

Review Article

Role of Gut Microbiota in the Pharmacological Effects of Natural Products

Chuyue Pan, Qinglong Guo , and Na Lu 

State Key Laboratory of Natural Medicines, Jiangsu Key Laboratory of Carcinogenesis and Intervention, Department of Basic Medicine, School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, 24 Tongjiaxiang, Nanjing 210009, China

Correspondence should be addressed to Qinglong Guo; qinglongguo@hotmail.com and Na Lu; nalu@cpu.edu.cn

Received 6 February 2019; Revised 31 March 2019; Accepted 9 April 2019; Published 15 April 2019

Guest Editor: Chongshan Dai

Copyright © 2019 Chuyue Pan et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Increasing evidence has demonstrated that natural products derived from traditional Chinese medicine, such as ginseng, berberine, and curcumin, possess a wide variety of biological activities on gut microbiota, which may cause changes in the composition of intestinal microbiota, microbial metabolites, intestinal tight junction structure, and mucosal immunology. These changes will eventually result in the exertion of the pharmacological effects by treatment with these natural products. In this review, we will discuss how gut microbiota is influenced by commonly used natural products. Furthermore, our findings are expected to provide novel insight into how these untargeted natural products function via gut microbiota.

1. Introduction

The relationship between gut microbiota and human diseases has been a major topic of interest for many studies. Increasing evidence has suggested that gut microbiota plays an important role in diseases, including obesity [1], type 2 diabetes mellitus (T2DM), cardiovascular diseases [2], and cancer [3, 4]. In many studies, bacteria-deficient mice have been reported to consume more calories than normal mice [5], and it was more difficult for these mice to become obese [6]. Studies in germ-free mice have indicated that gut microbiota was associated with weight gain, lipid synthesis, and fat storage. In addition, high-fat diet- (HFD-) induced obesity is usually accompanied with diabetes [7], cardiovascular diseases, and liver diseases such as nonalcoholic fatty liver disease (NAFLD). Besides, gut microbiota, which can be part of the tumor microenvironment, communicates with tumor cells, and some immune cells [8], and may be the key factor in the process of HFD-induced cancer progression [9].

In recent years, interest in the pharmacological activities of natural products has significantly increased. *In vitro* studies and clinical data have demonstrated positive effects of natural products on many diseases [10, 11]. The aim of this study was to discuss the effects of natural products on the composition of gut microbiota, metabolites, intestinal tight

junction proteins, and mucosal immunity and to provide novel insight into future therapies.

2. Effect of Natural Products on Composition of Gut Microbiota

The gut microbiota is hypothesized to play a critical role in metabolic diseases, such as obesity and T2DM. An increasing number of studies have shown that natural products exert antiobesity activities by modulating the composition of gut microbiota. For example, MDG-1, a water-soluble polysaccharide extracted from the root of *Ophiopogon japonicus* Ker Gawl has been reported to regulate body metabolism, including weight loss, antiobesity, and antidiabetes. Shi et al. [12] demonstrated that, in HFD-induced obese mice that were treated with MDG-1 at a high dose of 300 mg/kg for 12 weeks, the ratio of Firmicutes/Bacteroidetes (F/B) decreased to normal levels. In addition, it was found that, in a HFD-induced diabetic mouse model, MDG-1 decreased the number of pathogenic bacteria (*Escherichia coli* and *Streptococcus*) [13]. Green tea, commonly consumed in Asia, has also been reported to have an antiobesity activity [14], and the alteration of gut microbiota composition has been presumed as one of its mechanisms of action. When sundried green tea was

fermented, it restored the increased Bacteroides/Prevotella (B/P) ratio [15] and significantly decreased the F/B ratio in HFD mice after 8 weeks of treatment. Epigallocatechin gallate (EGCG), the main type of catechin in green tea, could inhibit the formation of rat abdominal adipose tissue after a 4-week treatment regimen. In their study, it was revealed that EGCG-treated rats showed a dramatic decrease of *Clostridium* spp. and an increase of Bacteroides in feces [16]. Moreover, Chang et al. [17] reported that a water extract of *Ganoderma lucidum* (Curtis) P. Karst. (WEGL) prevented weight gain and fat accumulation in HFD-induced obese mice. Furthermore, endotoxemia and insulin resistance were found to be improved by WEGL for the modification of gut dysbiosis. The F/B ratio and levels of endotoxin-bearing Proteobacteria were also restored to normal levels. However, several bacteria increased (*Parabacteroides goldsteinii*, *Bacteroides* spp., *Anaerotruncus colihominis*, *Roseburia hominis*, and *Clostridium*), which negatively correlated with obesity. The authors suggested that WEGL or polysaccharides could be used as prebiotic agents for the treatment of obesity and modulating obesity-related metabolic disorders [17].

Lonicerae japonicae flos is famous for its anti-inflammatory activity and has widely been used in Asia for years. In animal studies using HFD-fed animals, administration of unfermented *Flos Lonicera* (UFL) or fermented *Flos Lonicera* (FFL) significantly reduced body weight (BW) and adipose tissue weight and decreased lipid accumulation in the liver with ameliorated serum total cholesterol, HDL, and triglyceride levels. As suggested by the authors, alterations in the relative abundance of *Lactobacillus* spp., *Bifidobacterium* spp., and B/F ratio in the intestinal tract were supposed to be one of the mechanisms of UFL or FFL [18]. In addition, the amount of *Bifidobacterium* spp. in the cecal pool of HFD-induced mice was increased by pomegranate peel extract (PPE), which is known for its beneficial effects, including anti-inflammatory and antimicrobial activities [19].

Berberine, the main active ingredient of Chinese herb *Coptis chinensis*, is known as an antidiabetes drug and can regulate blood glucose [20, 21]. Berberine has been shown to be beneficial for HFD-induced insulin resistance, as it improves insulin sensitivity and reduces the homeostasis assessment of the insulin resistance (HOMA-IR) value. As reported by Sun et al., administration of berberine reduced the ratio of F/B and partly recovered the composition of gut microbiota changed by HFD feeding. Furthermore, it also showed that both the diversity and richness of gut microbiota were significantly decreased after berberine administration [22]. These findings were supported by Zhang et al., who showed that the partial least squares (PLS) regression model predicted the relationship between the changes in composition of gut microbiota and host phenotype [23].

In addition to animal studies, several studies of natural products have been performed on human gut microbiota. Xu et al. reported that Gegen Qinlian Decoction (GQD), a traditional Chinese herbal formula, reshaped the gut microbiota in a clinical study in which 187 T2D patients were enrolled. The data showed that the symptoms of T2D, such as fasting blood glucose levels and hemoglobin A1c

(HbA1c) levels, were ameliorated in GQD-treated patients, with increased amounts of beneficial bacteria, including *Faecalibacterium*, *Gemmiger*, *Bifidobacterium*, and *Escherichia* [11]. Another clinical study involving ten obese Korean women was conducted to investigate the antiobesity activity of the water extract of *Ephedra sinica* Stapf, which revealed that, in seven of the ten obese women, BW and body mass index (BMI) were decreased after administration of this herb. Interestingly, the antiobesity effect of ginseng varied when the composition of gut microbiota was altered. The abundance of *Subdoligranulum*, *Oscillibacter*, and *Akkermansia* in the gut associated with changes in BW and BMI, whereas *Lactobacillus* was linked to body fat percentage [10].

Natural products also play an important role in the improvement of gastrointestinal tract function. Several Chinese medicine products such as Red Ginseng and Semen Coicis were found to relieve the symptoms of ulcerative colitis (UC) [24, 25]. After Red Ginseng and Semen Coicis treatment in rats, the structure of gut microbiota was altered, which may be beneficial for promoting the growth of probiotics, such as *Bifidobacterium* and *Lactobacillus*, and for inhibiting the growth of pathogenic bacteria [25]. In a double-blind, randomized clinical trial containing 54 patients, it was revealed that the combination of herbal medicine (*Gwakhyangjeonggisan*, GJS) and probiotics (Duolac7S, DUO) alleviated the symptoms of diarrhea-predominant irritable bowel syndrome (D-IBS) by changing the composition of gut microbiota. Beneficial intestinal microbe counts, including *Bifidobacterium brevis*, *Bifidobacterium lactis*, *Streptococcus thermophilus*, *Lactobacillus rhamnosus*, *Lactobacillus plantarum*, and *Lactobacillus acidophilus*, were synergistically enhanced by GJS combined with DUO, suggesting that a combined treatment of herbal medicine and probiotics might provide a promising implication for clinical treatment of D-IBS [26, 27].

3. Effect of Natural Products on Metabolites of Gut Microbiota

In the human intestine, microbes are vital contributors to the host metabolism, considering that numerous important components, such as vitamin K, folate, indoles, gamma amino butyric acid, and short-chained fatty acids (SCFAs), are produced by microbiota [28–30]. In general, these metabolites are involved in many physiological and pathophysiological processes, which may be related to several diseases, including cardiovascular diseases [29], allergic reactions [30], T2DM [31], and various types of cancers [8, 32]. By changing the bacterial structure, natural products may regulate the metabolism of the microbiome, Zhao et al. found that the abundance of genes encoding SCFA production and the fecal butyric acid concentration were notably increased by a high fiber diet from traditional Chinese medicinal food plants, and several T2DM parameters were found to be improved after treatment, and they identified 15 positive responders of SCFA which played an important role in maintaining intestinal homeostasis [31]. When total saponins and polysaccharides (active constituents of *P. kingianum*) were administered to diabetic rats, the abundance of the content of certain bacterial

taxa and fecal SCFAs in rats was upregulated, while the lipopolysaccharide (LPS) concentration was downregulated [33]. These results suggested that natural products might be the treat levels of protective metabolites and that detrimental metabolites can contribute to metabolic diseases. Chen *et al.* reported that sulfate-reducing bacteria were significantly decreased after *Gynostemma pentaphyllum* (GpS) treatment in *Apc^{Min/+}* mice. As a result, the level of harmful molecular hydrogen sulfide produced by sulfate-reducing bacteria was also reduced [34].

Gut microbiota can also impact the metabolism of natural products and therefore influence their treatment effects. It has been demonstrated that commensal bacteria regulate countless genes involved in drug metabolism and hepatic expression of drug-metabolizing enzymes [35–37]. Therefore, the microbial activity in metabolic phenotype development is important, especially for pharmacokinetics [35], because treatment effects of components of traditional Chinese herbs may be enhanced by biotransformation. For instance, many glycoside compounds are hydrolyzed by gut flora when administered orally, and thereby, the solubility is improved to allow for easy absorption. Ginsenoside Rb1 [37] and aglycone of baicalin [38] are biotransformed to a more active form, aglycone. After transformation, they harbor a much better bioavailability. On the contrary, the activity of several molecules can be transformed to an inactive form and reduce their bioactivities. Ru *et al.* found that berberine is metabolized to dihydroberberine (dhBBR), which is easier to absorb but has less active properties, although in the blood it can be oxidized to berberine [39]. Several herbs are toxic and their harmful metabolites can also be more or less toxic [40, 41]. Human intestinal microbiota can metabolize aconitine, an alkaloid that can induce systemic acute toxicity, to be less harmful to the body through acetylation and esterification [40]. However, aristolochic acid in *Radix Aristolochiae Fangchi* can cause acute renal injury, and long term administration can increase the risk of cancer. Its main microbial metabolite aristolochic acid I, the most toxic component of the *Aristolochia* herbs, is particularly cytotoxic in the kidney [42].

From another point of view, gut microbiota has played an important role on the pharmacokinetics and pharmacodynamics of natural products. The loss of gut microbiota or dysbiosis may reduce the efficacy of traditional Chinese medicine. Liu *et al.* reported that rats treated with broad-spectrum antibiotics show a different pharmacological response to Shaoyao-Gancao decoction (SGD) when compared with control mice. The antibiotics inhibited the absorption of SGD and reduced biotransformation of SGD in the colon. Two constituents of SGD have significantly reduced AUC_{0-24h} after antibiotics treatment, but the half-lives ($T_{1/2}$) and mean retention times (MRT) did not remarkably change [43]. It seems that gut microbiota mainly affects the blood concentration and AUC of herb medicines. Furthermore, Shen *et al.* used 5% dextran sulfate sodium (DSS) to disturb gut microbial homeostasis and observed a quicker absorption (less T_{max}) and a lower max concentration (C_{max}) of ginsenoside Rb1 in DSS-treated mice. Once given drugs to restore the balance, these changes recovered, which

indicated the importance of the intestinal flora in drug metabolism [44]. Thus, it is of importance to consider the influence of gut microbiota in clinical medicine. Digoxin is an example of a drug that decreases drug efficacy when it is metabolized by microbiota. It has been reported that gut microbiota can degrade digoxin to its inactive form, such as dihydrodigoxin and dihydrodigoxigenin [45], which hardly bind $Na^+ - K^+ - ATPase$ of cardiac cells [46]. Conversely, some new effects can be functioned during the interaction between drugs and gut microbiota. In a study by Ru *et al.*, the mechanism of antihyperlipidemia function and pharmacokinetics in beagle dogs was determined. Different from effects such as anti-inflammatory and antidiabetes activities, berberine induced the production of butyrate by upregulating butyrate-producing microbiota [47]. All studies involving novel effects or mechanism may have direct applications to clinical medicines.

In conclusion, natural products can affect the metabolism of gut microbes, and the microbiome can change the metabolic process of natural components.

4. Effect of Natural Products on Improving Gut Tight Junction through Regulating Intestinal Microbes

In intestinal epithelial cells, tight junctions usually function as a barrier to defense against bacterial endotoxin. In addition, LPS-induced disruption of tight junctions can lead to dysregulation of intestinal epithelial cells, as well as of the immune system [48]. A HFD could increase LPS release induced by gut microbiota, thereby impairing the expression of tight junction proteins leading to the increase of intestinal permeability [49]. Furthermore, HFD elevated the LPS concentration in plasma, and subsequently increased the secretion of adipokines. In a recent study, it was shown that *Lactobacilli* positively associated with human BMI and blood glucose values [50]. In addition, it was reported that *Lactobacilli* could reduce the LPS level, decrease blood glucose levels, and inflammation in HFD mice. Besides, *Lactobacilli sakei* OK67 could restore the expression of colonic tight junction protein expression and ameliorate HFD-induced hyperglycemia [51].

Moreover, in previous studies, it was demonstrated that nanoparticle loaded with berberine could protect tight junction against inflammation induced by LPS. And berberine-loaded nanoparticles turned out to be useful in the restoration of tight junctions in intestinal epithelial cells (IEC) [52]. Li *et al.* and Gu *et al.* reported that berberine could inhibit intestinal epithelial tight junction damage caused by proinflammation cytokines [53]. Pretreatment with berberine could reduce the intestinal permeability and improve LPS-induced redistribution of tight junction-related protein claudin-1 and claudin-4 [54]. Combined, these results indicated that berberine improved bacterial endotoxin induced intestinal barrier disruption and play a significant role in the maintenance of the intestinal epithelial tight junction.

Besides berberine, other natural products also showed powerful functions to protect the intestine from LPS-induced

gut microbiota. In a previous study the effects of curcumin were tested on Caco-2 cells and HT-29 cells, and it was found that curcumin could attenuate the disruption of intestinal epithelial barrier functions. Curcumin reduced the release of IL-1 β secreted from LPS, induced IEC and macrophages, and prevented the disintegration of tight junction proteins, such as ZO-1, claudin-1, claudin-7, and actin filaments [55]. Therefore, curcumin can be a potential compound for treating intestine barrier injury through increasing the expression of tight junction proteins.

Similarly, *Flos Lonicera*, one of the most well-known traditional Chinese medicines, could modulate tight junctions at the cell-based level. It not only restored the side effects induced by LPS but also increased several microbiota, which had beneficial effects on maintaining the integrity of the intestinal barrier [18]. For example, Chelakkot *et al.* demonstrated that *akkermansia-muciniphila* could activate tight junction-related signaling of AMPK, especially in obesity and T2D patients [56]. In another study, it was suggested that the polyphenolic compound resveratrol (Res), which is found in grape seeds, grape skin, and red wine, attenuated intestinal barrier impairment and bacterial translocation induced by deoxynivalenol (DON) [57, 58]. Ling *et al.* reported that Res mainly facilitated claudin-4 expression to build up the tight junction complex and to resist DON-induced barrier dysfunction [59].

Together, these findings demonstrated that natural products can exert positive effects on the intestinal barrier by upregulating tight junction proteins, reducing inflammation, and increasing the abundance of probiotics. Gut microbiota disorders increased the secretion of LPS, thereby leading to a series of metabolic diseases [60, 61]. However natural products can directly or indirectly act on microbes to alleviate the condition.

5. Effect of Natural Products on Intestinal Mucosal Immunity

The intestinal mucosal immunity system consists of gut-associated lymphoid tissue (GALT), lymphocytes, and various immune-related factors. At present, it is believed that digestive system diseases, autoimmune diseases, pediatric allergic diseases, and tumors are closely related to intestinal mucosal immunity [62, 63]. Natural products may provide an alternative treatment approach for these diseases.

Many metabolic diseases are related to intestinal inflammation and gut microbiota, and it is the intestinal mucosal immunity that is the connection between them. As previously reported, the induction of IL-22 in innate lymphoid cells and CD4⁺T cells is impaired in obese mice, and IL-22 deficiency in mice has shown that mice are prone to developing metabolic disorders [64]. Intestinal mucosal immunity in obese mice contributed to obesity-related insulin resistance via preserving the gut barrier and remitting fat inflammation [65].

Gut microbiota regulates host innate and adaptive immunity. Dysbiosis of gut microbiota can cause severe intestinal diseases [66]. Segmented filamentous bacteria can activate CD4⁺T cells and produce IL-17A to promote inflammation in the intestine [67]. Microbiota such as *Clostridium clusters*

promoted the development of intestinal regulatory T cells (T reg), which are significantly decreased in colonic germ-free mice [68, 69]. Moreover, in the small intestine, TH17 cells secrete cytokines, such as IL-17/IL-22 to regulate the inflammation status in colon. However, *Clostridium arthromitus* and metabolites from microbiota, such as luminal adenosine triphosphate and tryptophan, promoted the development of TH17 cells [70–72]. Commensal bacteria modulated the abundance and activation of $\gamma\delta$ T cells, which produced IL-17 to promote inflammation in the intestine [73]. Gut microbiota could also inhibit natural killer T cells (iNKT) [74, 75].

Innate lymphoid cells (ILCs) share functional characteristics with T cells in the lamina propria. Gut microbiota may regulate the ILC either through direct recognition or by indirect induction of cytokine secretion by other cells [76]. On the contrary, microbiota can also regulate the activation of ILCs via inducing the production of IL-25, which confirms the opinion that microbiota is important for homeostasis [77, 78].

IgA constitutes approximately 75% of the total antibody production in mammals and is the most abundant immunoglobulin in mucosal secretions [79]. Gut microbiota is a strong inducer of IgA production. For example, orally administered flagellin abrogated IgA secretion in the intestine [80].

Recent studies have shown that berberine had beneficial effects on intestinal immune cells and immune factors. Moreover, berberine also inhibited the expression of various immune factors and reduced the low-grade inflammation [81]. For example, berberine has been widely used in the treatment of UC via modulating T reg cells and TH cells in the colon [82]. Researchers in China revealed that berberine improved lipid metabolism in the liver by changing microbiota and by regulating bile acid metabolism and the FXR pathway in the intestine [83]. In addition, *M. charantia* improved insulin resistance via decreasing the F/B ratio in the intestines of diabetic rats [84]. Therefore, it improved the inflammation status in the intestine and diabetes mellitus [85]. Curcumin could improve pancreatic β cells and decrease glucose levels, as well as other metabolic profile in T2D or atherosclerosis through inhibition of iNOS and COX-2 [86, 87]. Furthermore, a curcumin-supplemented diet increased the richness of *lactobacillales* and improved the index of colon tumors [88]. Ginsenoside also protected cardiac function and decreased blood glucose levels [89].

Natural products modulate the immune status via changing the level of immune factors, such as IL-22, as well as activating T reg cells or inhibiting the development of Th17 cells. Natural products can also decrease systemic inflammation via improving insulin resistance as well as other metabolic profiles. Natural products have promising therapeutic effects on metabolic diseases by improving the immune status in the body.

6. Conclusion

In the past, numerous studies have demonstrated that natural products derived from traditional Chinese medicine implement their pharmacological properties through restoring gut

homeostasis, including alteration of microbiota composition, adjustment of microbiota metabolites, enhancement of the expression of tight junction proteins, and enhancing mucosal immunity. Therefore, we conclude that gut microbiota and its subsequent changes of intestinal environment play very important roles in mediating the pharmacological effects of natural products. Given the fact that various roles of gut microbiota were gradually elucidated in human diseases and health, we hypothesize that the important roles of gut microbiota will increase and will be more realized and illuminated. It is to be expected that an increased number of potential drug targets arising from gut microbiota will be discovered.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

- [1] R. E. Ley, P. J. Turnbaugh, S. Klein, and J. I. Gordon, "Microbial ecology: human gut microbes associated with obesity," *Nature*, vol. 444, no. 7122, pp. 1022–1023, 2006.
- [2] C. L. Gentile and T. L. Weir, "The gut microbiota at the intersection of diet and human health," *Science*, vol. 362, no. 6416, pp. 776–780, 2018.
- [3] G. Guglielmi, "How gut microbes are joining the fight against cancer," *Nature*, vol. 557, no. 7706, pp. 482–484, 2018.
- [4] M. Sigal, C. Y. Logan, M. Kapalczynska et al., "Stromal R-spondin orchestrates gastric epithelial stem cells and gland homeostasis," *Nature*, vol. 548, no. 7668, pp. 451–455, 2017.
- [5] B. S. Wostmann, C. Larkin, A. Moriarty, and E. Bruckner-Kardoss, "Dietary intake, energy metabolism, and excretory losses of adult male germfree wistar rats," *Laboratory Animals*, vol. 33, no. 1, pp. 46–50, 1983.
- [6] F. Bäckhed, J. K. Manchester, C. F. Semenkovich, and J. I. Gordon, "Mechanisms underlying the resistance to diet-induced obesity in germ-free mice," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 104, no. 3, pp. 979–984, 2007.
- [7] R. E. Ley, F. Bäckhed, P. Turnbaugh, C. A. Lozupone, R. D. Knight, and J. I. Gordon, "Obesity alters gut microbial ecology," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 31, pp. 11070–11075, 2005.
- [8] L. Zitvogel, R. Daillère, M. P. Roberti, B. Routy, and G. Kroemer, "Anticancer effects of the microbiome and its products," *Nature Reviews Microbiology*, vol. 15, no. 8, pp. 465–478, 2017.
- [9] C. L. Sears and W. S. Garrett, "Microbes, microbiota, and colon cancer," *Cell Host & Microbe*, vol. 15, no. 3, pp. 317–328, 2014.
- [10] M. Y. Song, B. S. Kim, and H. Kim, "Influence of *Panax ginseng* on obesity and gut microbiota in obese middle-aged Korean women," *Journal of Ginseng Research*, vol. 38, no. 2, pp. 106–115, 2014.
- [11] J. Xu, F. Lian, L. Zhao et al., "Structural modulation of gut microbiota during alleviation of type 2 diabetes with a Chinese herbal formula," *The ISME Journal*, vol. 9, no. 3, pp. 552–562, 2015.
- [12] L.-L. Shi, Y. Li, Y. Wang, and Y. Feng, "MDG-1, an Ophiopogon polysaccharide, regulate gut microbiota in high-fat diet-induced obese C57BL/6 mice," *International Journal of Biological Macromolecules*, vol. 81, pp. 576–583, 2015.
- [13] L.-Y. Wang, S. Wang, Y. Wang, K.-F. Ruan, and Y. Feng, "Effect of MDG-1 on oral glucose tolerance and intestinal microecological balance in diabetic mice," *World Chinese Journal of Digestology*, vol. 19, no. 19, pp. 2058–2062, 2011.
- [14] M. Taghizadeh, N. Farzin, S. Taheri et al., "The Effect of Dietary Supplements Containing Green Tea, Capsaicin and Ginger Extracts on Weight Loss and Metabolic Profiles in Overweight Women: A Randomized Double-Blind Placebo-Controlled Clinical Trial," *Annals of Nutrition and Metabolism*, vol. 70, no. 4, pp. 277–285, 2017.
- [15] D.-B. Seo, H. W. Jeong, D. Cho et al., "Fermented green tea extract alleviates obesity and related complications and alters gut microbiota composition in diet-induced obese mice," *Journal of Medicinal Food*, vol. 18, no. 5, pp. 549–556, 2015.
- [16] T. Unno, M. Sakuma, and S. Mitsuhashi, "Effect of dietary supplementation of (-)-epigallocatechin gallate on gut microbiota and biomarkers of colonic fermentation in rats," *Journal of Nutritional Science and Vitaminology*, vol. 60, no. 3, pp. 213–219, 2014.
- [17] C. Chang, C. Lin, and C. Lu, "Ganoderma lucidum reduces obesity in mice by modulating the composition of the gut microbiota," *Nature Communications*, vol. 6, p. 7489, 2015.
- [18] J.-H. Wang, S. Bose, G.-C. Kim et al., "Flos Lonicera ameliorates obesity and associated endotoxemia in rats through modulation of gut permeability and intestinal microbiota," *PLoS ONE*, vol. 9, no. 1, Article ID e86117, 2014.
- [19] A. M. Neyrinck, V. F. Van Hée, L. B. Bindels, F. De Backer, P. D. Cani, and N. M. Delzenne, "Polyphenol-rich extract of pomegranate peel alleviates tissue inflammation and hypercholesterolaemia in high-fat diet-induced obese mice: potential implication of the gut microbiota," *British Journal of Nutrition*, vol. 109, no. 5, pp. 802–809, 2013.
- [20] Y. S. Lee, W. S. Kim, K. H. Kim et al., "Berberine, a natural plant product, activates AMP-activated protein kinase with beneficial metabolic effects in diabetic and insulin-resistant states," *Diabetes*, vol. 55, no. 8, pp. 2256–2264, 2006.
- [21] Y. F. Zhang, X. Y. Li, D. J. Zou et al., "Treatment of type 2 diabetes and dyslipidemia with the natural plant alkaloid berberine," *The Journal of Clinical Endocrinology & Metabolism*, vol. 93, no. 7, pp. 2559–2565, 2008.
- [22] H. Sun, N. Wang, Z. Cang et al., "Modulation of Microbiota-Gut-Brain Axis by Berberine Resulting in Improved Metabolic Status in High-Fat Diet-Fed Rats," *Obesity Facts*, vol. 9, no. 6, pp. 365–378, 2017.
- [23] X. Zhang, Y. Zhao, M. Zhang et al., "Structural changes of gut microbiota during berberine-mediated prevention of obesity and insulin resistance in high-fat diet-fed rats," *PLoS ONE*, vol. 7, no. 8, Article ID e42529, p. e42529, 2012.
- [24] P. Wan, H. Chen, Y. Guo, and A.-P. Bai, "Advances in treatment of ulcerative colitis with herbs: From bench to bedside," *World Journal of Gastroenterology*, vol. 20, no. 39, pp. 14099–14104, 2014.
- [25] M. Guo, S. Ding, C. Zhao et al., "Red Ginseng and Semen Coicis can improve the structure of gut microbiota and relieve the symptoms of ulcerative colitis," *Journal of Ethnopharmacology*, vol. 162, pp. 7–13, 2015.
- [26] S. J. Ko et al., "Effect of Korean herbal medicine combined with a probiotic mixture on diarrhea-dominant irritable bowel syndrome: a double-blind, randomized, placebo-controlled trial," *Evid Based Complement Alternat Med*, vol. 2013, p. 824605, 2013.
- [27] S.-J. Ko, B. Ryu, J. Kim et al., "Effect of herbal extract granules combined with probiotic mixture on irritable bowel syndrome

- with diarrhea: study protocol for a randomized controlled trial," *Trials*, vol. 12, p. 219, 2011.
- [28] P. D. Cani, "Human gut microbiome: Hopes, threats and promises," *Gut*, vol. 67, no. 9, pp. 1716–1725, 2018.
- [29] J. M. Brown and S. L. Hazen, "Microbial modulation of cardiovascular disease," *Nature Reviews Microbiology*, vol. 16, no. 3, pp. 171–181, 2018.
- [30] C. McKenzie, J. Tan, L. Macia, and C. R. Mackay, "The nutrition-gut microbiome-physiology axis and allergic diseases," *Immunological Reviews*, vol. 278, no. 1, pp. 277–295, 2017.
- [31] L. Zhao et al., "Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes," *Science*, vol. 359, no. 6380, pp. 1151–1156, 2018.
- [32] C. Ma, M. Han, and B. Heinrich, "Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT," *Cells*, vol. 360, no. 6391, 2018.
- [33] H. Yan, J. Lu, Y. Wang, W. Gu, X. Yang, and J. Yu, "Intake of total saponins and polysaccharides from *Polygonatum kingianum* affects the gut microbiota in diabetic rats," *Phytomedicine*, vol. 26, pp. 45–54, 2017.
- [34] L. Chen, M. S. Brar, F. C. C. Leung, and W. L. W. Hsiao, "Triterpenoid herbal saponins enhance beneficial bacteria, decrease sulfate-reducing bacteria, modulate inflammatory intestinal microenvironment and exert cancer preventive effects in *ApcMin/+* mice," *Oncotarget*, vol. 7, no. 21, pp. 31226–31242, 2016.
- [35] S. P. Claus et al., "Colonization-induced host-gut microbial metabolic interaction," *MBio*, vol. 2, no. 2, pp. e00271–e00210, 2011.
- [36] F. P. Selwyn, J. Y. Cui, and C. D. Klaassen, "Special section on drug metabolism and the microbiome RNA-seq quantification of hepatic drug processing genes in germ-free mice," *Drug Metabolism and Disposition*, vol. 43, no. 10, pp. 1572–1580, 2015.
- [37] J. Xu, H.-B. Chen, and S.-L. Li, "Understanding the Molecular Mechanisms of the Interplay Between Herbal Medicines and Gut Microbiota," *Medicinal Research Reviews*, vol. 37, no. 5, pp. 1140–1185, 2017.
- [38] K. Noh, Y. Kang, M. Nepal et al., "Role of intestinal microbiota in baicalin-induced drug interaction and its pharmacokinetics," *Molecules*, vol. 21, no. 3, p. 337, 2016.
- [39] R. Feng, J. Shou, Z. Zhao et al., "Transforming berberine into its intestine-absorbable form by the gut microbiota," *Scientific Reports*, vol. 5, no. 1, p. 12155, 2015.
- [40] M. Zhang, C. S. Peng, and X. B. Li, "In vivo and in vitro metabolites from the main diester and monoester diterpenoid alkaloids in a traditional chinese herb, the aconitum species," *Evid Based Complement Alternat Med*, vol. 2015, 23 pages, 2015.
- [41] X.-W. Chen, E. S. Serag, K. B. Sneed, and S.-F. Zhou, "Herbal bioactivation, molecular targets and the toxicity relevance," *Chemico-Biological Interactions*, vol. 192, no. 3, pp. 161–176, 2011.
- [42] J. Li, L. Zhang, Z. Jiang et al., "Toxicities of aristolochic acid I and aristololactam I in cultured renal epithelial cells," *Toxicology in Vitro*, vol. 24, no. 4, pp. 1092–1097, 2010.
- [43] M. Liu, J. Yuan, W. Hu et al., "Pretreatment with broad-spectrum antibiotics alters the pharmacokinetics of major constituents of Shaoyao-Gancao decoction in rats after oral administration," *Acta Pharmacologica Sinica*, vol. 40, no. 2, pp. 288–296, 2019.
- [44] H. Shen, X.-J. Gao, T. Li et al., "Ginseng polysaccharides enhanced ginsenoside Rb1 and microbial metabolites exposure through enhancing intestinal absorption and affecting gut microbial metabolism," *Journal of Ethnopharmacology*, vol. 216, pp. 47–56, 2018.
- [45] E. K. Mallory, A. Acharya, S. E. Rensi, P. J. Turnbaugh, R. A. Bright, and R. B. Altman, "Chemical reaction vector embeddings: towards predicting drug metabolism in the human gut microbiome," in *Proceedings of the Pacific Symposium*, pp. 56–67, Kohala Coast, Hawaii, USA, 2018.
- [46] J. Lindenbaum, D. G. Rund, V. P. Butler, D. Tse-Eng, and J. R. Saha, "Inactivation of Digoxin by the Gut Flora: Reversal by Antibiotic Therapy," *The New England Journal of Medicine*, vol. 305, no. 14, pp. 789–794, 1981.
- [47] R. Feng, Z. Zhao, S. Ma, F. Guo, Y. Wang, and J. Jiang, "Gut microbiota-regulated pharmacokinetics of berberine and active metabolites in beagle dogs after oral administration," *Frontiers in Pharmacology*, vol. 9, p. 214, 2018.
- [48] S. Guo, R. Al-Sadi, H. M. Said, and T. Y. Ma, "Lipopolysaccharide causes an increase in intestinal tight junction permeability in vitro and in vivo by inducing enterocyte membrane expression and localization of TLR-4 and CD14," *The American Journal of Pathology*, vol. 182, no. 2, pp. 375–387, 2013.
- [49] P. D. Cani, R. Bibiloni, C. Knauf et al., "Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice," *Diabetes*, vol. 57, no. 6, pp. 1470–1481, 2008.
- [50] J. ŠtĚpetova, E. Sepp, H. Kolk, K. Lõivukene, E. Songisepp, and M. Mikelsaar, "Diversity and metabolic impact of intestinal *Lactobacillus* species in healthy adults and the elderly," *British Journal of Nutrition*, vol. 105, no. 8, pp. 1235–1244, 2011.
- [51] S.-M. Lim, J.-J. Jeong, K. H. Woo, M. J. Han, and D.-H. Kim, "Lactobacillus sakei OK67 ameliorates high-fat diet-induced blood glucose intolerance and obesity in mice by inhibiting gut microbiota lipopolysaccharide production and inducing colon tight junction protein expression," *Nutrition Research*, vol. 36, no. 4, pp. 337–348, 2016.
- [52] S.-J. Wu, T.-M. Don, C.-W. Lin, and F.-L. Mi, "Delivery of berberine using chitosan/fucoidan-aurine conjugate nanoparticles for treatment of defective intestinal epithelial tight junction barrier," *Marine Drugs*, vol. 12, no. 11, pp. 5677–5697, 2014.
- [53] C.-H. Chang, W.-Y. Huang, C.-H. Lai et al., "Development of novel nanoparticles shelled with heparin for berberine delivery to treat *Helicobacter pylori*," *Acta Biomaterialia*, vol. 7, no. 2, pp. 593–603, 2011.
- [54] L. Gu, N. Li, J. Gong, Q. Li, W. Zhu, and J. Li, "Berberine ameliorates intestinal epithelial tight-junction damage and down-regulates myosin light chain kinase pathways in a mouse model of endotoxemia," *The Journal of Infectious Diseases*, vol. 203, no. 11, pp. 1602–1612, 2011.
- [55] J. Wang, S. S. Ghosh, and S. Ghosh, "Curcumin improves intestinal barrier function: Modulation of intracellular signaling, and organization of tight junctions," *American Journal of Physiology-Cell Physiology*, vol. 312, no. 4, pp. C438–C445, 2017.
- [56] C. Chelakkot, Y. Choi, D. Kim et al., "Akkermansia muciniphila-derived extracellular vesicles influence gut permeability through the regulation of tight junctions," *Experimental & Molecular Medicine*, vol. 50, no. 2, p. e450, 2018.
- [57] P. Pinton, C. Braicu, J. Nougayrede, J. Laffitte, I. Taranu, and I. P. Oswald, "Deoxynivalenol impairs porcine intestinal barrier function and decreases the protein expression of claudin-4 through a mitogen-activated protein kinase-dependent mechanism," *Journal of Nutrition*, vol. 140, no. 11, pp. 1956–1962, 2010.
- [58] P. Raj, S. Zieroth, and T. Netticadan, "An overview of the efficacy of resveratrol in the management of ischemic heart disease,"

- Annals of the New York Academy of Sciences*, vol. 1348, no. 1, pp. 55–67, 2015.
- [59] E. Chong, S.-L. Chang, Y.-W. Hsiao et al., “Resveratrol, a red wine antioxidant, reduces atrial fibrillation susceptibility in the failing heart by PI3K/AKT/eNOS signaling pathway activation,” *Heart Rhythm*, vol. 12, no. 5, pp. 1046–1056, 2015.
- [60] P. D. Cani et al., “Metabolic endotoxemia initiates obesity and insulin resistance,” *Diabetes*, vol. 56, no. 7, pp. 1761–1772, 2007.
- [61] C. L. Boulange et al., “Impact of the gut microbiota on inflammation, obesity, and metabolic disease,” *Genome Medicine*, vol. 8, no. 1, p. 42, 2016.
- [62] Y. Merga, B. J. Campbell, and J. M. Rhodes, “Mucosal barrier, bacteria and inflammatory bowel disease: possibilities for therapy,” *Digestive Diseases*, vol. 32, no. 4, pp. 475–483, 2014.
- [63] P. Rawla, S. S. Bandaru, and A. R. Vellipuram, “Review of infectious etiology of acute pancreatitis,” *Gastroenterology Research*, vol. 10, no. 3, pp. 153–158, 2017.
- [64] X. Wang, N. Ota, P. Manzanillo et al., “Interleukin-22 alleviates metabolic disorders and restores mucosal immunity in diabetes,” *Nature*, vol. 514, no. 7521, pp. 237–241, 2014.
- [65] H. Luck, S. Tsai, J. Chung et al., “Regulation of obesity-related insulin resistance with gut anti-inflammatory agents,” *Cell Metabolism*, vol. 21, no. 4, pp. 527–542, 2015.
- [66] H. Chung and D. L. Kasper, “Microbiota-stimulated immune mechanisms to maintain gut homeostasis,” *Current Opinion in Immunology*, vol. 22, no. 4, pp. 455–460, 2010.
- [67] D. A. Hill and D. Artis, “Intestinal bacteria and the regulation of immune cell homeostasis,” *Annual Review of Immunology*, vol. 28, pp. 623–667, 2010.
- [68] M. B. Geuking, J. Cahenzli, M. A. E. Lawson et al., “Intestinal bacterial colonization induces mutualistic regulatory T cell responses,” *Immunity*, vol. 34, no. 5, pp. 794–806, 2011.
- [69] K. Atarashi, T. Tanoue, T. Shima et al., “Induction of colonic regulatory T cells by indigenous *Clostridium* species,” *Science*, vol. 331, no. 6015, pp. 337–341, 2011.
- [70] K. Atarashi, J. Nishimura, T. Shima et al., “ATP drives lamina propria TH17 cell differentiation,” *Nature*, vol. 455, no. 7214, pp. 808–812, 2008.
- [71] I. I. Ivanov, K. Atarashi, N. Manel et al., “Induction of intestinal Th17 cells by segmented filamentous bacteria,” *Cell*, vol. 139, no. 3, pp. 485–498, 2009.
- [72] T. Zelante, R. Iannitti, C. Cunha et al., “Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22,” *Immunity*, vol. 39, no. 2, pp. 372–385, 2013.
- [73] J. Duan, H. Chung, E. Troy, and D. L. Kasper, “Microbial colonization drives expansion of IL-1 receptor 1-expressing and IL-17-producing γ/δ T cells,” *Cell Host & Microbe*, vol. 7, no. 2, pp. 140–150, 2010.
- [74] T. Olszak, D. An, S. Zeissig et al., “Microbial exposure during early life has persistent effects on natural killer T cell function,” *Science*, vol. 336, no. 6080, pp. 489–493, 2012.
- [75] D. An et al., “Sphingolipids from a symbiotic microbe regulate homeostasis of host intestinal natural killer T cells,” *Cell*, vol. 165, no. 1–2, pp. 123–133, 2014.
- [76] N. Satoh-Takayama, C. A. J. Voshenrich, S. Lesjean-Pottier et al., “Microbial flora drives interleukin 22 production in intestinal NKp46+ cells that provide innate mucosal immune defense,” *Immunity*, vol. 29, no. 6, pp. 958–970, 2008.
- [77] S. Sawa et al., “RORgammat+ innate lymphoid cells regulate intestinal homeostasis by integrating negative signals from the symbiotic microbiota,” *Nat Immunol*, vol. 12, no. 4, p. 320, 2011.
- [78] A. Mortha, A. Chudnovskiy, D. Hashimoto et al., “Microbiota-dependent crosstalk between macrophages and ILC3 promotes intestinal homeostasis,” *Science*, vol. 343, no. 6178, Article ID 1249288, p. 1249288, 2014.
- [79] A. J. Macpherson, M. B. Geuking, E. Slack, S. Hapfelmeier, and K. D. McCoy, “The habitat, double life, citizenship, and forgetfulness of IgA,” *Immunological Reviews*, vol. 245, no. 1, pp. 132–146, 2012.
- [80] Y. Cong, T. Feng, K. Fujihashi, T. R. Schoeb, and C. O. Elson, “A dominant, coordinated T regulatory cell-IgA response to the intestinal microbiota,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 46, pp. 19256–19261, 2009.
- [81] J. Gong, M. Hu, Z. Huang et al., “Berberine attenuates intestinal mucosal barrier dysfunction in type 2 diabetic rats,” *Frontiers in Pharmacology*, vol. 8, p. 42, 2017.
- [82] H. Cui, Y. Cai, and L. Wang, “Berberine regulates Treg/Th17 balance to treat ulcerative colitis through modulating the gut microbiota in the colon,” *Frontiers in Pharmacology*, vol. 9, p. 571, 2018.
- [83] R. Sun, N. Yang, B. Kong et al., “Orally administered berberine modulates hepatic lipid metabolism by altering microbial bile acid metabolism and the intestinal FXR signaling pathway,” *Molecular Pharmacology*, vol. 91, no. 2, pp. 110–122, 2017.
- [84] J. Bai, Y. Zhu, and Y. Dong, “Response of gut microbiota and inflammatory status to bitter melon (*Momordica charantia* L.) in high fat diet induced obese rats,” *Journal of Ethnopharmacology*, vol. 194, pp. 717–726, 2016.
- [85] B. Bao, Y.-G. Chen, L. Zhang et al., “*Momordica charantia* (Bitter Melon) reduces obesity-associated macrophage and mast cell infiltration as well as inflammatory cytokine expression in adipose tissues,” *PLoS ONE*, vol. 8, no. 12, Article ID e84075, p. e84075, 2013.
- [86] S. Chuengsamarn, S. Rattanamongkolgul, B. Phonrat, R. Tungtrongchitr, and S. Jirawatnotai, “Reduction of atherogenic risk in patients with type 2 diabetes by curcuminoid extract: a randomized controlled trial,” *The Journal of Nutritional Biochemistry*, vol. 25, no. 2, pp. 144–150, 2014.
- [87] Y. Pan, Y. Wang, L. Cai et al., “Inhibition of high glucose-induced inflammatory response and macrophage infiltration by a novel curcumin derivative prevents renal injury in diabetic rats,” *British Journal of Pharmacology*, vol. 166, no. 3, pp. 1169–1182, 2012.
- [88] R.-M. T. Mcfadden, C. B. Larmonier, K. W. Shehab et al., “The role of curcumin in modulating colonic microbiota during colitis and colon cancer prevention,” *Inflammatory Bowel Diseases*, vol. 21, no. 11, pp. 2483–2494, 2015.
- [89] D. Dai, C.-F. Zhang, S. Williams, C.-S. Yuan, and C.-Z. Wang, “Ginseng on cancer: potential role in modulating inflammation-mediated angiogenesis,” *American Journal of Chinese Medicine*, vol. 45, no. 1, pp. 13–22, 2017.



Hindawi

Submit your manuscripts at
www.hindawi.com

