

Traditional Chinese Medicine Herbs and Gut Microbiota

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Abstract

The gut microbiota plays an important role in the human body, for example, they are responsible for the metabolism of some dietary factors. Many diseases are related to the imbalances in the gut microbiota. Accumulating evidence shows that traditional Chinese medicine herbs may prevent or treat some diseases through interacting with gut microbiota. Oral administration of Chinese herbs may change the composition of intestinal flora, and the ingredients in Chinese herbs can be catalyzed into bioactive metabolites by some intestinal microbes, resulting in their pharmacological effects. However, the interaction between Chinese herbs and gut microbiota remains unclear. One of the main challenges is the complexity and diversity of the components of Chinese herbs and intestinal flora. Recently, the correction among diseases, gut microbiota, and Chinese herbs through many methodologies are studied by using novel methods and techniques, such as high-throughput gene sequencing, real-time quantitative PCR, and metabolomics analysis as well as the multivariate data statistics. In the future, the clarified mechanism will open a new avenue for the prevention or treatment of diseases by taking Chinese herbs which regulate the composition of gut microbiota, which may achieve the goals of the personalized medicine.

Keywords: Chinese herbs; Gut microbiota; Health; Metabolism

Gut Microbiota

The intestinal system refers to the digestive tract starting from the pylorus of the stomach to the anus in the digestive system and mainly includes the small intestine, large intestine, and rectum. The small intestine is an important digestive organ in the human body and performs the functions of absorption, excretion, and immunity. It is mainly responsible for the digestion and absorption of most substances, such as sugar, lipids, protein, and vitamins. The large intestine is mainly

responsible for the absorption of water in the food residue, and the food residue is excreted through the rectum. The intestines can secrete digestive juices containing nutrient-degrading enzymes and bile to assist digestion. The intestinal flora may also assist in the digestion, absorption, or metabolism of substances in certain diets [1].

At present, about 10^{14} bacterial species are known to be symbiotic with the human body, accounting for about 1-2 Kg of body weight, but the number of cells

constituting the human body is only about 10^{13} [2]. The number of different genes of human intestinal bacteria is higher than 3 million, but the human genome consists of only about 22,000 genes [3]. It is known that there are at least 1000 kinds of bacteria in the intestines of healthy adults, mainly consisting of four types: Firmicutes (38.8%), Bacteroidetes (27.8%), Actinobacteria (8.2%), and Proteobacteria (2.1%); however, the proportion is different in children and the elderly, and various lifestyle also changes the composition of the intestinal flora [4]. The intestinal flora can be roughly divided into good bacteria, bad bacteria, and neutral bacteria. Many studies have found that the intestinal flora has a great influence on human health. The development of many diseases, including intestinal bacterial infections, inflammatory bowel disease, colorectal cancer, liver cancer, is often accompanied by an imbalance of intestinal bacteria [5]. Therefore, to study more about the relationship between the intestinal flora and health may assess the health status and prevent/treat diseases in humans by analyzing the profile of gut microbiota in the future [6].

Gut Microbiota and Health

In recent years, some studies have confirmed the association of certain intestinal bacteria with specific diseases. For example, the presence of *Bacteroides* in the intestine can drive CD8⁺ T cells to the intestinal tract to inhibit the development of inflammatory bowel disease (IBD) [7]. When *Lactobacillus reuteri* is implanted into mice treated with tryptophan, *L. reuteri* can metabolize tryptophan into indole-3-lactic acid which promotes the transformation of intestinal epithelial CD4⁺ T cells into immunoactive CD4⁺CD8 $\alpha\alpha$ ⁺ T cells [8]. The bioactivities of *Akkermansia muciniphila* are known to prevent obesity, diabetes, and non-alcoholic fatty liver (NAFLD), etc [9,10]. An implantation of *A. muciniphila* in the intestinal tract can improve the resistance in cancer immunotherapy in mice [11]. *Bacteroides thetaiotaomicron*, *Faecalibacterium prausnitzii*, and *Holdemania filiformis* can also respond to cancer immunotherapy in patients with malignant melanoma [12]. Among them, *B. thetaiotaomicron* can reduce the concentration of serum glutamic acid in mice and increase lipid hydrolysis and fatty acid oxidation in adipocytes, thereby reducing fat accumulation and delaying weight gain [13]. In addition, it found that a high-salt diet reduces the number of *Lactobacillus murinus* in mice and humans, thereby increasing the number of proinflammatory T helper 17 (T_H17) cells; however, oral administration of *L. murinus* can reduce the number of TH17 cells and decrease the blood pressure in the hypertensive mice [14].

One of the hottest topics in biomedical research is to explore the effects of gut microbiota on the development of nervous system and cognitive functions [15]. Accumulating evidence suggests a crucial role of intestinal flora in the progression of Alzheimer's disease. As compared with the normal human intestinal flora, there are fewer Firmicutes and Bifidobacterium but more Bacteroidetes in the intestines of patients suffering from Alzheimer's disease [16]. It was also found that extracellular amyloids (known as curli fibers) secreted by *Escherichia coli* (strain K12) contain the main structure of curli subunit gA (CsgA) which assist in the adsorption of bacteria and the production of biofilms, which are related to pathogenicity [17]. A CsgA amyloid precursor of approximately 18 kDa contains a pathogen-associated molecular pattern (PAMP) similar to the amyloid-beta 42 (A β 42) peptide and is recognized by the human immune system toll-like receptor 2 [18]. Other intestinal bacterial species, such as *Bacillus*, *Pseudomonas*, *Staphylococcus*, and *Streptomyces* may also possess bacterial amyloids [19]. Furthermore, when some genes in the gut bacteria are eliminated or mutated, it prolongs the lifespan of *Caenorhabditis elegans*, delays tumor progression, and reduces amyloid-beta accumulation [20].

Gut Microbiota and Metabolism

Since the intestinal flora of the human body has some genes that are responsible for the production of enzymes, they may involve in biochemical metabolism in the intestine, such as sugars, proteins, fatty acids, cholesterol, vitamins, and other foreign compounds, and then the body may further absorb these metabolites [21]. For example, in addition to dietary fiber, some flora can metabolize short-chain fatty acids into n-butyrate, acetate, butyrate, isobutyrate, propionate, valerate, isovalerate, hexanoate, etc [21,22]. These flora may be the clormicrobials IV and XIVa of the Firmicutes, including *Eubacterium*, *Roseburia*, *Faecalibacterium*, and *Coproccoccus*, which may cause decreased intestinal pH, inhibit growth of pathogens, provide energy to intestinal cells; improve obesity, insulin resistance, type 2 diabetes; and prevent colorectal cancer [23]. Other gut bacteria can metabolize amino acids into bioactive products. For example, L-tryptophan can be metabolized into a neurotransmitter tryptamine or an antioxidant indole-3-propionic [24]. *Lactobacilli*, *Bifidobacteria*, *Enterobacter*, *Clostridium*, *Bacteroides* and other intestinal flora can metabolize bile acid into cholate, hyocholate, deoxycholate, chenodeoxycholate, α -muricholate, etc., which promote the absorption of lipid and lipid-soluble vitamins, maintain function of the intestinal barrier, and regulate the triglyceride, cholesterol, glucose levels and other

functions of the body [25]. *F. prausnitzii* and *Bifidobacterium* have been shown to be involved in the metabolism of choline, thus producing methylamine, dimethylamine, trimethylamine, trimethylamine-*N*-oxide, dimethylglycine, betaine, etc., thereby regulating fat metabolism and blood sugar balance and preventing non-alcoholic fatty liver, obesity, diabetes, and cardiovascular disease [26]. In addition, *Bifidobacterium* can synthesize a variety of vitamins in the intestine, including vitamin K, vitamin B12, folic acid, thiamine, riboflavin, etc., which provide endogenous vitamins to the body [27].

Since intestinal flora varies in different people, there may be differences in the metabolism and absorption of some food components between individuals. For example, *Eubacterium coprostanoligenes* in the gut microbiota in some population that can decompose 50% of dietary cholesterol in the intestines into coprostanol that is not easily absorbed by the body [28]. Heterocyclic amines, such as 2-amino-3-methylimidazo [4,5-*f*] quinolone (IQ), are carcinogens that are easily produced during the process of baking foods, but an *E. coli* strain with the β -glucuronidase (*uidA*) gene in the intestine can transform IQ into hydrolysable IQ-glucuronide; however, some bacteria may metabolize IQ into more toxic 7-hydroxy IQ which cannot be metabolized by the *E. coli* strain [29]. In addition, diet and medication can also change the intestinal flora, which affects the metabolism of substances in the intestinal tract. It reported that intermittent fasting causes the changes in the composition of the intestinal flora in normal mice, which increases the levels of acetic acid and lactic acid, as well as the conversion of white fat into beige fat, thereby resulting in weight loss and liver protection; however, this phenomenon is not observed in mice with intestinal flora deficiency [30]. Another study found that a high-fat and low-carbohydrate ketogenic diet has an anti-epileptic effect, because this diet can increase the number of the intestinal bacteria, *Akkermansia* and *Parabacteroides*, thus improving the content of gamma-aminobutyric acid (GABA) which inhibits nerve conduction in the hippocampus [31]. Taken together, these studies indicate that diet does change the composition of the intestinal flora and affect the physiological condition and metabolism in mammals.

Influence of Chinese Herbal Medicine on Gut Microbiota-Related Diseases

Many studies have demonstrated that Chinese herbal medicines can alleviate many diseases, including obesity, diabetes, nonalcoholic steatohepatitis, ulcerative colitis, cancer, chronic kidney disease, Alzheimer's disease, etc.

Changing the composition of the intestinal flora could be one of the main mechanisms by which Chinese herbal medicine improves symptoms of such diseases. If Chinese herbs could promote the growth of beneficial bacteria as well as inhibit the growth of harmful bacteria/pathogenic bacteria, the host could keep healthy. The active ingredients in the Chinese herbs that promotes the growth of the intestinal flora may be carbohydrates or sugar-containing compounds, such as inulin, fructo-oligosaccharides, galacto-oligosaccharides, etc [32]. Intestinal bacteria can metabolize some sugars into short-chain fatty acids, which may eventually inhibit the growth of harmful bacteria /pathogenic bacteria [22-24]. Additionally, other components in Chinese herbs may also contribute to the influence on the growth of beneficial and harmful/pathogenic bacteria.

For example, oral administered with *Ginseng Radix Rubra* (hong shen) increases the level of *Lactobacillus* in the intestines of rats, and Bawei Xileisan containing watermelon (*Citrullus lanatus*, xī guā) and *Isatis indigotica* (bǎn lán gēn) leaves and stems increases the levels of *Bacteroides* and *Lactobacillus* species in the intestines of mice, hence such Chinese herbs may prevent ulcerative colitis [33,34]. Some Chinese herbs have also been found to effectively inhibit harmful bacteria/pathogenic bacteria in the intestines, such as *E. coli*, *Helicobacter pylori*, *Campylobacter jejuni*, *Enterococcus faecalis*, *Salmonella typhimurium*, *Bacillus subtilis*, *Klebsiella pneumoniae*, *Shigella dysenteriae*, *Pseudomonas aeruginosa*, etc [35]. A Chinese herbal formula mainly composed of *Artemisia Scopariae* Herba (yīn chén hāo), *Polygoni Cuspidati* Rhizoma (hǔ zhàng), *Curcuma Longae* Rhizoma (jiāng huáng), *Hyperici Japonici* Herba (dì ěr cǎo), and *Gardeniae Fructus* (zhī zǐ) can reduce the amount of bac *Escherichia*, *Shigella*, and *Sporacetigenium* in the intestines and improve the symptoms of nonalcoholic fatty liver [35]. In addition, mice administered *Ganoderma* (líng zhī) fruiting bodies were found to have increased intestinal flora comprising *Parabacteroides goldsteinii*, *Bacteroides*, *Anaerotruncus colihominis*, *Roseburia hominis*, *Clostridium methylpentosum*, *Clostridium XIVa*, *Clostridium XVIII*, and *E. coprostanoligenes*, but have a reduced flora comprising Firmicutes/Bacteroidetes, *Proteobacteria*, *Mucispirillum schaedleri*, *Escherichia fergusonii*, *Enterococcus*, *Lactococcus lactis*, *Clostridium lactatifermentans*, and *Oscillibacter valericigenes*, thereby leading to a reduction of weight and fat accumulation [36]. *Coptidis Rhizoma* (huáng lián) extract and its active ingredient, berberine, can significantly reduce body fat, blood sugar, blood lipids, etc., in high-fat diet mice; reduce the numbers of Firmicutes and Bacteroidetes in feces; and inhibit the growth of *Lactobacillus* in *in vivo* culture experiments [37].

Increased numbers of Bacteroidetes, Firmicutes, *Bifidobacterium*, *Lactobacillus*, *Akkermansia* and other bacteria were found in rats fed with *Lonicerae Flos* (jīn yīn huā) [38]. Besides, a report indicated that the saponins in *Gynostemma pentaphyllum* (jiǎogǔlán) could reduce colorectal carcinogenesis in *Apc^{Min/+}* mice with the alternation of the intestinal microflora, including the increased numbers of *Actinobacteria*, *Proteobacteria*, *Acinetobacter lwoffii*, *Allobaculum splD4*, *Bacteroides acidifaciens*, *Bifidobacterium pseudocatenuatum*, *Clostridium cocleatum*, *Parabacteroides distasonis*, *Streptococcus thermophiles*, and Bacteroidetes/Firmicutes; and the reduced numbers of Firmicutes, *Tenericutes*, *Verrucomicrobia*, *Cyanobacteria*, *Bacteroides uniformis*, *Deltatopotebacteria* [39]. *G. pentaphyllum* (jiǎogǔlán) saponins also inhibited tumor growth in BALB/c mice while *Clostridia* is decreased, and *Bataproteobacteria*, *Erysipelotrichi*, *Alcaligenaceae*, *Erysipelotrichaceae*, *Clostridium*, *C. cocleatum*, *B. acidifaciens* are increased in the intestine [40]. A study indicated that a Chinese herbal formula containing *Rehmanniae Radix* Praeparata (shú dì huáng), *Corni Fructus* (shān zhū yú), *Moutan Cortex* (mǔ dān pí), *Alismatis Rhizoma* (zé xiè), *Dioscoreae Rhizoma* (shān yào), and *Poria* (fú líng) improved cognitive impairment in SAMP8 mice, and increased intestinal *Adlercreutzia*, *Anaerotruncus*, *Ruminococcus*, *Coprococcus*, etc.; but reduced *Prevotella*, *Streptococcus*, *Veillonella*, *Bilophila*, etc., which may improve Alzheimer's disease [41].

The occurrence of diseases may be related to the intestinal bacteria, and Chinese herbs can alternate the composition of intestinal flora, which contribute to the prevention and/or treatment of diseases. Therefore, it is worthy to clarify the association between the Chinese herbs and intestinal flora, and further to establish a database of such relationship. Better understanding of the interactions among the Chinese herbs, intestinal flora, and diseases will support novel approaches for the development of health foods and drugs in the future.

Gut Microbiota Metabolize the Components in Chinese Herbs

When the Chinese herbs are administered clinically, they were often extracted with water or ethanol to form a decoction, or further concentrated into a paste, powder, or tablet. In general, most of the water extracts of Chinese herbs are hydrophilic compounds, while those with larger proportions in ethanol extracts are lipophilic compounds. Some compounds have low bioavailability and have to undergo structural transformation to form bioactive metabolites. The liver is an organ that mainly metabolizes

dietary components. However, many studies have proposed that precursors of active ingredients in Chinese herbs, after coming in contact with the intestinal flora, are further metabolized by the enzymes of the flora into substances that are more easily absorbed by the intestines; hence, the biological activity of the components of the Chinese herbs is further improved [37]. There are many types of intestinal bacteria, and different kinds of bacteria in the gastrointestinal tract secrete different metabolic enzymes that may participate in the metabolism of various types of active compounds [35].

Glycoside compounds are one of the main components of Chinese herbs, and some intestinal flora can hydrolyze glycosidic bonds to form hydrophobic aglycons [42]. Intestinal flora that have been shown to be capable of hydrolyzing glycosides, including *Bifidobacterium sp.*, *Eubacterium sp.*, *Bacteroides sp.*, *Fusobacterium K-60*, *Prevotella oris*, *Peptostreptococcus intermedius*, *Clostridium perfringens*, *Ruminococcus sp.*, *Clostridium innocum*, *Eubacterium sp.*, *Eubacterium sp.*, *Bifidobacterium sp.*, these can metabolize glycosyl-containing triterpenoids [43-46]. It was also found that *Bacteroides distasonis*, *Butyrivibrio fibrisolvans*, *Butyrivibrio sp.*, *Selenomonas ruminantium*, *Butyrivibrio sp.*, *Bifidobacterium dentium*, *Fusobacterium*, *Escherichia*, *Enterococcus sp.*, *Clostridium coccoides*, and *Bifidobacterium infantis* can hydrolyze glycosidic linkages of glycosyl-containing phenolic compounds [47-50]. In addition, some compounds are further broken down into smaller compounds by intestinal flora. For example, rutin can be metabolized into protocatechuic acid, 3-hydroxyphenyl-acetic acid, 3-(3-hydroxyphenyl)-propionic acid, 3,4-dihydroxyphenyl-acetic acid, 3-hydroxyhippuric acid, etc., which are small compounds that are absorbed by the large intestine [51].

Some Chinese herbs contain a large number of alkaloids. For example, aconite, a Chinese *Aconiti Radix* Wutou (wū tóu), can be converted into lipoaconitine by *Bacteroides fragilis*, *K. pneumoniae*, and *Clostridium butyricum* in the human intestinal tract [52]. The berberine component of *C. Rhizoma* (huáng lián) can be metabolized into dihydroberberine in the intestine of rats [53]. The bacteria that catalyze the transformation reaction of berberine include *Staphylococcus aureus*, *Enterococcus faecium*, *E. faecalis*, *Enterobacter cloacae*, *E. coli*, *Staphylococcus*, *P. aeruginosa*, *K. pneumoniae*, *Proteus mirabilis*, *Acinetobacter baumannii*, *Lactobacillus casei*, *Lactobacillus acidophilus*, *Bifidobacterium longum*, *Bifidobacterium breve*, etc. [53]. In addition, special bacteria capable of metabolizing rhein, a steroid

compound in *Rhei Radix* et Rhizoma (dà huáng), into rheinanthrone were found in the intestinal tract, namely *Bacteroides* sp. RHEIN-I and *Bacteroides* sp. RHEIN-II [54]. *Blautia* sp. AUH-JLD56 in the human small intestine converts arctiin, a lignin in *Arctii Fructus* (niú bàng), into arctigenin and (-)-3'-desmethyларctigenin [55]. Ellagitannins in many Chinese herbs can be broken down into small molecules urolithins by the human intestinal *Gordonibacter urolithinifaciens* sp. nov. and *Gordonibacter pamelaee* DSM 19378T [56]. It has also been found that *Eubacterium* sp. strain SDG-2, *Slackia equolifaciens* JCM 16059, *Slackia isoflavoniconvertens* JCM 16137, *Adlercreutzia equolifaciens* JCM 14793, *Asaccharobacter celatus* JCM 14811 can metabolize condensed tannins in Chinese herbs into several derivatives, such as valerolactone, benzoic acid, phenylacetic acid, phenylpropionic acid, and phenyllactic acid [57].

The Prospect of Gut Microbiota and Chinese Herbs

In the recent years, many researches on the interaction between Chinese herbs and intestinal flora as well as the health of organisms have attracted the attention of many scholars in order to understand how Chinese herbs can prevent or treat diseases [5,6]. One of the directions of research related to Chinese herbs to prevent/treat diseases by influencing intestinal bacteria is to explore the mechanisms by which Chinese herbs could change the intestinal flora, such as promoting the growth of probiotics-producing bacteria or inhibiting the growth of harmful bacteria/pathogenic bacteria. A good balance of the intestinal flora promotes the health of the host; hence, it is necessary to analyze the Chinese herbal ingredients that may affect the growth of the intestinal flora [32,41]. The intestinal flora may also affect the absorption, metabolism, and transformation of Chinese medicines administered orally and changes the efficacy of traditional Chinese medicine.

However, due to the complexity and diversity of the components of traditional Chinese medicine herbs and their endogenous metabolites, studies on the structure of the intestinal flora and the co-metabolism of the host have not been reported and need to be resolved. Previous studies on the intestinal flora and host metabolism have mostly been conducted as separate studies, that is, the changes of intestinal flora and the effects of bacterial changes on host metabolism have been studied separately. These studies do not clearly explain the impact of a specific flora change on host metabolism. In addition, since the intestinal flora metabolizes the components of Chinese herbs into biologically active

products [42,52,53]. In order to understand the interaction between intestinal bacteria and traditional Chinese medicine, studying only a single chemical component cannot meet research needs. Therefore, it is necessary to identify all chemical substances involved in the metabolic process, directly measure the flora in the intestinal tract, and provide accurate research models.

Recently, the microbiome has been extensively studied using high-throughput gene sequencing, real-time quantitative PCR, and metabolomics methods and techniques as well as the multivariate data statistics. Among the many variables, the main variables, which are significant and have high modeling abilities, are selected to construct a biological effect model with good stability and generalization ability. The specific biological effects of Chinese medicine, composition of the intestinal flora, and their interaction on host health can thus be analyzed. However, further studies are necessary to find biomarkers and endogenous metabolites related to specific biological effects and to explore the biological mechanism and material basis of traditional Chinese medicine through the study of co-metabolism between intestinal flora and host. Studies on the mutually beneficial symbiotic relationship and the role of intestinal flora on the health of the host and its role in the development of the disease will have a very important impact on human health.

Conflict of Interest

Declarations of interest: none.

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