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Review

Could the gut microbiota reconcile the oral bioavailability conundrum of traditional herbs?

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Chemical compounds studied in this paper:
Baicalin (PubChem CID: 64982)
Berberine (PubChem CID: 2353)
Daidzein (PubChem CID: 5281708)
Daidzin (PubChem CID: 107971)
(-)-Epigallocatechin gallate (PubChem CID: 65064)
Equol (PubChem CID: 91469)
Ginsenoside C-K (PubChem CID: 9852086)
Ginsenoside Rb1 (PubChem CID: 9898279)
Glycyrrhizin (PubChem CID: 14982)
trans- Resveratrol (PubChem CID: 445154)

ABSTRACT

Ethnopharmacological relevance: A wealth of information is emerging about the impact of gut microbiota on human health and diseases such as cardiovascular diseases, obesity and diabetes. As we learn more, we find out the gut microbiota has the potential as new territory for drug targeting. Some novel therapeutic approaches could be developed through reshaping the commensal microbial structure using combinations of different agents. The gut microbiota also affects drug metabolism, directly and indirectly, particularly towards the orally administered drugs. Herbal products have become the basis of traditional medicines such as traditional Chinese medicine and also been being considered valuable materials in modern drug discovery. Of note, low oral bioavailability but high bioactivity is a conundrum not yet solved for some herbs. Since most of herbal products are orally administered, the herbs' constituents are inevitably exposed to the intestinal microbiota and the interplays between herbal constituents and gut microbiota are expected. Emerging explorations of herb–microbiota interactions have an opportunity to revolutionize the way we view herbal therapeutics. The present review aims to provide information regarding the health promotion and/or disease prevention by the interplay between traditional herbs with low bioavailability and gut microbiota through gut microbiota via two different types of mechanisms: (1) influencing the composition of gut microbiota by herbs and (2) metabolic reactions of herbal constituents by gut microbiota.

Materials and methods: The major data bases (PubMed and Web of Science) were searched using “gut microbiota”, “intestinal microbiota”, “gut flora”, “intestinal flora”, “gut microflora”, “intestinal microflora”, “herb”, “Chinese medicine”, “traditional medicine”, or “herbal medicine” as keywords to find out studies regarding herb–microbiota interactions. The Chinese Pharmacopoeia (2010 edition, Volume I) was also used to collect the data of commonly used medicinal herbs and their quality control approaches.

Results: Among the 474 monographs of herbs usually used in the Chinese Pharmacopoeia, the quality control approach of 284 monographs is recommended to use high-performance liquid chromatography approach. Notably, the major marker compounds (> 60%) for quality control are polyphenols, polysaccharides and saponins, with significant oral bioavailability conundrum. Results from preclinical and clinical studies on herb–microbiota interactions showed that traditional herbs could exert heath promotion and disease prevention roles via influencing the gut microbiota structure. On the other hand, herb constituents such as ginsenoside C-K, hesperidin, baicalin, daidzin and glycyrrhizin could exert their therapeutic effects through gut microbiota-mediated bioconversion.

Conclusions: Herb–microbiota interaction studies provide novel mechanistic understanding of the traditional herbs that exhibit poor oral bioavailability. “Microbiota availability” could be taken consideration into describing biological measurements in the therapeutic assessment of herbal medicine. Our review should be of value in stimulating discussions among the scientific community on this relevant theme and prompting more efforts to complement herb–microbiota interactions studies.

Contents

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1. Introduction

The practice of traditional Chinese medicine (TCM) – mainly herbal medicine – plays an important role in health maintenance not only for the peoples of Asia, and is becoming more frequently used in the West as a form of complementary and alternative medicine (CAM). According to a 2014 market report on the China pharmaceutical industry released by the SFDA's Southern Medicine Economic Research Institute, the China's production of the Chinese Patent Drug sector was valued at ¥ 524 billion in 2013 (http://www.docin.com/p-855174018.html). Meanwhile, after the 10th consecutive year increase, the sales of herbal dietary supplements in the United States were about $ 6 billion in 2013, according to data from previous *HerbalGram* herb market reports (Lindstrom et al., 2014). Further, two herb-based new drug applications (*i.e.*, sinecatechins and crofelemer) have been approved by FDA in 2006 and 2012, respectively (Lee et al., 2015).

However, TCM differs in substance, methodology and philosophy to western medicine (Cheung, 2011). It stresses the maintenance of balance between the systems of the individual internal physiological systems and external environmental networks. The current challenge is to convince skeptic occidental medical doctors of the application of such medicines, serving better both the practitioners and the patients. However, research in TCM recently has been dominated by the search for its molecular, cellular and pharmacological bases, identifying active substances and investigating mechanisms of action (Tang, 2006). In spite of scientific advances of these works, limitations of this approach still exist. Alternatively, evidence-based approach based on modern scientific techniques (*e.g.*, systems biology–based 'omics technologies) and comparative effectiveness research approach are regarded as valid strategies for exploring TCM and CAM (Verpoorte, 2012; Witt et al., 2015).

Systems biology endeavors to quantify all of the molecular elements of a biological system (Hood et al., 2004). As a proposed approach to biomedical research, systems biology consciously combines reduction and integration of information across multiple spatial scales to identify and characterize parts and explore the ways in which their interaction with one another and with the environment resulting in the maintenance of the entire system (Kohl et al., 2010). Generally, humans contain proteins, polysaccharides, lipids and nucleic acids with which we can interfere using small-molecule therapeutic agents. Particularly, most of successful drugs achieve their activities by binding to and modifying the activity of a protein, with multiple consequences on various functions (Hopkins and Groom, 2002). Scientists in the pharmaceutical industry attempt to develop new chemical entities (NCEs) with desired actions against some particular families of 'druggable' proteins (Yıldırım et al., 2007). An assessment of 'the druggable genome', the subset of the ~25,000 genes in the human genome that express proteins able to bind drug-like molecules, is crucial to the development of post-genomic research strategies (Hopkins and Groom, 2002). Whole-genome sequencing approach presents enormous potential in personalized therapeutics (Cordero and Ashley, 2012).

However, human beings contain two interacting genomes, *i.e.*, the onstructurally fixed and genetically inherited human genome and the plastic and environmentally acquired human microbiome, most of which reside in the gut (Zhao et al., 2012). The mutualism and symbiosis of humans with the commensal gut microbe extends the human genome with a collection of microbial genomes approximately 100-times larger than the host genome (Han et al., 2010). The two genomes exchange their respective metabolically active molecules and exert influences on each other. In a given environment, the humans' health maintenance depends on harmonious integration work of them as a hologenome (Zhao and Shen, 2010). More importantly, the gut microbiota interacts with the host immune system, providing signals to promote the maturation of immune cells and the normal development of immune functions (Clemente et al., 2012). The intestinal microbe can also prompt immune cells to produce cytokines that can influence neurophysiology (Smith, 2015). The imbalance or dysbiosis of the gut microbiota has been implied in many human diseases, such as obesity, diabetes, inflammatory bowel disease, gastrointestinal cancers and infectious diseases (Han et al., 2010). Recent evidence suggests that diet and herbal medicines interact strongly with the gut microbiota which in turn would influence human health (Wang et al., 2011a; Zhang et al., 2012; Cotillard et al., 2013; Guo et al., 2015).

Not the same as target-based approach, integrated network-based strategy, for TCM takes a systems approach to understanding the individual's body as a whole and offers a comprehensive medical system that integrates fundamental theories, diagnostic methods and therapeutics based on a holistic and dynamic network-based approaches (Axling et al., 2011, Leung et al., 2014). These strategies would be beneficial for bridging the gap between TCM theory and modern clinical utilization. But the major roles of gut microbiota have little been studied on TCM actions. As most Chinese herbal medicines are orally administered and are suitable for chronic treatments (Qiu, 2007), they are inevitably exposed to the microbiota in the whole gastrointestinal tract resulting in enough spatio-temporal opportunity for their "intimate" contact. TCM might work both by modulating gut microbiota to regain ecological balance and by regulating genes within the host to regain metabolic/immune homeostasis (Zhao et al., 2012). Metagenomics metatranscriptomics, metaproteomics and metabolomics, these network-based approaches could provide powerful tools for better understanding novel mechanisms of TCM with detailed analyzes of gut microbial communities (Maccaferri et al., 2011; Martín et al., 2014; Rose et al., 2015; Wang et al., 2015b). On the other hand, the availability of TCM by gut microbiota should be taken into consideration to assess the therapeutic contribution of TCM.