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Impact of *Qi*-invigorating traditional Chinese medicines on intestinal flora: A basis for rational choice of prebiotics

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[ABSTRACT] According to the theory of traditional Chinese medicine (TCM), *Qi* (vital energy) is regarded as a driving force of biological activities in human body, including both nutrient substances and organ functions. *Qi*-invigorating TCMs are widely used to treat various symptoms and disorders, such as fatigue, obesity, immunosuppression, intestinal flora imbalance, and gastrointestinal diseases, in which *Qi* is considered to be reduced or depleted. Interestingly, abundant clinical evidences suggest that these disorders are associated with the alternation of intestinal flora, which directly affects disease status. Herein we review the interaction between gut microbiota and *Qi*-invigorating TCMs under healthy and disease conditions and discuss the mechanisms of action and applications of *Qi*-invigorating TCMs in enhancing health status through microbial alternation. A better understanding of the role of *Qi*-invigorating TCMs in modulating microbial composition and the association between intestinal microbiota and diseases would help reveal the clinical consequences of microbiota alteration and explore opportunities to harness this symbiotic relationship to improve public health.

[KEY WORDS] Gut microbiota; Traditional Chinese medicine; *Qi*

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Introduction

The adult human gastrointestinal tract is colonized by about 10^{14} microorganisms, consisting of at least 160 species per individual [1] which are dominated by *Bacteroides*, *Prevotella* and *Ruminococcus* [2]. Amazingly, it is estimated that the gut microbiota contains 150-fold more genes than the human genome [3]. Given their vital impact on nutritional, metabolic, physiological and immunological processes, intestinal flora is also referred to as the “forgotten organ” [4]. Under normal physiological conditions, those microbes can digest food and harvest energy, prevent pathogens from invading the organs or tissues, and enhance immunity [5]. It is indicated that the strong evolutionary force has driven the establishment of intestinal flora as indispensable human symbionts, because not only its digestive function benefits the human host, but the microbiota can also take in energy sources to nourish itself, thereby producing a great variety of metabolites with potential impacts on human health [4]. Additionally,

the interaction between gut microbiota and immune system contributes to the maintenance of normal immune functions as well as maturation of immune cells [1]. However, the imbalance in the composition of intestinal flora will interrupt the normal interaction with human host, thus leading to diseases [5]. Many diseases are observed to be associated with gut microbiota disorder, including inflammatory bowel disease (IBD), Crohn’s disease, gastric cancer, allergy, type 2 diabetes, obesity, and autism [6]. The involvement of gut microbiota in pathophysiology of human diseases has aroused great interest and has been intensively studied in recent years.

Traditional Chinese medicine (TCM), also known as Chinese materia medica, is one of the oldest medicine practices in human history. The essence of TCM is the “*Yin/Yang* Theory” (a philosophical concept that views the universe as a result of two opposing but interacting principles), which is extensively applied to the clinical diagnosis and treatments. In general, *Yin* represents the “female” or negative features while *Yang* represents the “male” or positive ones. *Yin* and *Yang* are complementary, exchangeable, and interdependent. According to the TCM theory, if the *Yin/Yang* balance of a human body is broken, in other words, deficiency occurs in *Yin* or *Yang*, the individual will become sick or turn into a sub-healthy status. *Qi* (vital energy) and *Xue* (blood) are two fundamental substances supporting daily

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activities, according to the TCM theory. *Qi* is generated when *Yin* and *Yang* interact with each other. Referring to the nutritive and refined substances flowing in the body as well as the functional status of tissues and organs, *Qi* represents longevity and its depletion is linked to death [7]. The deprivation of *Qi* can be caused by many factors such as malnutrition, aging, fatigue, chronic diseases and long-term surgery, leading to symptoms such as cough, dizziness, diarrhea, pale complexion, short breath, muscle weakness, obesity, and immune-deficiency.

In TCM practice, tonic herbs, along with a few animal sourced medicines (e.g., deer blood), are used for strengthening the body and curing diseases caused by *Qi* deficiency. Some tonic herbs, such as the *Dioscoreae Rhizoma* (yam), are also common in Chinese diet. In fact, food therapy has earned its reputation throughout history by its function and convenience of use. Based on their uses, tonic medicines are classified into four categories: *Qi*-invigorating, *Xue*-enriching, *Yin*-nourishing, and *Yang*-promoting. Typical *Qi*-invigorating herbs include *Astragali Radix*, *Ginseng Radix et Rhizoma* (ginseng), yam, *Codonopsis*, *Coicis Semen*, *Atractylodis Macrocephalae Rhizoma*, *Glycyrrhizae Radix et Rhizoma* (licorice), and *Schisandra Chinensis Fructus*, and exemplary *Qi*-invigorating multi-ingredient decoctions (called Tang in Chinese) include “Dai-Kenchu-To”, “Sijunzi Tang”, “Lizhong Tang”, “Buzhong Yiqi Tang”, and “Shenlingbaizhu San”.

In clinical practice, TCMs are usually made into decoctions by boiling the herbs in water, according to a particular weight proportion of active ingredients. *Qi*-invigorating TCMs are mostly relevant to intestinal flora because they are often administrated orally used to treat diseases with gut microbial dysbiosis [8]. Since those TCMs inevitably interact with gut microbiota when passing through the gastrointestinal tract, many researchers have investigated metabolites of *Qi*-invigorating TCMs by intestinal flora and realized that indeed these metabolites have important pharmacological activities and play various roles in the disease treatment [8]. On the other hand, *Qi*-invigorating TCMs also have an impact on the quantity or abundance of gut microbiota [9].

In this article, we will briefly review the interaction between gut microbiota and *Qi*-invigorating TCMs from two aspects: the metabolism of *Qi*-invigorating TCM by intestinal flora and the change of local microflora after TCM treatment. The mechanisms by which *Qi*-invigorating TCMs enhance health status through microbial alternation are also discussed. A better understanding of gut microbiota changes before and after receiving *Qi*-invigorating TCMs would be helpful to elucidate the mechanism of action for tonic drugs and provide guidance for drug design, including decoction formation and dosage form.

Metabolism of *Qi*-invigorating TCM by gut microbiota

An interesting phenomenon noticed by many researchers

in the last century is that a lot of herbs or their ingredients with strong activities *in vivo* do not show significant pharmacological activities *in vitro* [10]. It is quite clear now that the gut microbiota is crucial for treatment outcome and metabolism of herbs by gut microbiota is an integrant part of drug biotransformation. A considerable proportion of orally administered herbal preparations are transformed by intestinal flora to their corresponding metabolites, some of which are bioactive metabolites, before being absorbed in the gastrointestinal tract [9-12]. For example, the major ginsenosides (ginsenosides Rb1, Rb2, and Rc) from ginseng are metabolized to 20-*O*- β -D-glucopyranosyl-20(*S*)- protopanaxadiol, named compound K (CK), which exhibits anti-allergic, anti-inflammatory, and antitumor activities more potently than the parental ginsenoside Rb1, suggesting that CK is responsible for the pharmacological effects observed for orally administered ginseng [9]. Astragaloside IV (AST) is a constituent of *Astragali Radix* that shows poor bioavailability *in vivo*. However, the gut microbiota can transform AST into cycloastragenol, a highly bioavailable triterpenoid saponin that has significant telomerase activating and antioxidant activities, making it an ideal functional food and anti-aging drug [10]. Glycyrrhizin, which also has the same problem of low bioavailability, can be metabolized by intestinal flora into glycyrrhetic acid that is easily absorbed [11]. Liquiritin, another main component in glycyrrhiza, can be metabolized by hydrolysis, hydrogenation, methylation, deoxygenation and acetylation under microbiota metabolism, with the major pathway being the conversion of liquiritigenin [12].

Alternation of gut microbiota after treatment with *Qi*-invigorating TCMs

Impact of Qi-invigorating herbs on gut microbiota

The interaction between *Qi*-invigorating TCMs and gut microbiota has been highlighted by pharmacognostic scientists. As mentioned above, intestinal flora is involved in the absorption and transformation of TCMs, and the latter can influence the activity and composition of gut microbiome through affecting the growth and abundance of specific bacteria. The variations in bacteria affected by *Qi*-invigorating TCMs have been observed in many studies with either *in vitro* culture [8, 16, 25-26] or gut microbiota from mammals [13-15, 17-24, 27-30]. In general, *Qi*-invigorating TCMs are able to promote the growth of probiotic bacteria or/and inhibit pathogen colonization in the intestines, improving health, and therefore are considered as prebiotics. Exemplary changes in gut microbiota by *Qi*-invigorating herbs are listed in Table 1.

For example, yam, an extensively cultivated food in Asia, is used in treating diarrhea, diabetes, anorexia, spermatorrhea, and leukorrhagia [8]. An early research has demonstrated that a great deal of lactose-fermenting bacteria is found in feces of rats fed with Chinese yam extract, suggesting that yam could induce or convert some intestinal flora into health benefiting

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