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## Review Article

# China's contribution to gut microbiota research

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## Abstract

Gut microbiota research is a hot topic. With the advancement of high throughput sequencing technology, gut microbiota provides a sally port for the pathogenesis of diseases, the mechanism of drug action and the strategy of treatment selection. The transformation potential of gut microbiota research is gradually being valued. This paper focuses on the study of gut microbiota, highlights the contribution of China and puts forward some views in this field.

The research on gut microbiota has become an important focus in recent years. There are tens of trillions of bacteria living in the human intestinal tract, which play an important role in digestion and absorption, nutritional metabolism, and immune regulation [1]. Right from birth gut microbiota become an indispensable part of our lives [2,3]. With the development of scientific techniques, our understanding of the role of gut microbiota has reached new heights. Chinese researchers have also made important contributions in the field of gut microbiota.

From ancient clinical applications to current diseases association, the research on gut microbiota has undergone a long development. In the 4th century AD, Hong Ge, an ancient Chinese medical scholar, recorded a case of treating food toxin diarrhea with fecal water in his "Handbook of Prescription for Emergency". This is the first recognized record of original Fecal Microbiota Transplantation (FMT) in the world [4]. Shizhen Li also recorded, in the Compendium of Materia Medica, prescriptions for treating diseases with human or animal feces. Chinese physicians have thus known of the importance of gut microbiota for at least a thousand years. The progress of modern medicine has enabled the study of gut microbiota to become more advanced. Immune cells in the intestine are mobile and can transmit signals to organs throughout the body. The gut microbiota can help the host maintain the balance of intestinal immunity and regulate the immune homeostasis. Gut microbiota and immune cells constantly communicate to identify foreign antigens, so that the immune

system can respond. The intestinal mucosal barrier separates gut microbiota from the intestinal epithelium, and immune cells at the mucosa inhibit the translocation of microbiota. If the intestinal mucosal barrier is broken, foreign antigens will invade the gut. The resulting systemic immune inflammation will gradually affect the intestinal and extra-intestinal organs, causing chronic inflammation and immune-related diseases.

The intestinal-hepatic axis has specifically become a significant research topic in recent years. The enterococci occurring in quail are commonly found in the intestines of healthy people. However, some studies have found that the bacteria can migrate to the liver, mesentery and other tissues and organs, resulting in autoimmune hepatitis [5]. This finding suggests that intestinal bacteria may translocate to lymph nodes and liver through the damaged intestinal mucosal barrier, triggering the occurrence of diseases in extra-intestinal organs. Intestinal microorganisms also interact with the nervous, immune, endocrine and other major systems through intestinal-brain axis pathways, to regulate the various functions of our body. This flora-host "communication" is essential for maintaining our health. The main pathological feature of Parkinson's disease is the accumulation of misfolded  $\alpha$ -synuclein in the brain. Some researchers have hypothesized that pathological  $\alpha$ -synuclein can spread from the intestine to the brain through the vagus nerve [6,7]. This concept laid a good foundation for the idea of "intestinal treatment of encephalopathy". More and more researchers have gradually recognized that the pathogenesis of chronic diseases should be



studied from the perspective of gut microbiota [8]. Imbalanced gut microbiota is associated with the progression of many other diseases, such as inflammatory bowel disease [9], primary biliary cholangitis [10], autism [11], Alzheimer's disease [12], nephropathy [13], psoriasis [14], obesity [15], diabetes [16], and atherosclerosis [17]. The intestine–liver axis, intestine–brain axis, intestine–kidney axis and intestine–skin axis are associated with the occurrence and development of disease. The ultimate goal of flora research is not just to explain the association between the flora and disease, but to explore new ways for clinical diagnosis and treatment of diseases. In the future, FMT, strain development, probiotics and clinical application of targeted antibiotics will be paid more attention. Throughout the history of flora research, from phenomena to essence, from association to cause and effect, from basic research to clinical transformation, each course reflects the continuous progress of flora concept.

The clinical transformation of gut microbiota research is worthy of attention. The human intestinal microbial genome is the second human genome. The contribution of Chinese scientists to this field is very important. The earlier works included examination of intestinal microbiology, followed by the launch of the human intestinal metagenome project. In addition, many important breakthroughs have been made by Chinese clinical researchers in recent years. Zheng and Li, et al. found that microbial biomarkers in the stool specimens were expected to diagnose early hepatocellular carcinoma [18]. Ma, et al. found changes in gut microbiota in patients with primary biliary cholangitis and autoimmune hepatitis [19]. Fang and Yu, et al. found that gut microbiota was closely related to colorectal cancer [20,21]. These studies will lay a solid foundation for the transformation and application of gut microbiota. Transforming the results of gut microbiota research into clinical application is the common goal of researchers. FMT is an effective method to reconstitute the gut microbiota population. Although ancient Chinese medical experts have already proposed the theory and practice of using feces to cure diseases. More than 5,000 clinical treatments of FMT have been implemented by Zhang, et al. with satisfactory efficacy and safety [22,23]. In the field of FMT for inflammatory bowel disease, Zhang, et al. has taken the lead in the world. With the deepening of the concept of FMT and the progress of methodology, domestic researchers have extended FMT to the clinical treatment of a variety of chronic diseases. In 2016, Ren, et al. found that FMT helped to remove hepatitis B antigen from patients with chronic hepatitis B [24]. In fact, we carried out an early clinical study on FMT for Parkinson's disease, and it is the first such study in the world [25]. We believe that more high-quality research data will be published. The application of FMT in extra-intestinal diseases has received unprecedented attention [26,27]. Of the 367 clinical studies involving FMT, 84 (24%) were registered in China [28]. This is an important contribution of Chinese researchers in this field, as well as the clinical transformation of gut microbiota research. In addition to FMT, Chinese researchers also focus on probiotics research, development and their clinical application. Zhang, et al. has established the largest original lactic acid bacteria resource bank in China, and screened functional probiotics

by combining modern medicine with molecular biology techniques. The types of probiotics marketed are limited, and the development of new probiotics needs to be accelerated. Technological advances limit the clinical transformation of flora research. *Akkermansia muciniphila*, a type of bacteria in the human intestinal tract, contribute to lose weight and resist cancer, etc. [29,30]. Recently, Wang, et al. have reported that pasteurised *A. muciniphila* or a specific outer membrane protein (Amuc\_1100) can blunt colitis and CAC through the modulation of CD8<sup>+</sup> cytotoxic T lymphocytes [31]. This provides new ideas for the treatment of inflammatory bowel disease in the future. However, due to the limitations of isolation and culture technology, there are many limitations in its clinical transformation and application. The progress of methodology, strain screening, commercial production and clinical trial demonstration will all accelerate the pace of clinical application.

We propose some views on microbiota research. First, gut microbiota-related research will continue to grow. Recent studies have found that enzymes produced by gut microbiota can remove A antigen from red blood cells and thereby transform A blood into omnipotent O blood [32]. This important finding may alleviate the current situation of insufficient blood supply in the future. Such studies have challenged our superficial understanding of microbiota. Human understanding of the relationship with gut microbiota is in its infancy but is expected to dramatically continue. Second, advances in methodology will promote the clinical transformation of flora research. The clinical value of FMT is likely groundbreaking in its time and has been gradually recognized. but the current methodology limits the clinical transformation. FMT includes strict donor screening, optimized fecal bacteria preparation methods, and appropriate ways of flora transplantation [33]. Zhang, et al. invented Intelligent Fecal Microbiota Separation System (GenFMTEr) and Transendoscopic Enteral Tubing (TET), which promoted the clinical transformation of microbial transplantation research [34]. Third, microflora research brings opportunities for the development of Traditional Chinese Medicine (TCM). It is difficult for international researchers to recognize fully the theory of TCM's holistic conditioning of the human body. In fact, there is a dynamic relationship between the intestinal tract and brain, lung, liver and kidney to maintain normal physiological activities. From the perspective of TCM, we can better understand gut microbiota. *Cordyceps sinensis* and *Ganoderma lucidum* extracts can treat obesity and type II diabetes by regulating gut microbiota [35,36]. We have found that *Gynura segetum* herb can also help optimize the gut microbiota structure, but the toxic components of pyrrolidine alkaloids limit its clinical application (data are not yet published). It can be seen that the regulating effect of TCM on gut microbiota is a problem worthy of attention. The study of gut microbiota and its metabolomics may provide ideas for the development of TCM. From ancient to modern times, from TCM to integrative medicine, from phenomenological to causal, from disease diagnosis to therapeutic targets, from cognitive limitations to clinical transformation, gut microbiota research has been both a challenge and an opportunity.

Recently, Chinese scientists highlighted seven facts and five initiatives for gut microbiome research [37]. The facts



include that (1) the gut microbiome is the leading edge of scientific research; (2) basic and translational research of the gut microbiome is expanding globally; (3) the gut microbiome contributes to health and diseases; (4) gut dysbiosis is only one factor in disease; (5) gut microbiome research is still at its infancy; (6) chaos and conflict of interest exist in gut microbiome research; (7) self-purification and discipline mechanisms exist in gut microbiome research, and the initiatives include that (1) follow the normative ethical principles to carry out research; (2) avoid hype and packaging; (3) disclose conflict of interest and reveal safety and risk issues actively; (4) abide by laws and disciplines and adhere to evidence-based scientific rules; (5) actively participate in science popularization and education and promote public participation.

In summary, China's contribution is very important, mainly in the original use of gut microbiota, the progress of gut microbiota with diseases, and the clinical application of FMT. China will continue to contribute to the global research of intestinal flora.

### Author contributions

Xiao-Zhong Yang designed the research; Hong-Gang Wang wrote the paper.

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