Chapter 10
Roles of Herbal Medicine in Modulating Gut Microbiota Associated with Health and Diseases

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Abstract The perturbation of gut microbiota is increasingly recognized to be associated with human health and diseases. The modulation of the gut microbiotal community as a means to alleviate disease conditions provides a unique opportunity for herbal medicine, due to the two-way interaction between gut microbiota and herbal medicine. Herbal medicine contains a range of polyphenols that require action from gut microbiota to effectively perform their biological function. The gut microbiota are subsequently stimulated through this action. In this chapter, we outline the associations between gut microbiota and disease (particularly inflammatory bowel disease (IBD), diabetes, and cancer), and the roles of herbal medicine in alleviating disease conditions through modulating gut microbiota. In addition, we discuss the functional uses and challenges of herbal medicine, which include the quality control and elucidating mechanisms of action. Finally, we describe how a metabonomics technique can provide a means for the quality control of herbal medicines and can be an efficient tool for elucidating the molecular mechanisms of different herbal treatments. Future research on herbal medicine should be focused on

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directly measuring altered gut microbiota and integrating this with a mechanistic metabonomics evaluation.

Keywords Gut microbiota • Diseases • Metabonomics • Herbal medicine

10.1 Introduction

Humans have a large number of microbiota resident in the gut. Interactions between host metabolism and gut microbiota, between gut microbiota themselves, and between food/medicine ingested and gut microbiota make the human gut a very complex system. There are approximately about 1,000 microbial species present in the mammalian gut, which codevelop with the host throughout the host's lifetime. Microbes play an important role in host nutrition and health by supplying and digesting nutrients, preventing pathogen colonization, and maintaining balanced mucosal immunity, which is vital for our health. A shift in the gut microbial composition can stimulate a specific disease-prone (dysbiosis) or disease-protective activity (probiosis). For example, *Lactobacillus reuteri* strains can produce thiamine to benefit the host [1], whereas *Bifidobacteria* may inhibit the colonization of potential pathogens by competing with the nutrients and the binding site on the mucosa [2]. The gut microbial community is very complex and dynamic [3], which can be affected by the host's genome, birth, age [4], nutrition [5], lifestyle, disease [6], and therapeutic interventions (e.g., antibiotics [7], herbal medicines [8], and surgery treatments [9]). In turn, the unbalanced microbial colonies may disturb the physiological homeostasis, leading to various diseases such as colon cancer, inflammatory bowel disease (IBD) [10], irritable bowel syndrome (IBS) [11], obesity [12–14], diabetes [15], cardiovascular disease [16], autism [17], and allergic asthma [18]. The close associations between the gut microbiotal community and disease status give a unique opportunity for treatment by using traditional herbal medicine, via restoring the balance of the gut microbiotal community. Shaping the balance of the gut microbiotal community by herbal medicine involves a two-way interaction. The active biological ingredients of the herbal material are largely polyphenolic compounds, which often cannot be absorbed directly by humans. Fortunately, however, enzymes secreted by gut microbiota can metabolize these non-bioavailable phytochemicals, facilitating their utilization. The enzyme-producing bacteria in return are selectively stimulated, thereby modifying the balance of the gut microbiota [8, 19] (Fig. 10.1).

The beneficial effects of herbal medicine have gained growing interest in herbal remedies, leading to a strong growth in consumer demand in plant-based products. The current global market for plant-based health products is estimated to hit 93.15 billion dollars by 2015 (http://www.nutraingredients-usa.com). Prominent concerns regarding the quality of phytomedicines are that they contain mixtures of many compounds, which are often derived from plants or animal origins. Traditionally, the quality of these herbs is assessed by the experiences of herbal practitioners, who sometimes

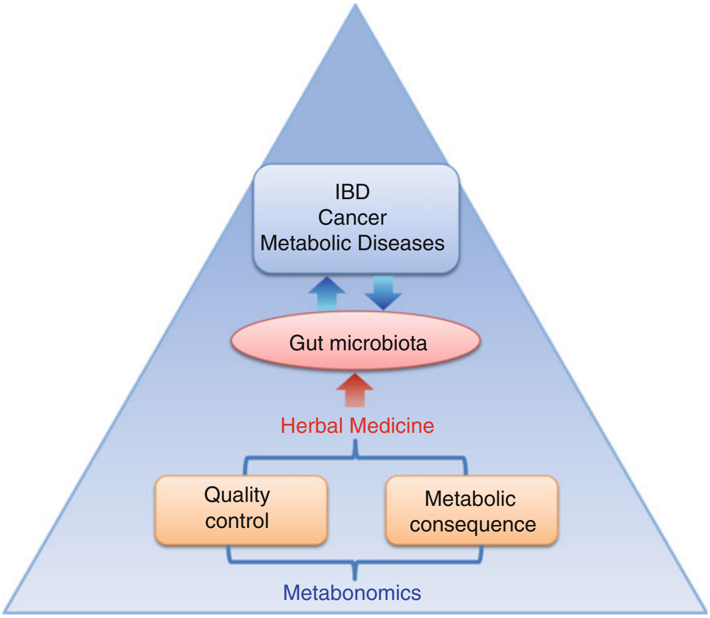

Fig. 10.1 A summary of the key roles of metabonomics in herbal medicine and the herbal medicine alleviating disease conditions via modifications of gut microbiota

refer to “active” molecules or arbitrarily chosen “marker” compounds in complex plant extracts. The lack of scientifically accepted standards for herbal medicine has long been an obstacle preventing herbal medicine from being recognized and integrated into the standard healthcare system in Western countries. Therefore, one of the challenges that phytomedicinal practitioners have encountered is the quality control of herbal medicine. As a consequence of the lack of efficient quality control tools, large variations of phytomedical products are encountered. For example, an analysis of 14 commercially available feverfew samples showed that each batch generated a unique and characteristic spectra profile, with two of the batches being markedly different from the other 12 [20]. The development of new quality control methods based on the entire biochemical composition of the preparation without reference to “active” molecules will help improve the quality and will make it more acceptable. Modern metabonomics techniques appear to be well suited for this purpose. Metabonomics involves the study of multivariate metabolic responses of complex organisms to physiological and/or pathological stressors, including the consequent disruption of systems regulation [21–24]. Metabonomics involves multivariate analysis of data from Nuclear magnetic resonance (NMR) and mass spectrometry (MS) spectroscopy. The commonly used multivariate data analysis tool includes a range of pattern recognition techniques and random forest method as detailed in Chaps. 2 and 3. Using ^{1}H NMR spectroscopy, a wide range of plant metabolites can be detected including sugars, amino acids, organic acids, and polyphenols. In such cases, all the chemical components present in a single plant extract can be viewed simultaneously as a

Table 10.1 Summary of alternations of gut microbiota associated with diseases and corresponding herbal medicine treatment

Diseases	Gut microbiota	Herbal medicine
IBD	*Bacteroides fragilis*, *enterococci*, *lactobacilli*, *bifidobacteria* [34]	Quercetin [26, 27]
		Curcumin [28]
		Prebiotics [32, 33]
		Echinacea purpurea [34]
Metabolic diseases	*Lactobacillus*, *Clostridium* [38]	*Jiangtang Xiaozhi* [39, 40]
	Enterococcus faecalis [42]	*Mimosa pudica*, *Emblica officinalis*, *Azadirachta indica* [42]
		Huangguaxiang [43]
Cancer	*H. pylori*	*Juzentaihoto* [45–48]
		Pelargonium sidoides [49, 50]
		Calophyllum brasiliense Camb. (*Clusiaceae*), *Mouriri elliptica* Martius (*Melastomataceae*), and *Hancornia speciosa* Gomez (*Mangaba*) [51–53]

"metabolic fingerprint." The holistic nature of metabonomics can overcome the drawback of considering "active components" (Table 10.1).

A single-component drug is the major characteristic of many Western medicines, and the metabolism of the drug and the molecular target are often clearly defined. However, herbal medicine consists of multiple components in nature, with mixtures of various herbs; thus, the identification of molecular mechanisms and acting targets is hindered by the complexity of the herbal medicine. Traditional drug discovery routes are unsuitable for evaluating the mechanism of action of herbal medicines. Metabonomics, on the other hand, measures the endpoint metabolic perturbations of an intervention, including the multiple components of the herb. Therefore, the metabonomics technique can also be adopted to evaluate mechanisms of a given complex herbal medicine. The advantage of utilizing such a technique is its holistic nature, which can provide important clues as to how herbal medicine really works.

In this chapter, we discuss the roles of gut microbiota in diseases and the ways in which herbal medicine could alleviate disease conditions via modification of the gut microbiotal community. In addition, the challenges encountered in herbal medicine will be discussed and examples of possible solutions are shown.

10.2 Herbal Medicine Affects the Association Between Disease State and Gut Microbiota

Many diseases are closely associated with an imbalanced gut microbiota, and herbal medicines are capable of alleviating these disease conditions by offsetting the imbalance of the microbiotal community. Inflammatory bowel disease (IBD) is one such disease. IBD primarily includes ulcerative colitis (UC) and Crohn's disease (CD) and is a significant public health burden. The pathogenesis of IBD has not yet been identified, but it has been widely accepted that the combination and interaction of genetics, environmental influences, and immunologic abnormalities contribute to the occurrence and perpetuation of this disease [25]. Aminosalicylates, antibiotics, and a range of immunomodulation drugs are used to manage IBD conditions. Complementary improvement of IBD conditions using nondigestible food ingredients has also gained increased recognition. Quercetin is a flavonoid commonly present in food and other plant materials. Reports have shown that quercetin has antiviral, antioxidant, and anti-inflammatory properties [26]. Quercetin-containing microcapsules have been given to mice with acetic acid-induced colitis, which have demonstrated that quercetin treatment is able to decrease neutrophil recruitment, attenuate histological alterations, and reduce macroscopical damage. In addition, quercetin-containing microcapsules can also prevent the reduction of the anti-inflammatory cytokine IL-10 and provide antioxidant properties [27]. Curcumin is another component abundant in plant foods that possesses anti-inflammatory and antioxidant activity and has been demonstrated to be a therapeutic agent for IBD [28]. These phytochemicals are known to be metabolized by gut microbiota [29]; hence, despite the anti-inflammatory and antioxidant actions of these phytochemicals, the amelioration of IBD conditions via modification of gut ecosystems could be one of the underlying mechanisms. This is because the bioavailability and bioactivity of these phytochemicals depend on enzymes of the gut microbiota [30]. The gut ecosystem could in turn be modified by the phytochemical ingested. Indeed, probiotics supplementations have been suggested to be beneficial in IBD [31], and long-term ingestion of prebiotics can selectively stimulate or limit the growth and/or activity of bacteria in the colon, and thus provides a more sustainable effect on colonic bacteria, which improves host health [32]. Nondigestible dietary fibers can act as prebiotics, and it has been reported that ingesting a number of different dietary fibers seems to be beneficial in IBD [33]. They also demonstrated that children with CD who achieved remission by either complete or partial enteral feeding displayed significant modifications to their fecal microbiota. The profiles of fecal microbiota were stable over time for healthy children, which suggested that targeting enteral microbiota using phytochemicals or prebiotics can help achieve remission for IBD patients. Many herbal-based materials have shown antimicrobial effects against certain pathogenic bacteria in vitro; hence, there is an expectation for significant changes in gut microbiota in vivo. A study was performed on the effects of the dietary supplement of *Echinacea purpurea* on aerobic and anaerobic bacteria common to the human gastrointestinal tract. They found that human subjects who consumed 1,000 mg of standardized *E. purpurea* for 10 days had significantly increased total aerobic bacteria, particularly *Bacteroides fragilis*. Supplementation did not significantly alter the number of enteric bacteria, enterococci, lactobacilli, bifidobacteria, or total anaerobic bacteria [34].

Similar to IBD, type 2 diabetes is believed to be a result of complex gene-environmental interactions. Recent evidence points to the importance of gut microbiota as an environmental factor in metabolic diseases, including obesity [14, 35] and diabetes [36]. Diabetic patients showed clear dysfunction of choline metabolism, indicating a close association between gut microbiota and diabetes [37]. It was further suggested that the presence of *Lactobacillus* species correlated positively with the levels of fasting glucose and glycosylated hemoglobin, whereas the presence of *Clostridium* species correlated negatively with the levels of fasting glucose, glycosylated hemoglobin, insulin, C peptide, and plasma triglycerides [38]. Metformin is the first line of drug in delaying the onset of diabetic condition, and the low-risk alternative herbal medicines are often used to improve glucose tolerance. The *Jiangtang Xiaozhi* capsule is a traditional Chinese herbal formulation, consisting of *radix astragali* and *rehmannia* root, *radix pseudostellariae* and *Mongolian snakegourd* root. There have been animal studies and a small clinical trial, along with studies of the effects of the individual herbs, which showed that the formula has a great potential to improve diabetic condition [39]. Recently, a large clinical trial, including 71 participants treated with *Jiangtang Xiaozhi* capsules for 16 weeks, showed a significant difference in the levels of fasting insulin between the treatment group and the placebo group. Patients taking *Jiangtang Xiaozhi* had a significant improvement in high-density lipoprotein (HDL) level compared to the placebo group [40]. Although attention has not yet been paid to scrutinizing changes of gut microbiota after treating the diabetic patients on this particular case, many of the diabetes-alleviating drugs possess strong antimicrobial properties [41]. Other studies have shown that antidiabetic herbal plants have antibacterial activity, which is not surprising given the fact that most of the phytochemicals become bioavailable after interacting with gut microbiota. Some Indian herbal medicines, which have been known for their hypoglycemic activities, were screened for four Gram-negative and three Gram-positive bacteria. The results showed that the extract of *Mimosa pudica* has a strong antibacterial activity against Gram-positive bacteria such as *Enterococcus faecalis* and *Proteus vulgaris*. Authors have also demonstrated that extracts of *Emblica officinalis* have a broad spectrum of antimicrobial activity followed by *Syzygium cumunii* and *Azadirachta indica* [42]. *Huangguaxiang* (*Matteuccia struthiopteris*) was investigated on the hypoglycemic activities of streptozotocin-induced diabetic rats. The results showed that treatment with *Huangguaxiang* for 8 weeks significantly reduced the levels of triglycerides, low-density lipoprotein, and cholesterol, while levels of bifidobacterium and lactobacillus were also altered following *Huangguaxiang* treatment [43].

The potential roles of herbal medicine in treating cancer or preventing cancer metastasis mainly lie in the possible synergic effects of phytochemicals with chemotherapies and/or the promotion of the immunologic response of the host via interactions with enteric microbiota [44]. The traditional Japanese medicine *juzentaihoto*, containing ten different herbal plants, has been widely used for the prevention of various types of cancer metastasis [45, 46]. Antifungal effects have also been shown for *juzentaihoto* in preventing Candida infection [47, 48]. The most direct evidence for herbal medicine as a treatment for cancer via targeting microbiota is their use in treating *Helicobacter pylori* (*H. pylori*)-induced gastric cancer. *H. pylori*, a Gram-negative bacterium, is commonly found in the human stomach and can cause various diseases including gastritis, peptic ulcer, and gastric cancer. In addition to antibiotics treatment against *H. pylori*, treatments using alternative herbal medicine are common worldwide. The mode of action could be antibacterial activity, inhibition of adhesion of *H. pylori* to gastric mucus, or both in combination. The extract of *Pelargonium sidoides* roots, a South African herbal medicine, has been shown to inhibit *H. pylori* growth and has a strong adhesion to AGS cells and to intact gastric tissues from *H. pylori*-infected humans [49, 50]. A range of plants native to Brazil, including *Calophyllum brasiliense* Camb. (*Clusiaceae*), *Mouriri elliptica* Martius (*Melastomataceae*), and *Hancornia speciosa* Gomez (*Mangaba*), have also displayed anti-*H. pylori* activity among others [51–53].

Phytomedicine has been commonly used for treating many conditions, apart from the aforementioned cases, due to the fact that phytomedicines are normally comprised of many plant extracts with perhaps thousands of metabolites. In most cases, the molecular mode of action of the active ingredients of these herbal extracts is unknown [54]. In addition, the origins of the plant, time of harvest, and preparation methods will affect the efficacy of the phytomedicine. Therefore, authenticating the medicinal plant and elucidating the mechanism of action using an objective tool, such as metabonomics, would be a way forward to tackle the many research challenges in this area.

10.3 Challenges and Solutions in Herbal Medicine

10.3.1 Assessing the Quality of Phytomedicine

Currently, the quality control of phytomedicines is carried out based on the active ingredients present in a plant. A drawback of this method is that some of the unknown ingredients may have potential synergic interactions with each other and may have certain biological functions. As a consequence, the mechanism of action of these products becomes an impossible task. Thus, the quality control of both raw and final products in a holistic manner is necessary to ensure the consistency of these products and to provide a fundamental ground for further understanding the molecular mechanisms of these products.

Metabonomics that employs ^{1}H NMR spectroscopy facilitates the simultaneous detection of chemical components present in a plant extract as a “metabolic fingerprint” and can meet the requirements for the quality control of an herbal medicine in a holistic manner. Multiple-component analysis, based on the combination of high-resolution NMR spectroscopy with pattern recognition, has been employed to investigate the effects of origin on the chemical compositions of chamomile (*Matricaria recutita*). Clear differences between chamomiles from Northern Africa (Egypt) and Eastern Europe (Hungary and Slovak Republic) can be seen. Chamomiles also have distinguished profiles from Hungary and Slovak Republic based on their metabolomic compositions, despite being close in terms of geographic location. Furthermore, this method is effective for monitoring the “purity” of chamomile samples, such as the percentage of stalks mixed with flowers, suggesting that this is an excellent method for authenticity and quality control [55]. From a processing point of view, NMR-based metabonomics methods have also been extremely powerful in distinguishing samples extracted with different methods and samples collected at different seasons and dried with different procedures [56]. Metabonomics studies have also been carried out on the extracts of *Artemisia annua* to discriminate samples from different sources and classify them according to their antiplasmodial activity, without preknowledge of this activity [57]. The use of partial least squares analysis also allows the predictions of actual values of such activities for independent samples not used in the model construction. Another study was conducted on the complex pharmaceutical preparations, such as *St. John's wort*, using multivariate analysis of full-resolution ^{1}H NMR spectral data [58]. The results showed that ten preparations from markets were compositionally diverse, and such diversity resulted from plant extract preparation rather than post-extraction processes. The combination of NMR technique and LC-DAD-MS method has been used to investigate the differences between three *Salvia miltiorrhiza* Bunge (SMB) cultivars. The study demonstrated that the combinational use of these methods was effective for plant metabonomics phenotype analysis [59]. These examples are only a reflection on the developments in this area and are by no means exhaustive. In fact, many studies have also been carried out in terms of phytomedicines and authenticity, and it is conceivable that such applications of metabonomics technology will be extended much further in the near future.

10.3.2 Elucidating the Mechanisms of Phytomedicine

Since herbal medicine is a mixture of many plant materials with many chemical components, it is almost impossible to conduct classic pharmacological assays to clearly demonstrate metabolisms of each chemical or unravel specific drug target in an herbal-based drug. These difficulties have restricted their use worldwide. Metabonomics simplifies the complexity by measuring the endpoints of an intervention or a drug effect and hence could provide an alternative strategy for the assessment of herbal medicine. The utilization of a metabonomic approach to evaluate the metabolic action of an herbal medicine has been demonstrated in the human ingestion of chamomile tea [60]. A total of 14 participants were given chamomile tea every morning, and urine samples were collected after one and a half hours after drinking the tea. The metabonomics analysis of urine samples was able to show that chamomile ingestion is a mild intervention to the human body in general, and it causes a reduction in oxidative stress and alters the state of gut microbiota, which was reflected by alternations in the levels of hippurate. The effects of chamomile ingestion on human metabolism were not completely recoverable within a successive week after ingestion. It could suggest that the recovery of gut microbiota is a long process. Metabonomics was also used to evaluate the mechanism of *Xia Yu Xue* decoction, which is a traditional Chinese medicine used for treating liver diseases. Metabolic trajectory showed the trend of renormalization of the *Xia Yu Xue* decoction to CCl_4-induced liver dysfunction. In addition, changed metabolites indicated modulations of energy metabolism, microflora metabolism, amino acid and fatty acid metabolism, which are found to be associated with *Xia Yu Xue* decoction ingestion [61]. The traditional medical treatment targets on the balances of *yin* and *yang*. "Kidney-yang deficiency syndrome" is one of the conditions that relate to functional disorders associated with the hypothalamic-pituitary-gland axis [62]. *Epimedium* (Berberidaceae) is known in Chinese medicine as able to strengthen "yang" and is often used to treat "kidney-yang deficiency." The metabonomics technique was applied to investigate the capability of *Epimedium koreanum* to restore metabolic disorder in animals with "kidney-yang deficiency." After 15 days of orally administering *Epimedium koreanum* extract, metabolic disorders associated with "kidney-yang deficiency" returned to normal. These disordered metabolic pathways included amino acid metabolism, lipid metabolism, and energy metabolism. Importantly, *Epimedium koreanum* ingestion possessed effects on balancing gut microbiota [63]. Most herbal medicines contain a range of polyphenolic compounds, which often act as active ingredients. Gallic acid is one of these polyphenolic compounds, which has been shown to inhibit xanthine oxidase [64, 65], ribonucleotide reductase [66, 67], and histamine release in mast cells [68]. Systematically analyzing the metabolic effects of gallic acid to the metabonomes of rat plasma, liver, urine, and feces showed that gallic acid promoted oxidative stress and resulted insignificant metabolic changes involving glycogenolysis, glycolysis, tricarboxylic acid cycle (TCA), and the metabolism of amino acids, purines, and pyrimidines, together with gut microbiota functions [69].

10.4 Concluding Remarks

In this chapter, we have shown examples of the close associations between human diseases and the gut microbiota living within us, and we have exemplified how herbal medicine could treat disease and maintain health by modifying gut microbiota. In addition, we have emphasized the advantages and challenges of herbal medicine. The literature has shown that there is a potential for future research on the efficacies of herbal medicine and the requirement for international standards for herbal medicine to be established. We have shown that metabolomics can facilitate the understanding of the intrinsic quality of herbal medicine and the evaluation of the therapeutic effects of the complex herbal formulas. This technique should be equally effective for evaluating mineral treatment and acupuncture, which have not been discussed in this chapter. Understanding the mechanisms of action is a necessary step for herbal medicine to be more adoptable worldwide, which should certainly be warranted some attention. It is with no doubt that further development of the metabonomics technique, such as high-sensitivity and high-specificity detection of metabolites, as well as advances in effective molecular identification, would promote the process of evaluation and acceptance of herbal medicine. Although metabonomics can provide a great understanding of the molecular mechanisms of herbal medicine, direct measurement of alterations in gut microbiota associated with herbal treatment using microbiological assays is still lacking. Biological assays evaluating changes in gut microbiotia should be concurrently joined with a metabonomics evaluation of the mechanisms of specific herbal formulas to provide a comprehensive view on the action of herbal medicine.

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