

Gut Microbiota in Health and Disease: A Comprehensive Review of Microbiome-Driven Therapeutics

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Abstract

The human gastrointestinal microbiome is a highly intricate network of trillions of biological microorganisms that include complex microbial ecosystems that are useful to the human health status by governing digestion, immunity, metabolism, and neurological health. Microbial imbalance, also known as dysbiosis, has been associated with diverse pathologies, such as gastrointestinal diseases (e.g. IBD, IBS), metabolic disorders (e.g. obesity, diabetes) and neuropsychiatric disorders. Future microbiota-based interventions including probiotics, prebiotics, synbiotics, postbiotics, and fecal microbiota transplantation (FMT) provide hopeful avenues that solve this problem by restoring microbe-biotic balance and alleviating these disorders. FMT proved to be amazing in frequent infections of *Clostridioides difficile*, whereas probiotics and prebiotics have revealed promise in treating IBS and metabolic disorders. There are, however, some difficulties such as the absence of clear mechanisms of actions, strain-specific variability, and the necessity of personalized methods. As well, the functions of non-bacterial microbiota (e.g., fungi, viruses) are understudied. This article will summarize the recent literature, show the current achievements in treatment, and outline research gaps in light of necessity to conduct more clinical trials and interdisciplinary research to realize the full potential of microbiome-based medicine. Filling these gaps may transform the treatment approaches to the disease of the gut and bodywide diseases.

Keywords: Gut Microbiota, Dysbiosis, Probiotics, Prebiotics, Fecal Microbiota Transplantation, Microbiome Therapeutics.

Background

Gut microbial ecosystem is the population of trillions of microorganisms (primarily bacteria, but also fungi, viruses and archaea) inhabiting the human gastrointestinal tract (1). These microorganisms are critical in the digestion process, regulation of the immune system, mood, and behaviors (2). The gastrointestinal tract of a human harbours a complex and evolving assemblage of microorganisms, which are commonly termed the gut microbiota (3). This cluster of diverse microbial community of bacteria, archaea, viruses, fungi, and protozoa is essential in

the health of the host (4). An estimate is that there are trillions of microbes in the human gut, including more than 1,000 distantly related bacterial species, with hundreds of bacterial species mostly in the phyla *Firmicutes*, *Bacteroidetes*, *Actinobacteria* and *Proteobacteria* (5). The gut microbiome that consists of all the genomes of these microbes, is found to harbor 100-fold or more genomic information compared to the human genome owing to its tremendous metabolic potential and regulatory capacity (6).

Gut microbiota colonization of the human body starts at birth, and it is in a dynamic stage throughout infancy due to various factors, found mostly in the mode of delivery, breastfeeding, diet, exposure to antibiotics and the environmental condition (7). So much so that by the age of three, there is a relatively stable adult-like microbial composition, which with age, lifestyle and disease statuses continues to evolve (8). These microbes undertake a broad range of critical duties such as the digestion of dietary fibers, the synthesis of vitamins (among them B and K), host metabolism regulation, immune-modulation and defence against pathogenic microbes (9). Specifically, fermentation of indigestible carbohydrates has led to the generation of short-chain fatty acids (SCFAs), which play an important role in maintaining colonic health, regulating the immune response, and energy metabolism (10). The role of a well-balanced and diverse microbiota in the gut commonly known as eubiosis has been taken into consideration more in recent years (11). Dysbiosis, or an aberration in the structure or activity of the intestinal microbiome, on the contrary, has been related not only to a broad range of gastrointestinal conditions, comprising inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) but also to systemic disease, including obesity, type 2 diabetes, cardiovascular disease, autoimmune disease, and neuropsychiatric maladies as well (12-14). This accumulating evidence has created enormous curiosity in the use of probiotics, prebiotics, synbiotics, postbiotics and fecal microbiota transplantation (FMT) as therapeutic interventions against alterations in the gut microbiota (15-17).

Therapeutic Uses of Gut Microbiota

Fecal Microbiota Transplantation (FMT)

Fecal Microbiota Transplant (FMT) is one of the long-standing therapeutic uses of the microbiota of the gut (18). This process entails insertion of processed fecal matter of a well person into the intestinal system of a sick client (19). FMT aims to restore a natural microbial composition and maturity of the gut microbiome possibly impaired by a disease or antibiotic intake, or other environmental and hereditary factors (20). FMT has proven to be a huge success when treating *Clostridioides difficile* infection (CDI) specifically those that are either difficult to treat cases or those that are recurrent cases of infections even after the use of traditional antibiotics to treat them (21). CDI can frequently occur following an extended antibiotics therapy, which disturbs the normal composition of gut microbiome and permits pathogenic strains, such as *C. difficile*, to settle and take over the intestinal environment (22). Through regulation of the overgrowth of pathogens and restoration of a stable intestinal ecosystem, FMT successfully eliminates the overgrowth of pathogenic microbes and balances its microbiome again by reintroducing a diverse and healthy microbial population (23). In addition to its potential in CDI, FMT is also under active study as possible benefit in multiple other diseases caused by gut dysbiosis (24). It has been investigated as a potential therapy in controlling the inflammatory bowel disease (IBD) including ulcerative colitis and Crohn disease where gut microbiota alteration can potentially lead to persistent inflammation in the bowel tract (25-28). Despite inconclusive results and the necessity of more clinical trials, FMT has already demonstrated its potential in remission induction in a part of IBD patients (29). It also finds use in the study of irritable bowel syndrome (IBS), a popular functional gastrointestinal disease that is believed to be caused by imbalance of the microbes, immune stimulation, and alteration in gut-brain communication (30-32). Even more interesting to note, scientists are now studying the gut microbiota-central nervous system

causation paving the way to FMT as a potential therapeutic solution in autism spectrum disorder and other neurological conditions, including Parkinson and even in major depressive disorder (33, 34). The rationale of such studies involves the notion of gut-brain axis which is a composite two-way communication linkage between the gut microbiome and the brain made possible via neural, immune, and hormonal systems (35-37).

Probiotics

Probiotics are defined as live microorganisms, which provide benefit to host and primarily refers to the live bacteria, and few yeasts in sufficient quantity when taken in (38). They are usually taken by eating dietary supplements or natural fermented food (e.g. yogurt, kefir, sauerkraut or kimchi) (39). The main idea of probiotic treatment is to improve or repair a healthy organism with the microbiome, especially those with dysbiosis of the microbiome of gut because of the disease, antibiotics, or unhealthy eating (40-42). The probiotics were quite researched in the treatment of bowel health, and most prevalent used to treat the occurrence of antibiotic-related diarrhea (AAD), which is a typical side effect of an antibiotic treatment during which the breakdown of the intestinal microbiome causes the manifestation of gastrointestinal symptoms (43-46). In this essence, some probiotics have exhibited considerable effectiveness including: *Lactobacillus rhamnosus GG* and *Saccharomyces boulardii* (47, 48).

Besides the use in improvement of AAD, probiotics are also employed as a treatment to help improve mild gastrointestinal problems, such as irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD), especially ulcerative colitis (49, 50). Although probiotics are not considered a separate treatment of such chronic conditions, they can possibly decrease the symptoms of bloating, gas, abdominal pain, and bowel inconsistency (51, 52). Moreover, certain strains of probiotics would help in managing lactose intolerance because they help in lactose digestion through production of enzyme lactase (53). There is also some evidence that probiotics would affect immune response, low level systemic inflammation, and metabolism positively (54, 55). Nevertheless, the efficacy of probiotics is extremely strain-specific, and their effects differ based on the disorder under treatment, the dose, and the prevalence of the cuts microbiota composition of an individual (56). In general, despite the relatively low toxicity of probiotics as a method of microbe-based treatment, their application to the clinical practice needs paying special attention to the choice of strain, composition, and length of treatment in order to achieve the best outcomes (57, 58).

Prebiotics

Prebiotics are food ingredients that are non-digestible carbohydrates (usually dietary fibre) that have a selective effect in favoring the growth or activity of one or more health-promoting bacteria in the gastrointestinal tract whereas exerting a non-effect or less marked effect on the activity or growth of the overall bacterial content of the gastrointestinal tract, thus promoting (but not inducing) health benefits in the host (59, 60). Whereas, probiotics introduce live microorganisms in the gut, prebiotics act as food sources of the indigenous beneficial microbes, specifically, Bifidobacteria and Lactobacilli and stimulate their growth and metabolism (61). Inulin, fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS), resistant starches: these are some of the widely studied and commonly used prebiotics; as they cannot be digested in the upper gastrointestinal tract, they reach the colon where they are fermented by the host tissue microbiota (62). The fermentation is utilized to produce short chain fatty acids (SCFAs) namely, butyrate-acetate and propionate, they are important to safer intestinal barrier, regulation of the immune response, display of anti-inflammatory effects across the gut and far (63).

Prebiotics have been linked with a variety of health advantages, which comprise fluids health preservation, filed decrease in gastrointestinal inflammation, and increases of minerals absorption, especially calcium and magnesium, which are vital in mending bones (64). Moreover, prebiotics through promoting a balanced microbial ecosystem could prevent the development of metabolic diseases (obesity and type 2 diabetes), as well as could also contribute to the regulation

of appetite and body weight by gut-brain signaling pathways (65). There is now an increased use of incorporating them in functional foods and dietary supplements, not only as preventative agents but also as supplements to treatment in such diseases as inflammatory bowel disease (IBS), irritable bowel syndrome (IBS) and colorectal cancer (66). Prebiotics are generally safe and are well-tolerated; however, on occasions excessive dosages may cause gastrointestinal discomfort that includes bloating and flatulence because of over-fermentation (67). However, selective application of prebiotics is an attractive and non-invasive approach to influence the intestinal microbiota to the benefit of the host (68).

Synbiotics

Synbiotics are a combination of probiotics (live beneficial microorganisms) and prebiotics (non-digestible fibres that supports the growth of these microorganisms), synbiotics are formulated to work together to improve the survival, colonization and activity of beneficial bacteria in the gastrointestinal tract (69). Synbiotic therapy is based on the fact that probiotics do not succeed, when introduced into the intestine, because of the lack of a suitable environment that would help them proliferate in the intestine and perform their metabolic activity, hence, synbiotic therapy maximizes their therapeutic potential (65). This combined strategy not only allows addressing some of the shortcomings that are inherent in probiotics, e.g., their failure to survive the acidic gastric environment, but also provides the opportunity to make the introduced or pre-existing beneficial microbes flourish and realize their health-beneficial properties during a longer period (70).

Synbiotics are under investigation as the means of manipulating the gut microbiome in a number of clinical situations, such as gastrointestinal disorders, metabolic disorders and immune system disorders (71). As an example, it has been found that synbiotic formulations may be effective in relieving irritable bowel syndrome (IBS) symptoms, boosting immune system, lowering systemic inflammation, and promoting integrity of gut barrier (72). They are also under investigation regarding their potential use in managing metabolic syndrome, where alterations in the bowel microbiome have the ability to alter lipid metabolism, insulin sensitivity and weight (73). Also, after their potential use as antimicrobials, antibiotic treatment or gastrointestinal infection, synbiotics can assist in returning the microbial balance and guard against opportunistic infections, including *Clostridioides difficile* (74). The effectiveness of synbiotics is based considerably upon the particular mix of probiotic strains and prebiotic substrates included, since not all may be synergist (75). Scientifically based careful formulation should therefore be called upon to maximise clinical benefits of this compound. Consequently, synbiotics present an interesting horizon in microbiota-focused medication, providing a greater and longer-term approach to fuel gut and general health (76).

Postbiotics

The postbiotics are the bioactive compounds that are produced as probiotics perform the fermentation processes inside the gut (77). Contrary to probiotics, which are living microorganisms, or prebiotics, which are the substrates, postbiotics, are non-living microbial products or byproducts that can have positive impacts on the health of the host (78). These are a number of molecules that include short chain fatty acids (SCFAs) including butyrate, acetate and propionate, enzymes, peptides, polysaccharides, cell wall fragments and bacterial lysates (79). Specifically, SCFA has received much attention because of its centrality in preserving intestinal barrier integrity, inflammation, and energy production to colonocytes (80). Beneficial gut bacteria produce postbiotics during normal fermentation of dietary fibers and other complex carbohydrates, and exert both local effects in the gut and systemic effects via the circulation (81).

The therapeutic ability of postbiotics is related to their capacity of regulation of the immune system, antioxidant effect, and anti-inflammatory effect, and they have a high interest in the prevention and treatment of gastrointestinal and systemic diseases (82). As an example, butyrate

was demonstrated to reduce the levels of pro-inflammatory cytokines and reinforce the intestinal mucosal barrier, which plays a vital role in such diseases as inflammatory bowel disease (IBD) and colorectal cancer. Also, postbiotics have the capacity to favor antioxidant effects, shield infection even by pathogenic germs, as well as encourage both metabolic and neurological processes through the gut-brain axis (83). Since postbiotics are dead, they have a minimal risk associated with microbial veracity, genetic conveying, or infectious issues, making them particularly attractive to the vulnerable groups, including neonates, immunocompromised patients, and the elderly. With a stable composition, and generally safety profile, and a growing body of evidence pointing to efficacy, postbiotics can be considered a new and promising category of microbiome-based therapeutics, more clinical study is required before a full picture of their molecular mechanisms of action can be developed and ideal applications to medicine can be identified (84).

Diseases Targeted by Microbiota-Based Therapy

Gut microbiome has such an important role in ensuring immune, metabolic, and neurological homeostasis, microbiota-based treatments have proven highly promising in preventing and treating a diverse array of diseases, gastrointestinal, as well as systemic (85). Fecal microbiota transplantation (FMT) has been applied in a variety of clinical conditions, but the most established one is the use of FMT as an adjunctive treatment in patients with recurrent *Clostridioides difficile* infection (CDI), which has shown extensive rates of efficacy in eliminating recurrence in resistant antibiotic cases (86). Within the context of inflammatory bowel diseases (IBD), which entails ulcerative colitis and Crohn disease, probiotic and prebiotics and FMT therapies have been explored with respect to their capacity to suppress gut inflammation and rectify dysbiosis, however, with mixed results varying on the degree of IBD and microbial profile. The other is irritable bowel syndrome (IBS), a functional bowel disorder in which microbial dysbiosis has been linked and the microbiota-based therapy has been involved in relief of symptoms (bloating pain, and Hindgut abnormalities) (87).

In addition to gastrointestinal disease, microbiota-based interventions are also being studied in metabolic diseases, especially obesity and type 2 diabetes, in which the intestinal flora regulates insulin resistance and energy gain and deposition of fats (88). The impact of the gut microbiome in neurological health has been of interest more recently both in autism spectrum disorders (ASD) and other mental diseases such as depression and anxiety. These are believed to be through the gut-brain axis, which is a complex communication system between the central nervous system and the enteric microbiome through the immune, neural and endocrine routes (89). Studies involving experiments indicate that alteration of gut flora could influence the level of neurotransmitters, stress responses, and behavior. The effectiveness of cancer therapy has also become a possible determinant of the gut microbiome in oncology, with great effort applied in its role in improving the efficacy of the immune checkpoint inhibitors on cancer immunotherapy (90). Some commensal bacteria have now shown the ability to enhance anti-tumor immunity and active research continues to define how microbiota engineering could enhance anti-tumor response and mitigate side-effects of treatment. Altogether, these findings demonstrate how broad are the effects of gut microbiome on human health and disease setting the path towards use of microbiota-based treatments as a novel tool in contemporary medicine (91).

Study Gaps

Although there is multiple researches of literature regarding the microbiota of the gut and its possible use as therapy, there exist holes in it. To start with, the mechanisms of the action of particular microbial strains or their metabolites (e.g., postbiotics) remain unclear, especially in the case with systemic diseases such as neurological or metabolic syndromes. Second, although FMT demonstrates some potential in terms of treatment of such conditions as IBD and IBS, its long-term effectiveness, safety, and optimal conditions of practice (e.g. selection of donors, administration methods) are yet to be researched. Third, strain specific and individual differences

in the reaction to probiotics, prebiotics and synbiotics actually require the more individual attention, although standardised recommendations are not yet available. Moreover, the majority of research has been done on bacterial constituent ignoring fungi, viruses, and archaea contributions to the gut ecosystem. And the final and perhaps most obvious issue is that clinical trials are generally not so diverse, which constrains the applicability of results. These gaps might be filled to make microbiota-based treatments more accurate and efficient.

Rationale

Gut microbiota is a key determinant of human health with important impacts on digestion, immunology, metabolism, or even neurology. Dysbiosis has been associated with a multiplicity of diseases: gastrointestinal disease, metabolic diseases, and mental illnesses. Although probiotics, prebiotics, synbiotics, postbiotics, and fecal microbiota transplantation (FMT) therapies have some promise, their mechanisms, efficacy, and ideal applications are not totally comprehended. The proposed study will summarize the available evidence, determine gaps in research, and point out the perspectives of microbiota-based treatment. In bridging these gaps, the value of the research is to find personalized, effective treatments of guts and the overall diseases, and eventually change the fate of the patients and increase the potential of therapeutic opportunities in microbiome medicine.

Conclusion

Gut microbiome is a complicated and evolving environment involved in sustaining human health by affecting digestion, immunity, metabolism, and even neurological ability. The dysbiosis has been reported to be the cause of various diseases, including not only diseases of the gastrointestinal tract such as IBD and IBS, but also systemic diseases, among which one can distinguish obesity, diabetes, and neuropsychiatric diseases. The new approaches to therapy, such as probiotics, prebiotics, synbiotics, postbiotics, and FMT have a great potential to change the microbial imbalance and resolve these disorders. Nevertheless (there are) issues, which consist in fine mechanisms, maximisation of treatment regimes, tolerance to variability of response between individuals. Future studies should target the personalized microbiome-based treatments, their long-term safety and the roles of less-studied parts of microbiome (fungi and viruses). By closing this gap, a microbiota-based intervention might transform contemporary medicine by supplying it with new, effective methods of treatment of the gut, and the disease of the systemic body. Further multidisciplinary cooperation and clinical investigations will be required to fully realize the potential of the gut microbiome in human wellbeing.

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