intake on the human gut microbiota. Food Funct. 7, 1788–1796. doi: 10.1039/C6FO00106A

Ko, S. J., Kim, J., Han, G., Kim, S. K., Kim, H. G., Yeo, I., et al. (2014). Laminaria japonica combined with probiotics improves intestinal microbiota: a randomized controlled clinical trial. J. Med. Food 17, 76–82. doi: 10.1089/maf.2013.3054

Koeth, R. A., Wang, Z., Levison, B. S., Buffa, J. A., Org, E., Sheehy, R. T., et al. (2013). Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat. Med. 19, 576–585. doi: 10.1038/nm.3145

Koopen, A. M., Groen, A. K., and Nieuwdorp, M. (2016). Human microbiome as therapeutic intervention target to reduce cardiovascular disease risk. Curr. Opin. Lipidol. 27, 615–622. doi: 10.1097/MOL.0000000000000337

Koutsos, A., Tuohy, K. M., and Lovegrove, J. A. (2015). Apples and cardiovascular health—is the gut microbiota a core consideration? Nutrients 7, 3959–3998. doi: 10.3390/nu7063959

Laparra, J. M., and Sanz, Y. (2010). Interactions of gut microbiota with functional food components and nutraceuticals. Pharmacol. Res. 61, 219–225. doi: 10.1016/j.phrs.2009.11.001

Laxminarayan, R., Matsoso, P., Pant, S., Brower, C., Rottingen, J. A., Klugman, K., et al. (2016). Access to effective antimicrobials: a worldwide challenge. Lancet 387, 168–175. doi: 10.1016/S0140-6736(15)00474-2

Leal-Diaz, A. M., Noriega, L. G., Torre-Villalvazo, L., Torres, N., Aleman-Escordillas, G., Lopez-Romero, P., et al. (2016). Agaumel concentrate from Agave salmiana and its extracted saponins attenuated obesity and hepatic steatosis and increased Akkermansia muciniphila in C57BL/6 mice. Sci. Rep. 6:34242. doi: 10.1038/srep34242

Ley, R. E., Turnbaugh, P. I., Klein, S., and Gordon, J. I. (2006). Microbial ecology: human gut microbes associated with obesity. Nature 444, 1022–1023. doi: 10.1038/4441022a

Li, F., Jiang, C., Krauss, K. W., Li, Y., Albert, I., Hao, H., et al. (2013). Microbiome remodelling leads to inhibition of intestinal farnesoid X receptor signalling and decreased obesity. Nat. Commun. 4:2384. doi: 10.1038/ncomms3384

Li, J., Lin, S., Vanhoutte, P. M., Woo, C. W., and Xu, A. (2016). Akkermansia Muciniphila Protects Against Atherosclerosis by Preventing Metabolic Endotoxemia-Induced Inflammation in ApoE−/− Mice. Circulation 133, 2434–2446. doi: 10.1161/CIRCULATIONAHA.115.019645

Li, T., Chen, Y., Gua, C., and Li, X. (2017). Elevated circulating trimethylamine N-Oxide levels contribute to endothelial dysfunction in aged rats through vascular inflammation and oxidative stress. Front. Physiol. 8:350. doi: 10.3389/fphys.2017.00350

Li, X. S., Obeid, S., Klingenberg, R., Gencer, B., Mach, F., Raber, L., et al. (2017). Gut microbiota-dependent trimethylamine N-oxide in acute coronary syndromes: a prognostic marker for incident cardiovascular events beyond traditional risk factors. Eur. Heart J. 38, 814–824. doi: 10.1093/eurheartj/ehw382

Li, X., Guo, J., Ji, K., and Zhang, P. (2016). Bamboo shoot fiber prevents obesity in mice by modulating the gut microbiota. Sci. Rep. 6:32953. doi: 10.1038/srep32953

Li, Y., Yao, J., Han, C., Yang, J., Chaudhry, M. T., Wang, S., et al. (2016). Quercetin, inflammation and immunity. Nutrients 8:167. doi: 10.3390/nu80303167

Liao, Z. L., Zeng, B. H., Wang, W., Li, G. H., Wu, F., Wang, L., et al. (2016). Impact of the Consumption of Polyphenols on Early Atherosclerotic Lesion Formation and Intestinal Bifidobacteria in High-Fat-Fed ApoE−/− Mice. Front. Nutr. 3:42. doi: 10.3389/fnut.2016.00042

Liu, J. P., Zou, W. L., Chen, S. J., Wei, H. Y., Yin, Y. N., Zou, Y. Y., et al. (2016). Effects of different diets on intestinal microbiota and nonalcoholic fatty liver disease development. World J. Gastroenterol. 22, 7353–7364. doi: 10.3748/wjg.v22.i32.7353

Liu, T. W., Cephas, K. D., Holscher, H. D., Kerr, K. R., Mangian, H. F., Tappenden, K. A., et al. (2016). Ndongestible fructans alter gastrointestinal barrier function, gene expression, histomorphology, and the microbiota profiles of diet-induced obese C57BL/6 Mice. J. Nutr. 146, 949–956. doi: 10.1093/jn/nqw129

Liu, W., Zhao, S., Wang, J., Shi, J., Sun, Y., Wang, W., et al. (2017). Grape seed proanthocyanidin extract ameliorates inflammation and adiposity by modulating gut microbiota in high-fat diet mice. Mol. Nutr. Food Res. 61:1601082. doi: 10.1002/mnfr.201610082

Frontiers in Microbiology | www.frontiersin.org 18 November 2017 | Volume 8 | Article 2146
Liu, Z., Chen, Z., Guo, H., He, D., Zhao, H., Wang, Z., et al. (2016). The modulatory effect of infusions of green tea, oolong tea, and black tea on gut microbiota in high-fat-induced obese mice. Food Funct. 7, 4869–4879. doi: 10.1039/C6FO00301A

Ma, G., Pan, B., Chen, Y., Guo, C., Zhao, M., Zheng, L., et al. (2017). Trimethylamine N-oxide in atherogenesis: impairing endothelial self-repair capacity and enhancing monocyte adhesion. Biosci Rep. 37:BSR20160244. doi: 10.1042/BSR20160244

Makishima, M., Okamoto, A. Y., Repa, J. J., Tu, H., Learned, R. M., Luk, A., et al. (1999). Identification of a nuclear receptor for bile acids. Science 284, 1362–1365. doi: 10.1126/science.284.5418.1362

Marques, F. Z., Nelson, E., Chu, P. Y., Horlock, D., Fiedler, A., Ziemann, M., et al. (2017). High-fiber diet and acetate supplementation change the gut microbiota and prevent the development of hypertension and heart failure in hypertensive mice. Circulation 135, 964–977. doi: 10.1161/CIRCULATIONAHA.116.024545

Martel, J., Ojcius, D. M., Chang, C. J., Lin, C. S., Lu, C. C., Ko, Y. F., et al. (2016). Anti-obesogenic and antiadipogenic effects of plants and mushrooms. Nat. Rev. Endocrinol. 13, 149–160. doi: 10.1038/nrendo.2016.142

Maruyama, T., Miyamoto, Y., Nakamura, T., Tamai, Y., Okada, H., Sugiyama, E., et al. (2002). Identification of membrane-type receptor for bile acids (M-BAR). Biochem. Biophys. Res. Commun. 298, 714–719. doi: 10.1006.bbrc.2001.6006

Masumoto, S., Terao, A., Yamamoto, Y., Mukai, T., Miura, T., and Shoji, T. (2016). Non-absorbable apple pectinoids prevent obesity associated with gut microbiota and metabolic changes. Sci. Rep. 6:31208. doi: 10.1038/srep31208

Mayerhofer, C. C. K., Ueland, T., Broch, K., Vincent, R. P., Cross, G. F., Dahl, C. P., et al. (2017). Increased Secondary/Primary Bile Acid-Ratio in Chronic Heart Failure. J Card Fail. 23, 666–671. doi: 10.1016/j.cardfail.2017.06.007

Mcfadden, R. M., Larmonier, C. B., Shehab, K. W., Midura-Kiela, M., Ramalingam, R., Harrison, C. A., et al. (2015). The role of curcumin in modulating colonic barrier. Cell Metab. 21, 1079–1089.

Mei, L., Tang, Y., Li, M., Yang, P., Liu, Z., Yuan, J., et al. (2015). Co-administration of Cholesterol-Lowering Probiotics and Anthraquinone from Cassia obtusifolia L. Ameliorate Non-Alcoholic Fatty Liver. PLoS ONE 10:e0138078. doi: 10.1371/journal.pone.0138078

Meyer, K. A., and Bennett, B. J. (2016). Diet and gut microbial function in metabolic and cardiovascular disease risk. Curr. Diab. Rep. 16:93. doi: 10.1007/s11892-016-0791-x

Micha, R., Penalvo, J. L., Cudhea, F., Imamura, F., Rehm, C. D., and Mozaffarian, D. (2017). Association Between Dietary Factors and Mortality From Heart Disease, Stroke, and Type 2 Diabetes in the United States. JAMA 317, 912–924. doi: 10.1001/jama.2017.0947

Michaud, T. (1974). Microbial bile acid transformation. Am. J. Clin. Nutr. 27, 1341–1347.

Moore-Indias, I., Cardona, F., Tinahones, F. J., and Queipo-Ortuno, M. I. (2014). Human gut microbial gene catalogue established by metagenomic sequencing. Nature 464, 59–65. doi: 10.1038/nature08821

Pedersen, B. V., et al. (2017). A purified membrane protein from Akkermansia muciniphila or the gut microbiota and fat storage in a mouse model with high-fat-induced obesity. Food Funct. 5, 1241–1249. doi: 10.1039/c6fo00630a

Qian, J., Li, R., Raes, J., Arumugam, M., Burgdorf, K. S., Manichanh, C., et al. (2010). The human gut microbial gene catalogue established by metagenomic sequencing. Nature 464, 59–65. doi: 10.1038/nature08821

Robbins, G. R., Wen, H., and Ting, J. P. (2014). Inflammamosomes and metabolic disorders: old genes in modern diseases. Mol. Cell 54, 297–308. doi: 10.1016/j.molcel.2014.03.029

Romano, K. A., Vivas, E. I., Amador-Noguez, D., and Rey, F. E. (2015). Intestinal microbiota composition modulates choline bioavailability from diet and accumulation of the proatherogenic metabolite trimethylamine-N-oxide. MBio 6:e02481. doi: 10.1128/mBio.02481-14

Roopchand, D. E., Carmody, R. N., Kuhn, P., Moskal, K., Boja-Silva, P., Turnbaugh, P. J., et al. (2015). Dietary Polyphenols Promote Growth of the Gut Bacterium Akkermansia muciniphila and Attenuate High-Fat-Diетed Metabolic Syndrome. Diabetes 64, 2847–2858. doi: 10.2337/db14-1916

Saad, M. J., Santos, A., and Prada, P. O. (2016). Linking Gut Microbiota and Inflammation to Obesity and Insulin Resistance. Physiology (Bethesda) 31, 283–293. doi: 10.1152/physiol.00041.2015

Samuel, B. S., Shaito, A., Motoike, T., Rey, F. E., Backhed, F., Manchester, J. K., et al. (2008). Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr4. Proc. Natl. Acad. Sci. U.S.A. 105, 16767–16772. doi: 10.1073/pnas.0808567105

Sayin, S. I., Wahlstrom, A., Felin, J., Jantti, S., Marschall, H. U., and Backhed, F. (2016). Gut microbiota regulates bile acid metabolism by reducing the levels of tauro-beta-muricholic acid, a naturally occurring FXR antagonist. Cell Metab. 21, 172–185. doi: 10.1016/j.cmet.2015.01.003

Schroder, B. O., and Backhed, F. (2016). Signals from the gut microbiota to distant organs in physiology and disease. Nat Med 22, 1079–1089. doi: 10.1038/nm.4185
Schugar, R. C., Shih, D. M., Warrier, M., Helsey, R. N., Burrows, A., Ferguson, D., et al. (2017). The TMAO-Producing Enzyme Flavin-Containing Monoxygenase 3 Regulates Obesity and the Beiging of White Adipose Tissue. Cell Rep. 19, 2451–2461. doi: 10.1016/j.celrep.2017.05.077

Seldin, M. M., Meng, Y., Qi, H., Zha, W., Wang, Z., Hazen, S. L., et al. (2016). Trimethylamine N-Oxide promotes vascular inflammation through signaling of mitogen-activated protein kinase and nuclear factor-kappB. J. Am. Heart Assoc. 5:e002767. doi: 10.1161/JAHA.115.002767

Senthong, V., Li, X. S., Hudec, T., Coughlin, J., Wu, Y., Levison, B., et al. (2016a). Plasma Trimethylamine N-Oxide, a gut microbe-generated phosphatidylcholine metabolite, is associated with atherosclerotic burden. J. Am. Coll. Cardiol. 67, 2620–2628. doi: 10.1016/j.jacc.2016.03.546

Senthong, V., Wang, Z., Fan, Y., Wu, Y., Hazen, S. L., and Tang, W. H. (2016b). Trimethylamine N-oxide and mortality risk in patients with peripheral artery disease. J. Am. Heart Assoc. 5:e002437. doi: 10.1161/JAHA.116.002437

Senthong, V., Wang, Z., Li, X. S., Fan, Y., Wu, Y., Tang, W. H., et al. (2016c). Intestinal microbiota-generated metabolite trimethylamine-N-oxide and 5-year mortality risk in stable coronary artery disease: the contributory role of intestinal microbiota in a COURAGE-like patient cohort. J. Am. Heart Assoc. 5:e002816. doi: 10.1161/JAHA.116.002816

Shang, Q., Shan, X., Cai, C., Hao, J., Li, G., and Yu, G. (2016). Dietary fucoidan modulates the gut microbiota in mice by increasing the abundance of Lactobacillus and Ruminococcaceae. Food Funct 7, 3234–3232. doi: 10.1039/C6FO0309E

Shin, N. R., Lee, J. C., Lee, H. Y., Kim, M. S., Whon, T. W., Lee, M. S., et al. (2017). Isomalto-oligosaccharides, a prebiotic, functionally augment microbial translocation in short bowel syndrome. J. Intern. Med. 281, 1908–1914. doi: 10.1111/joim.12328

Singh, D. P., Singh, J., Boparai, R. K., Zhu, J., Mantri, S., Khare, P., et al. (2011). Chronic rhein treatment improves recognition memory in rats fed a high-cholesterol diet. J. Nutr. Biochem. 22, 438–445. doi: 10.1016/j.jnutbio.2011.05.005

Sweeney, T. E., and Morton, J. M. (2013). The human gut microbiome: a review links innate immunity and fatty acid-induced insulin resistance. J. Clin. Invest. 119, 3015–3025. doi: 10.1172/JCI228898

Shi, L.-L., Wang, Y., and Feng, Y. (2015). [Effect of MDG-1, a polysaccharide from Coix lacryma-jobi var. ma-yuen] in rats fed a high-cholesterol diet. Int. J. Food Sci. Nutr. 66, 783–789. doi: 10.3109/09637486.2016.1088941

Tang, W. H., Wang, Z., Shrestha, K., Borowski, A. G., Wu, Y., Troughton, R. W., et al. (2015b). Intestinal microbiota-dependent phosphatidylcholine metabolites, diastolic dysfunction, and adverse clinical outcomes in chronic systolic heart failure. J. Card. Fail 21, 91–96. doi: 10.1016/j.cardfail.2014.11.006

Thomas, C., Giioelllo, A., Noriega, L., Strehle, A., Oury, J., Rizzo, G., et al. (2009). TGR5-mediated bile acid sensing controls glucose homeostasis. Cell Metab. 10, 167–177. doi: 10.1016/j.cmet.2009.08.001

Thomas, C., Pelliccari, R., Pruzanski, A., Ouwerx, J., and Schoonjans, K. (2008). Targeting bile-acid signalling for metabolic diseases. Nat. Rev. Drug Discov. 7, 678–693. doi: 10.1038/nrd2619

Tolhurst, G., Heffron, H., Lam, Y. S., Parker, H. E., Habib, A. M., Diakogianni, E., et al. (2012). Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. Diabetes 61, 364–371. doi: 10.2373/dni/b11-1019

Trabelsi, M. S., Daoudi, M., Prawitt, J., Ducastel, S., Touche, V., Sayin, S. I., et al. (2015). Farnesoid X receptor inhibitors glucagon-like peptide-1 production by enteroendocrine L cells. Nat. Commun. 6:7629. doi: 10.1038/ncomms8629

Troseid, M., Hov, J. R., Nestvold, T. K., Thoresen, H., BERGE, R. K., Svarding, A., et al. (2016). Major increase in microbiota-dependent proatherogenic metabolite tMAO one year after bariatric surgery. Metab. Syndr. Relat. Disord. 14, 197–201. doi: 10.1089/met.2015.0120

Troseid, M., Ueland, T., Hov, J. R., Svarding, A., Gregersen, I., Dahl, C. P., et al. (2015). Microbiota-dependent metabolite trimethylamine-N-oxide is associated with disease severity and survival of patients with chronic heart failure. J. Intern. Med. 277, 717–726. doi: 10.1111/joim.12328

Turnbaugh, P. J., Ley, R. E., Hamady, M., Fraser-Liggett, C. M., Knight, R., and Gordon, J. I. (2007). The human microbiome project. Nature 449, 804–810. doi: 10.1038/nature06244

Vijay-Kumar, M., Aitken, J. D., Carvalho, F. A., Cullender, T. C., Mwangi, S., Sinivasan, S., et al. (2010). Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. Science 328, 228–231. doi: 10.1126/science.1179721

Wahlstrom, A., Sayin, S. I., Marschall, H. U., and Backhed, F. (2016). Intestinal crosstalk between bile acids and microbiota and its impact on host metabolism. Cell Metab. 24, 41–50. doi: 10.1016/j.cmet.2016.05.004

Welch, W. M., Lane, D. A., and Backhed, F. (2016). Gut microbiota interactions as moderators of human metabolism. Nature 535, 56–64. doi: 10.1038/nature18846

Wang, H., Chen, J., Hollister, K., Sowers, L. C., and Forman, B. M. (1999). Endogenous bile acids are ligands for the nuclear receptor FXR/BAR. J. Biol. Chem. 274, 15821–15826. doi: 10.1074/jbc.274.224.15821

Wang, J. H., Bose, S., Kim, G. C., Hong, S. U., Kim, J. H., Kim, J. E., et al. (2014). Flos Lonicera ameliorates obesity and associated endotoxemia in rats through modulation of gut permeability and intestinal microbiota. PLoS ONE 9:e86117. doi: 10.1371/journal.pone.0086117

Wang, J., Ghosh, S., and Ghosh, S. (2017). Curcumin improves intestinal barrier function: modulation of intracellular signaling, and organization of tight junctions. Am. J. Physiol. Cell Physiol. 322, C438–C445. doi: 10.1152/ajpcell.00235.2016

Wang, J., Jeschke, M. U., Zhang, H., Zhao, L., Zuo, T., and Zou, Y. (2014). Progesterone prevents clostridial overgrowth and intestinal leakiness in rats. Cell Metab. 20, 461–476. doi: 10.1016/j.cmet.2014.09.001

Wang, S., Huang, F. Z., Zhang, P., Wang, H., Zhang, Q., Yu, S., et al. (2016). Chronic rhein treatment improves recognition memory in high-fat diet-induced obese male mice. J. Nutr. Biochem. 36, 42–50. doi: 10.1016/j.jnutbio.2016.07.008
Wang, S., Li, Q., Zang, Y., Zhao, Y., Liu, N., Wang, Y., et al. (2017). Apple Poly saccharide inhibits microbial dysbiosis and chronic inflammation and modulates gut permeability in HFD-fed rats. *Int. J. Biol. Macromol.* 99, 282–292. doi: 10.1016/j.ijbiomac.2017.02.074

Wang, Y., Ames, N. P., Tun, H. M., Tosh, S. M., Jones, P. J., and Khafipour, E. (2016). High Molecular Weight Barley beta-Glucan Alters Gut Microbiota Toward Reduced Cardiovascular Disease Risk. *Front. Microbiol.* 7:129. doi: 10.3389/fmicb.2016.00129

Wang, Y., Shou, J. W., Li, X. Y., Zhao, Z. X., Fu, J., He, C. Y., et al. (2017). Berberine-induced bioactive metabolites of the gut microbiota improve energy metabolism. *Metabolism* 70, 72–84. doi: 10.1016/j.metabol.2017.02.003

Wang, Y., Tong, J., Chang, B., Wang, B., Zhang, D., and Wang, B. (2014). Effects of alcohol on intestinal epithelial barrier permeability and expression of tight junction-associated proteins. *Mol. Med. Rep.* 9, 2352–2356. doi: 10.3892/mmr.2014.2126

Wang, Z. N., Klipfel, E., Bennett, B. J., Koeth, R., Levison, B. S., Dugar, B., et al. (2011). Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. *Nature* 472, 57–82. doi: 10.1038/nature09992

Wang, Z., Roberts, A. B., Buffa, J. A., Levison, B. S., Zhu, W., Org, E., et al. (2015). Non-lethal Inhibition of Gut Microbial Trimethylamine Production for the Treatment of Atherosclerosis. *Cell* 163, 1585–1595. doi: 10.1016/j.cell.2015.11.055

Wiest, R., Albillos, A., Trauner, M., Bajaj, J., and Jalan, R. (2017). Targeting the gut-liver axis in liver disease. *J. Hepatol.* 67, 1084–1103. doi: 10.1016/j.jhep.2017.05.007

Wilson, A., Mclean, C., and Kim, R. B. (2016). Trimethylamine-N-oxide: a link between the gut microbiome, bile acid metabolism, and atherosclerosis. *Curr. Opin. Lipidol.* 27, 148–154. doi: 10.1097/MOL.0000000000000274

Wink, M. (2015). Modes of action of herbal medicines and plant secondary metabolites. *Medicines* 2,251. doi: 10.3390/medicines2030251

Woodside, J. V., Young, I. S., and McKinley, M. C. (2013). Fruit and vegetable intake and risk of cardiovascular disease. *Proc. Nutr. Sci.* 72, 399–406. doi: 10.1017/S0029665113003029

Woting, A., and Blaut, M. (2016). The intestinal microbiota in metabolic disease. *Nutrients* 8:202. doi: 10.3390/nu8040020

Wu, W., Sun, M., Chen, F., Cao, A. T., Liu, H., Zhao, Y., et al. (2016). Microbiota metabolite short-chain fatty acid acetate promotes intestinal IgA response to microbiota which is mediated by GPR43. *Mucosal Immunol.* 10, 946–956. doi: 10.1038/mi.2016.114

Xiao, M., Yang, J., Feng, Y., Zhu, Y., Chai, X., and Wang, Y. (2017). Metaproteomic strategies and applications for gut microbial research. *Appl. Microbiol. Biotechnol.* 101, 3077–3088. doi: 10.1007/s00253-017-8215-7

Xie, W., Gu, D., Li, J., Cui, K., and Zhang, Y. (2011). Effects and action mechanisms of berberine and *Rhizoma coptidis* on gut microbes and obesity in high-fat diet-fed C57BL/6j mice. *PLoS ONE* 6:e24520. doi: 10.1371/journal.pone.0042529

Xu, J. H., Xia, G. H., Lu, J. Q., Chen, M. X., Zhen, X., Wang, S., et al. (2017). Impaired renal function and dysbiosis of gut microbiota contributed to increased trimethylamine-N-oxide in chronic kidney disease patients. *Sci. Rep.* 7:1445. doi: 10.1038/s41598-017-01387-y

Xu, P., Wang, J., Hong, F., Wang, S., Jin, X., Xue, T., et al. (2017). Melatonin prevents obesity through modulation of gut microbiota in mice. *J. Pineal. Res.* 62:e12399. doi: 10.1111/jpi.12399

Yan, H., Lu, J., Wang, Y., Gu, W., Yang, X., and Yu, J. (2017). Intake of total saponins and polysaccharides from Polygonatum kingianum affects the gut microbiota in diabetic rats. *Phytomedicine* 26, 45–54. doi: 10.1016/j.phymed.2017.01.007

Yang, Y., Chen, G., Yang, Q., Ye, J., Cai, X., Tsering, P., et al. (2017). Gut microbiota drives the attenuation of dextran sulphate sodium-induced colitis by Huangqin decoction. *Oncotarget* 8, 48863–48874. doi: 10.18632/oncotarget.16458

Young, R. P., Hopkins, R. J., and Marsland, B. (2016). The Gut-Liver-Lung Axis. Modulation of the Innate Immune Response and Its Possible Role in Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Cell Mol. Biol.* 54, 161–169. doi: 10.1165/rcmb.2015-0250PS

Yu, H., Guo, Z., Shen, S., and Shan, W. (2016). Effects of taurine on gut microbiota and metabolism in mice. *Amino Acids* 48, 1601–1617. doi: 10.1007/s00726-016-2219-y

Zhang, X. H., Huang, B., Choi, S. K., and Seo, J. S. (2012b). Anti-obesity effect of resveratrol-amplified grape skin extracts on 3T3-L1 adipocytes differentiation. *Nutr. Res. Pract.* 6, 286–293. doi: 10.4162/nrp.2012.6.4.286

Zhang, X., Zhao, Y., Xu, J., Xue, Z., Zhang, M., Pang, X., et al. (2015). Modulation of gut microbiota by berberine and metformin during the treatment of high-fat diet-induced obesity in rats. *Sci. Rep.* 5:14405. doi: 10.1038/srep14405

Zhang, X., Zhao, Y., Zhang, M., Pang, X., Xu, J., Kang, C., et al. (2012a). Structural changes of gut microbiota during berberine-mediated prevention of obesity and insulin resistance in high-fat diet-fed rats. *PLoS ONE* 7:e42529. doi: 10.1371/journal.pone.0042529

Zhou, J., Ma, Y. H., Zhou, Z., Chen, Y., Wang, Y., and Gao, X. (2015). Intestinal absorption and metabolism of epimedium flavonoids in osteoporosis rats. *Drug Metab. Dispos.* 43, 1590–1600. doi: 10.1124/dmd.115.064836

Zhou, S. S., Xu, J., Zhu, H., Wu, J., Xu, J. D., Yan, R., et al. (2016). Gut microbiota-involved mechanisms in enhancing systemic exposure of ginsenosides by coexisting polysaccharides in ginseng decoction. *Sci. Rep.* 6:22474. doi: 10.1038/srep22474

Zhu, W., Gregory, J. C., Org, E., Buffa, J. A., Gupta, N., Wang, Z., et al. (2016). Gut Microbial Metabolite TMAO Enhances Platelet Hyperreactivity and Thrombosis Risk. *Cell* 165, 111–124. doi: 10.1016/j.cell.2016.02.011

Zhu, W., Wang, Z., Tang, W. H. W., and Hazen, S. L. (2017). Gut Microbe-Generated Trimethylamine N-Oxide From Dietary Choline Is Prothrombotic in Subjects. *Circulation* 135, 1671–1673. doi: 10.1161/CIRCULATIONAHA.116.025338

Zhu, Y., Jameson, E., Crosatti, M., Schafer, H., Rajakumar, K., Bugg, T. D., et al. (2014). Carnitine metabolism to trimethylamine by an unusual Rieske-type oxygenase from human microbiota. *Proc. Natl. Acad. Sci. U.S.A.* 111, 4268–4273. doi: 10.1073/pnas.1316569111

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