Current Research & Information on Pharmaceutical Sciences (CRIPS)
@NIPER, SAS Nagar, India

Review Article

Human Gut Microbiota - A Hidden Treasure

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Human gut is the harbor of a complex and dynamic population of microorganisms, known as gut microbiota, consisting of bacteria, yeasts, and viruses. Both beneficial and pathogenic microbes co-exist in the gut to provide a healthy ecosystem. Microbes help digest/metabolize foods, provide nutrients and vitamins to the host, and regulate the immune system. Any perturbation in the ecosystem alters the microbiota composition, which may lead to gastrointestinal (GI) complications such as constipation, ulcerative colitis (UC), inflammatory bowel diseases (IBD), irritable bowel syndrome (IBS), gastroesophageal reflux disease (GERD), and many more. Improper diet is one of the major causative factors for the complications. However, complications could be modulated and most likely reversed by proper diet. Pro- and prebiotics, the two supplementary diets, when consumed singly or in combination in adequate amounts, improve gut health and reduce inflammation. Fecal microbiota transplantation (FMT), another option to treat dysbiosis, has been found to be effective in the treatment of *C. difficile* infection (CDI) and recurrent *C. difficile* infection (rCDI) with a success rate of 90%. FMT has also been successfully utilized in relieving other GI related disorders. Physical exercise and fasting have also been shown to incur health benefits by altering gut microbiota.

Introduction

We are very familiar with the term bacteria.The word bacteria meant bad and harmful which spread infections and caused diseases. This was the concept that remained in mind in our childhood. However, all the bacteria are not harmful or infectious. They are present everywhere in the environment as well as in our body parts like skin, eyes, ears, lungs, and gut to name a few. It is estimated that only a small percentage of bacteria are harmful and the rest are either harmless or beneficial to life. Human gut is the harbor of a complex and dynamic population of microorganisms, known as gut microbiota which consists of bacteria, yeasts, and viruses.[1,2] Both beneficial and pathogenic microbes are present in the gut and it is impossible to harbor only beneficial microbes and avoid pathogenic ones. Beneficial microbes are a support system; which help us digest/metabolize foods, provide nutrients and vitamins to the host, and regulate the immune system.

The human gastrointestinal (GI) tract is one of the largest surface areas (250-400 sq. m),[3] which is in direct contact with the environment. On average during the lifespan of a normal human being about 60 tons of foods pass through the GI tract.[3] Foods we consume every day contain various microorganisms including harmful ones that may pose a great threat to gut homeostasis. It is the ecosystem of microbes present in the gut that is responsible of maintaining the homeostasis.

Some estimates predict the presence of more than 10^{14} microbes in our body, which is 10 times greater than the total number of human cells.[4] However, a revised estimate claims that the number of microbes in the body is actually of the same order as the number of human cells.[5] These microbes are capable of communicating with each other and the host, often known as commensal (one partner gets benefited while the other remains unaffected).[4]

Evolution and early colonization of gut microbiota

The evolution of gut microbiota took place over thousands of years. It is very dynamic in nature and both genetic and environmental factors drive its composition. All three domains of life - bacteria, archaea, and eukarya are found in human adults.[4] Colonization of microorganisms in the gut starts in the mother's womb[6] and attains a more or less stable state after birth within 2-3 years. At the time of birth, an infant inherits the microbes from the mother, though less in population and diversity. As the newborn encounters outside food microbiota composition attains maturity and stability over a period of time. The very first diet a newborn experiences after birth is milk. The nature of milk dictates the initial colonization; as in breastfed

infants, bacterial species *Lactobacillus* and *Bifidobacterium* are found to be present in abundance.[7] These bacteria are capable of breaking down human milk oligosaccharides to produce short-chain fatty acids (SCFA). SCFAs stimulate the immune system of the host to express immunoglobulins, which help fight infections and diseases. Micro-organisms that are set forth in formula-fed infants lack those bacteria and are dominated by *Enterococcus, Enterobacteria, Bacteroides, Clostridia,* and *Streptococcus*.[8] Various studies support that breastfed infants develop more stable and diverse microbiota and are better equipped in managing immune responses compared to formula-fed infants.[8]

Microbial composition in human gut

Microbes are found throughout the GI tract, starting from the mouth then the stomach, intestine, and finally in the colon. However, because of the acidic nature of the stomach, only those microbes survive here, which can withstand low pH. Since most of the microbes are acid sensitive their population is limited in the upper GI tract which keeps on increasing as we go down the tract and maximizes in the colon with predominantly anaerobes. Gut microbial composition varies considerably from person to person. The composition of gut microbiota attains more or less a stable state in adulthood and tries to maintain it in healthy adults. However, perturbation in gut microbiota affects the composition and may lead to metabolic disorders like obesity, diabetes, or inflammatory bowel disease (IBD).[9]

Factors affecting gut microbiota

Many researchers suggest that host genetics play a major role in determining gut microbiota composition. However, there is no clarity on the percentage contribution of inheritance. A study on >1000 twins suggested many microbial taxa whose abundances were influenced by host genetics.[10] The most heritable bacteria are Christensenellaceae, responsible for body mass index (BMI). Individuals with higher levels of *Christensenellaceae* bacteria in their guts were more likely to have a lower body mass index than those with low levels.[11] Although gut microbiota is established at an early stage of life it can be altered by various factors such as diet, age, use of antibiotics and illnesses, global location and ethnicity, and even mode of birth. All these factors are not always under the control of a person. However, the factor that is in individual's capacity to control is diet. Diet plays an important role in the composition of the microbiota, which in turn contributes to good health and long life.

Role of diet

Rothschild and coworkers claimed that host genetics has a minor role in gut microbiota composition suggesting more weightage on diet.[12] In one such observation, it was found that individuals sharing the same household but genetically unrelated share significant similarities in the microbiome.

Dietary substances dictate the constitution of gut microbes and functional capabilities. A person, mostly dependent on carbohydrates, is likely to possess microbes that are capable of digesting carbohydrates. On the other hand, a person preferring a protein diet is more likely to own microbes that are capable of metabolizing proteins. Plant-based diets induce a healthy and diverse population of microbes (*Firmicutes*) capable of metabolizing insoluble carbohydrates providing short-chain fatty acids (SCFAs) to the host. However, animal-based diets (western diet) promote the growth of *Bacteroidetes*, which produce amino acids on metabolism. Amino acids, in turn, are converted into SCFAs along with harmful compounds.[13] A person, consuming a balanced diet, is more likely to possess balanced microbiota composition; otherwise, selective microbes outgrow others putting the host at health risk. Therefore, a person is indirectly selecting microbes in the gut to flourish by choosing his/her own diet. Thus the proverb exactly fits here, "You are what you eat".

Role of antibiotics & illness

In the gut, a balance between beneficial and pathogenic microbes is maintained by a competitive environment in healthy persons. Beneficial microbes inhibit the growth of pathogenic microbes by signaling, competitive site binding, competing with nutrients, and producing chemicals that deter the growth of unwanted microbes.[8] However, microbial flora of the GI tract is disturbed when antibiotic treatment is opted for, in case of illness. Treatment with antibiotics eliminates both pathogenic and beneficial microbes indiscriminately preparing a ground for unwanted microbes to grow. It takes a long time for a person to return to a normal state after an antibiotic treatment, which may vary from person to person. In one of the experiments, it was shown that vancomycin, often used for the treatment of *C. difficile* infection (CDI), causes damage to microbial flora that may lead to recurrent *C. difficile* infection (rCDI), which is difficult to treat with antibiotics further.[14] In an another study, the production of key metabolites along with microbial ecosystem were found to be affected by the administration of β-lactams infused intravenously in humans.[3] Antibiotics are also making inroads into

humans and animals through the food chain. Poultry products are fed with excessive antibiotics to keep their growth unhindered. This is also causing health hazards to consumers undoubtedly, but the long-term effect is unclear.

Role of age

There is a considerable difference in constituents and diversity of microbes in aged and young populations. The microbial diversity attains a stable state in healthy adults and maintains a balance between the two most abundant bacterial phyla *Firmicutes* (Gram-positive) and *Bacteroidetes* (Gram-negative), whereby *Firmicutes* are present in excess. Aging process alters the F/B ratio in favor of *Bacteroidetes*. Any alteration in the F/B ratio has an adverse impact on the health of a person. Another major change that takes place in the aged population compared to young adults is the deterioration of immune response with increasing age. The immune response is directly related to levels of short-chain fatty acids (SCFAs) produced by the microbes, which decreases with increasing age. Acetate, propionate, and butyrate are the fundamental SCFAs, produced by some microbes in colon and consumed by our body for different functional activities. Particularly important amongst these is butyrate, which acts as an energy source and plays an important role in intestinal cell growth. SCFAs boost the immune system and reduce the production of anti-inflammatory agents, which protect us from illnesses like Crohn's Disease (CD) and inflammatory bowel disease (IBD).[15] Other age-related changes that take place are an increase in Gram-negative and pathogenic bacteria, which secret endotoxins leading to inflammatory activities and infections.[15]

Role of global location and ethnicity

Various types of diets (mostly depending on availability) are being consumed for centuries by people living in different parts of the world as a tradition or lifestyle. Therefore a country/region-specific colonization of microbes was developed over a period of time on the basis of traditional foods consumed by ethnic groups depending on their global location.[16]

Role of the mode of birth

It has been observed that the mode of birth (normal vs. C-section delivery) has a pronounced effect on the gut microbiota amongst newborns. Newborns are found to have *Lactobacillus* and *Prevotella* in abundance in case of normal delivery, acquired from the mother's vaginal microbiota, whereas *Streptococcus, Corynebacterium,* and *Propionibacterium,* received by skin contact of the mother, are found to dominate in newborns delivered through C-section.[8] These microbes gradually evolve to be part of the infant in course of time.

How to modulate gut microbiota

Modulation of gut microbiota is an effective option in case of dysbiosis (imbalance in the composition of microorganisms in the gut). The factors discussed here are the role of diet, probiotics, prebiotics, synbiotics, and the fecal microbiota transplantation (FMT). One of the reviewers suggested including the role of physical exercise and fasting on microbiota. Indeed, I am tempted to add this topic after going through the literature.

Diet as modulating factor

Types of bacteria in the human gut can be classified into 13 bacterial phyla as per the report by Yang et al of which *Firmicutes* contribute 65% and *Bacteroidetes* 30% (Fig. 1).[17] Any alteration in the *Firmicutes/Bacteroidetes* (F/B) ratio is regarded as dysbiosis. An increase in the F/B ratio is usually associated with obesity and a decrease in the ratio with inflammatory bowel disease (IBD).[1] Variety of plant fibers (from fruits, vegetables, and grains) provide a diverse and beneficial microbial community e.g. fructans and galactooligosaccharides were found to increase fecal abundance of *Bifidobacterium* and *Lactobacillus* species.[18] It has also come to the notice of researchers that even an abrupt change in diet can alter the composition overnight, although for a transient period only. Individuals, provided with a high-fat/low-fiber or low-fat/high-fiber diet, have been found to possess altered microbiota within 24 hours.[15] Short-term diet alteration can modulate the microbiota for a few days; however, to elicit a beneficial effect, a long-term or habitual diet needs to be executed.[18] Therefore, the saying of Hippocrates is so relevant to quote, "Let thy food be thy medicine and medicine be thy food."

Probiotics as modulating factor

Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit to the host. Probiotics consist mainly of bacteria and yeast. Commonly used bacterial species are *Lactobacillus* and *Bifidobacteria*, whereas *Saccharomyces boulardii* is the common species used in case of yeast.[19] Ingestion of probiotics brings positive change by promoting favorable bacteria in the gut. It is not clear whether probiotics are able to colonize or proliferate in the gut as the effect

observed is temporary. However, it is not necessary for probiotics to colonize to reap the benefits. Benefits associated with probiotics intake have been observed in diseases like antibiotic-associated diarrhea, insulin resistance, inflammatory bowel disease, and many others.[18] *Saccharomyces boulardii* administration has been observed to alter the F/B ratio and pronounced a positive effect on obesity and inflammation.[1] In type 2 diabetic patients, probiotic administration is found to reduce fasting blood glucose and HbA1. Probiotics hinder the growth of pathological microbes by preventing their adhesion or killing them by secreting antimicrobial compounds.[8] Varieties of probiotics are available in the market that may contain a single strain or a cocktail of microbes. Yogurt is a commonly used probiotic. Usually, probiotics contain high doses of microorganisms (10^6-10^7 CFU) to maintain an optimal concentration in the gut as some of the microorganisms are assumed to perish under gut atmosphere.

Prebiotics as modulating factor

Prebiotics are substrates that are selectively used by host microorganisms providing health benefits to the host. Prebiotics are specific foods and substances that can boost the growth of probiotics and other beneficial bacteria. They are mainly non-digestible carbohydrates/fibers found in fruits, vegetables, legumes, grains, and nuts. Prebiotics are not hydrolyzed by digestive enzymes nor are absorbed by the upper intestine but passed onto the colon as food for microbes, which in return produce short-chain fatty acids (SCFAs) benefitting the host. *Bifidobacterium, Lactobacillus* and lactic acid bacteria are found to grow on consumption of prebiotic, which have beneficial effects on the host. Consumption of galacto-oligosaccharides (GOS) and fructo-oligosaccharides (FOS) have been shown to increase the population of *Bifidobacterium* and *Lactobacillus*, whereas *Clostridium* population is decreased at the same time.[20] Health benefits have been observed in obese women, fed with inulin type fructan for three months, whose microbial profile and fat metabolism were altered.[18] Therefore, prebiotics are found to possess not only positive impact on microbial composition but also have health benefits associated with it.

Synbiotics as modulating factor - synergistic effect of (pro+pre) biotics

Synbiotics are mixtures of probiotics and prebiotics working synergistically in the digestive tract. Probiotics add live microorganisms, whereas prebiotics affect the microbes already present in the gut. Combination of these two adds up individual benefits and provides a gut atmosphere, where added microbes from probiotics benefit the host and harmful microbes are discouraged to grow by the prebiotics. It is quite possible that prebiotics provide an atmosphere for probiotics to survive longer in the intestine.

Fecal microbiota transplantation (FMT) as modulating factor

Fecal microbiota transplantation (FMT) is simply the process of placing fecal microbes from a healthy donor to patients with gastrointestinal disorder (dysbiosys).[21] FMT is practiced since centuries and the very first report came from China during the 4th century, where feces, called yellow soup, were used to treat diarrhea and food poisoning.[22] In subsequent centuries, it was used in China to treat other GI related disorders. In modern medical science first medical record of FMT was reported by Eiseman and his colleagues, who successfully treated patients with FMT for pseudomembranous colitis in 1958.[23] Subsequent use of FMT by Els (2013) for the treatment of *C. difficile* infection (CDI) and recurrent *C. difficile* infection(rCDI) with a success rate of almost 90%, placed it as effective and viable option for the treatment of gastrointestinal disorders.[24] After the success on CDI treatment, interest on FMT has grown many folds and FMT has been used for the treatment of ulcerative colitis (UC), inflammatory bowel diseases (IBD), irritable bowel syndrome(IBS), constipation, and other GI related

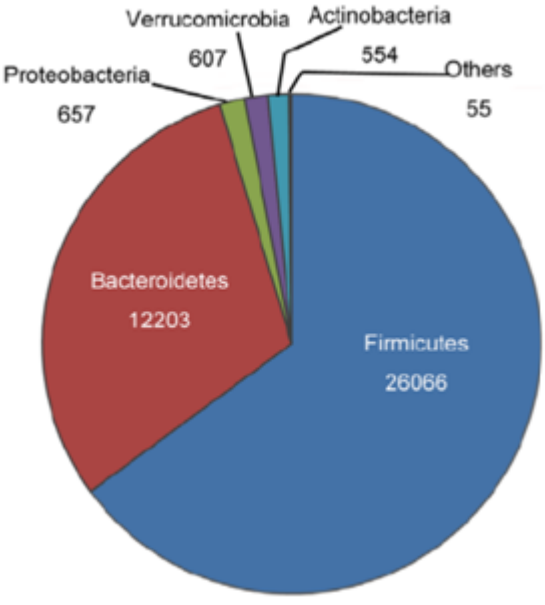

Figure 1. Gut bacteria composition. The pie chart shows the distribution of gut bacteria. Others are: *Spirochaetes, Fusobacteria, Deferribacteres, Cyanobacteria, Planctomycetes, Lentisphaerae,* TM7, and *Tenericutes*. Of the thirteen phyla, the *Firmicutes* and *Bacteroidetes* occupy 65% and 30% of the pie, respectively, while the rest eleven phyla take up 5%. (Picture reproduced with permission from the authors.)[17]

problems. Although very few serious side effects have been reported with FMT so far, the risk involved in transferring live organisms from a healthy donor to a serious patient cannot be ruled out. However, with effective tools for screening of donor (medical and lifestyle record), screening of harmful organisms in stool (e.g. resistant bacteria) and proper methods to prepare stool may reduce some of the adverse impacts.[25] It may be possible in the future to replace FMT with specific bacteria depending upon the disease to be treated (targeted bacteriotherapy).[25,26] In order to perform targeted bacteriotherapy, specific bacteria have to be identified with the disease concerned. This will probably eliminate the chances of transferring unwanted microbes from the donor to the patient. In comparison, probiotic/prebiotic treatment is temporary and lasts only for a few days whereas, FMT can persist for longer and repeat treatment/s can prolong it further.[21]

Physical Exercise and Fasting as modulating factor

The health benefits exerted by physical exercise are a well-known fact. However, not much is known about the influence of exercise on gut microbiota composition. Animal experiments on rodents by Allen and co-workers[27] indicated that exercise can alter the gut microbiota composition. They have demonstrated that microbial transplants from exercise-trained mice (donor) to mice with induced acute colitis (acceptor) led to differences in microbiota β-diversity, metabolite profiles, colon inflammation, and body mass. However, more research in humans is required to shed more light into this relationship.[27]

Research in animal models also supported the fact that fasting affected the microbiome. These studies showed that fasting increased microbial diversity, reduced inflammation, and increased production of short-chain fatty acids. Intermittent fasting also decreased cognitive impairment and increased levels of several hormones and neurotransmitters.The effect of fasting have been observed in individuals with increased levels of beneficial gut bacteria such as *Akkermansia, Faecalibacterium* and *Roseburia* after Ramadan, a religious fasting observed by the Muslims.[28]

Business Opportunities

Covid-19 pandemic has impacted businesses globally in many ways. But the synbiotics market has been impacted positively with a surge in consumption of these products and thus increased market share. During the initial period of Covid-19 pandemic, consumption of probiotics increased several fold. A survey conducted by Natural Marketing Institute in May 2020 concludes an exponential surge in consumption of probiotics in the US (66%), Italy (188%), and China (108%) over a period of 6 months.[29]

The global probiotics market was valued at USD 58 billion in 2021 and is projected to be USD 111 Billion in 2030. The market is projected to grow at a compound annual growth rate (CAGR) of 7.5% from 2021 to 2030.[29]

Entry of prebiotics as a supplementary diet into the market is more recent and hence market value is less compared to probiotics. The global prebiotics market size was valued at USD 6.05 billion in 2021 and is expected to grow at a compound annual growth rate (CAGR) of 14.9% from 2022 to 2030.[30]

Enormous possibilities exist to take advantage of the growing business opportunities and contribute to the healthcare industry for entrepreneurs from India. The major players in synbiotics, which came to my notice, are all MNCs. The presence of Indian companies, if at all any, is negligible.

Conclusion

Sedentary lifestyle and changing food habits (due to easy availability of global foods) are impacting the well-being of a person enormously. Gut-related diseases such as constipation, ulcerative colitis (UC), irritable bowel syndrome (IBS), gastroesophageal reflux disease (GERD), and inflammatory bowel disease (IBD) have become common illnesses and are expected to rise.

Diet, no doubt, is an important player in nurturing a healthy lifestyle. However, long-term or habitual planning is essential to reap the benefits. Pro- and/ or pre-biotics, when consumed in adequate amounts, improve gut health and reduce inflammation. They also play an important role in preventive healthcare by strengthening the immune system. Synbiotics has emerged as a supplementary diet with increasing awareness to treat illnesses in a natural way and its consumption is going to increase with more awareness and launch of new products. Prebiotics are susceptible to hydrolysis and a sizable portion of probiotics are assumed to perish in the stomach before reaching the intestine. Therefore, more research is required for new delivery techniques and personalization products (fine-tuning the requirements of a person) will be an added advantage. It may be assumed that people will carry gut cards in the future like soil cards (for farmers) to match the personalized requirements.

FMT has already been found to be the preferred

option for CDI and rCDI. It has also been successfully utilized for the treatment of constipation, ulcerative colitis (UC), irritable bowel syndrome (IBS), gastroesophageal reflux disease (GERD), and inflammatory bowel disease (IBD). Many more diseases are expected to be included for treatment with FMT in the future. Physical exercise and fasting also modulate gut microbiota and impart health benefits.

References

1. Stojanov S, Berlec A and Štrukelj B 2020 The influence of probiotics on the Firmicutes/Bacteroidetes ratio in the treatment of obesity and inflammatory bowel disease. Microorganisms 8 1715
2. https://www.healthydirections.com/articles/digestive-health/role-of-yeast-and-bacteria?closebox=true
3. Thursby E and Juge N 2017 Introduction to the human gut microbiota.Biochem. J. 474 1823
4. Baeckhed F, Ley R E, Sonnenberg J L, Peterson D A and Gordon J I 2005 Host-bacterial mutualism in the human intestine. Science 307 1915
5. Sender R, Fuchs S and Milo R 2016 Revised Estimates for the Number of Human and Bacteria Cells in the Body. PLoS Biol. 14 1002533
6. Blaser M J, Devkota S, McCoy K D, Relman D A, Yassour M and Young V B 2021 Lessons learned from the prenatal microbiome controversy. Microbiome 9 8
7. Bezirtzoglou E, Tsiotsias A and Welling G W 2011 Microbiota profile in Feces of breast- and formula-fed newborn by using fluorescence in situ hybridization (FISH). Anaerobe 17 478
8. Hasan N and Yang H 2019 Factors affecting the composition of the gut microbiota, and Its modulation. PeerJ 31440436
9. Choi S, Hwang Y J, Shin M J and Yi H 2017 Difference in the gut microbiome between ovariectomy-induced obesity and diet-induced obesity. J. Microbiol. Biotechnol. 27 2228
10. Goodrich J K, Waters J L, Poole C, Sutter J L, Koren O, Blekhman R, Beaumont M, Treuren W V, Knight R, Bell J T, Spector T D, Clark A G and Ley R E 2014 Human genetics shape the gut microbiome. Cell 159 789
11. https://www.newscientist.com/article/dn26519-composition-of-your-gut-bacteria-may-be-inherited/
12. Rothschild D, Weissbord O, Barkan E, Kurilshikov A, Korem T, Zeevi D, Costea P I, Godneva A, Kalka I N, Bar N and Shilo S 2018 Environment dominates over host genetics in shaping human gut microbiota. Nature 555 210
13. Windey K, Preter V D and Verbeke K 2012 Relevance of protein fermentation to gut health. Mol. Nutr. Food Res. 56 184
14. Zar F A, Bakkanagari S R, Moorthi K M L S T and Davis M B 2007 A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. Clin. Infect. Dis. 45 302
15. Kumar M, Babaei P, Ji B and Neilson J 2016 Human gut microbiota and healthy aging; recent developments and future prospective. J. Nutr. Health Aging 4 3
16. Mueller S, Saunier K, Hanisch C and Norin E 2006 Differences in fecal microbiota in different European populations in relation to age, gender, and country: a cross-sectionalstudy. Environ. Microbiol. 72 1027
17. Yang X, Xie L, Li Y and Wei C 2009 More than 9,000,000 unique genes in human gut bacterial community: estimating gene numbers inside a human body. PLoS One 4 6074
18. Leeming E R, Johnson A J, Spector T D and Roy C I L 2019 Effect of diet on the gut microbiota: rethinking intervention duration. Nutrients 11 2862
19. Rokka S and Rantamaki P 2010 Protecting probiotic bacteria by microencapsulation: challenges for industrial applications. Eur. Food Res. Technol. 231 1
20. Vandenplas Y, Zakharova I and Dmitrieva Y 2015 Oligosaccharides in infant formula: more evidences to validate the role of prebiotics. Br. J. Nutr. 113 1339
21. Wang J W, Kuo C H, Kuo F C, Wang Y K, Hsu W H, Yu F J, Hu H M, Hsu P I, Wang J Y and Wu D C 2019 Fecal microbiota transplantation: Review and update. J. Formos. Med. Assoc. 118 S23
22. Zhang F, Luo W, Shi Y, Fan Z and Ji G 2012 Should we standardize the 1,700-year-old fecal microbiota transplantation? Am. J. Gastroenterol. 107 1755
23. Eiseman B, Silen W, Bascom G S and Kauvar A J 1958 Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. Surgery 44 854
24. Van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal E G, de Vos W M, Visser C E, Kuijper E J, Bartelsman J F, Tijssen J G and Speelman P 2013 Duodenal infusion of donor feces for recurrent Clostridium difficile. N. Engl. J. Med. 368 407
25. Giles E M, D'Adamo G L and Forster S C 2019 The future of faecal transplants. Nat. Rev. Microbiol. 17 719
26. Mcilroy J R, Segal J P, Mullish B H, Quraishi M N, Gasbarrini A, Cammarota G and Ianiro G 2019 Current and future targets for faecal microbiota transplantation. Hum. Microbiome J. 11 100045
27. Allen J M, Mailing L J, Cohrs J, Salmonson C, Fryer J D, Nehra V, Hale V L, Kashyap P, White B A and Woods J A 2018 Exercise training-induced modification of the gut microbiota persists after microbiota colonization and attenuates the response to chemically-induced colitis in gnotobiotic mice. Gut Microbes 9 115
28. https://insight.microba.com/the-truth-about-intermittent-fasting-and-the-gut-microbiome/
29. Probiotics Market Size/Industry Report, 2021-2030 www.grandviewresearch.com/probiotics-market
30. Global Prebiotics Market Size, Share & Trends Report, 2030 www.grandviewresearch.com/industry-analysis/prebiotics-market.