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## Review article

# The gut microbiome and its use as a target for novel therapeutic modalities

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## ABSTRACT

**Background:** The human microbiome is the complete microorganisms in addition to their genes inhabiting the human body. The gut microbiome is the most important part of the human microbiome. The gut microbiome serves many benefits to the host. It can ferment non digestible substrates, boost the immune system, suppress the growth of harmful microbiota, modulate gut development, metabolize xenobiotics, produce short-chain fatty acids, and produce favorable vitamins to the host. Gut dysbiosis is a factor in many disease states as obesity, various metabolic disorders, inflammatory bowel syndromes, cardiovascular diseases, and cancer. So novel therapies that can improve the human microbiome especially gut microbiome can be an addition to the conventional therapeutics. Novel therapeutics that improve the gut microbiome includes probiotics, prebiotics, synbiotics, psychobiotics and some metabolites. Other modalities that affect the microbiome were invented as faecal microbiota transplantation, phages, and emerging miRNAs. Fecal microbiota transplantation is now an approved method for management of patients of recurrent pseudomembranous colitis.

## Introduction

The term microbiome (Micro is a Greek word used for "small" and bios for "life") was first used for the first time in 1952 by J.L. Moore. It was in Scientific Monthly magazine which was used as a concept of microorganisms in an environment [1]. The term microbiome is not widely used except after it was used by Nobel Laureate Microbiologist "Joshua Lederberg" in 2001 [1]. Another term which sometimes is used interchangeably with the human microbiome is the human microbiota; is the collection of microorganisms inhabiting the human body mainly the gut and other sites as skin, mouth, eye, vagina.

The study of microbial communities was revolutionized by the discovery of DNA, and new molecular technologies as sequencing technologies

and cloning techniques. These techniques have changed microbial ecology since metagenomics and high-throughput genome sequencing offer efficient methods for addressing the functional capabilities of individual microbes. Multi-omics technologies now offer precise data on microbial activity in the environment, such as the metatranscriptome, metaproteome, and metabolome methods [1,2,3].

In this review article, we will shed light on gut microbiome and then will discuss novel therapeutics that target to improve the gut microbiome as probiotics, prebiotics, synbiotics, psychobiotics and the use of fecal microbiota transplantation.

## Gut microbiome

Gut microbiome is the group of microbes present in human gastrointestinal tract. This

bacterial flora resides mainly in the large intestine. It weighs about 1.5 kilograms. These bacteria aid the digestive process in humans early after birth, and meanwhile both the intestinal epithelium and mucous layer that secretes, develop in a way that enables these flora to be tolerated, and provides support to these beneficial microbes [2].

Because of the low gastric pH, the majority of microbes reaching the stomach die. The main stomach flora include: *streptococcus* spp, *staphylococcus* spp, *lactobacillus* spp, and yeast species. *Helicobacter pylori* (*H. pylori*) settle on the mucosa of the stomach. *H. pylori* chronic infection can cause chronic gastritis and peptic ulcer disease, and stomach cancer [4].

Few microorganisms inhabit the small intestine due to its proximity to the stomach acidity. Gram-positive cocci and *Bacillus* are the dominant microbes present in the small intestine. Enterobacteriaceae present in the distal part of small intestine due to its alkaline pH. The intestinal microflora provide signals that regulate the development and function of the intestine. Small intestinal bacterial overgrowth may cause its insufficiency. The largest microbial flora in our body is present in the large intestine. The total bacterial load in stool is about 10<sup>11</sup> bacteria/g. Obligatory anaerobic bacteria such as *Bacteroides* and *Bifidobacterium* constitutes the great majority (99%) of the gut flora. These gut flora constitute about 60% of the dry mass of stool [4].

Many bacterial species (between 300 and 1,000 spp) live in the gut. Firmicutes and Bacteroidetes dominates gut microbiota (90%). Other bacterial phyla that can inhabit the large intestine are Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia. Fungi and protists can also be part of the intestinal flora [5].

The relationship between gut microbiota and human being is not only a commensalism, but one of mutuality and symbiosis. Gut microbiota perform many benefits to the host. It can ferment non digestible substrates, boost the immune system, suppress the growth of harmful microbiota, modulate gut development, metabolize xenobiotics, produce short-chain fatty acids, produce favorable vitamins to the host as vitamin K and produce hormones to direct the body toward fat storage. Gut microbiome also influences a variety of processes, including the maturation of immune and hematopoietic cells, the rate of thermogenesis in

brown adipose tissue, the expression of the circadian clock gene, and the health of the blood-brain barrier. [6].

The gut dysbiosis can be linked to many disease states within the human body, including periodontitis and caries, obesity, metabolic syndrome, fatty liver disease, inflammatory bowel diseases, cardiovascular diseases, cancer, as well as chronic kidney diseases [6, 7].

### **Novel therapeutic modalities acting on gut microbiome**

It is widely reported that the gut dysbiosis can be a factor in many disease states. Conventional therapeutics are effective in most disease states but unfortunately much conventional therapeutics have adverse effects. So novel therapies that can improve the human microbiome especially gut microbiome can be an addition to the conventional therapeutics.

Novel therapeutics that improve the gut microbiome include probiotics, prebiotics, synbiotics, psychobiotics and some metabolites. Other modalities that affect the microbiome were invented as faecal microbiota transplantation, phages, and emerging miRNAs. Faecal microbiota transplantation is now used to treat recurrent *C. difficile* [8].

### **Probiotics**

Probiotics are defined as live microbes taken as supplements that favorably affect the host by causing the microbiota balance in the GIT [9]. It should survive the conditions of digestive system and can pass through it. It should not be pathogenic to the host [10]. The probiotic organisms colonize the gut; suppress the penetration of pathogenic microscopic organisms to gut epithelium through the improvement of intestinal hindrance work. These probiotics can enhance host mucosal and systemic immunity. It can increase the production of vitamins, minerals, short-chain fatty acids (SCFAs), and growth modulators to enhance the intestinal epithelium. It promotes antioxidants, cytokines (IL-2 and IL-12), and anti-angiogenic factors [11].

The bacterial genera mostly used as probiotics are *lactobacilli*, *Bifidobacterium*, *Streptococcus*, *Bacillus*, *Enterococcus* and the fungus *Saccharomyces* [12].

The probiotics have anti-inflammatory effects so it reduces the necrosis which improve the colonic condition in inflammatory bowel diseases. The probiotics decrease blood cholesterol via many

mechanisms. It can assimilate cholesterol, and bind it to cellular surface. It can co-precipitate cholesterol, and interfere with the formation of micelle for intestinal absorption, and bile acids deconjugation through the secretion of bile salt hydrolase [13].

The probiotics have an effect in dental health as they are associated with decreased colony forming units (CFU) counts of cariogenic pathogens. Probiotics also suppress periodontal pathogens as *L. rhamnosus* GG could suppress the colonization of cariogenic *streptococci*, thus helping to reduce tooth decay incidence in children. Many probiotic strains can ameliorate halitosis as *Weissella cibaria* produce hydrogen peroxide that inhibits *Fusobacterium nucleatum* and its volatile sulphur compounds production [14].

Supplementing with probiotics mainly may help in preventing diarrhea by repopulating and maintaining beneficial gut bacteria and correcting bacterial imbalance. *Lactobacillus rhamnosus* GG is used to treat diarrhea in both adults and children, *Saccharomyces boulardii* and *Lactobacillus casei* have been shown to treat antibiotic-associated and infectious diarrhea. *Bifidobacterium lacti* decrease the frequency and severity of pediatric diarrhea [15].

Probiotics help in management of antibiotic resistance as using Probiotics in treating infectious diseases lessens the use of antibiotics so it can lessen the problem of antibiotic resistance. Probiotics can help to treat antibiotic resistant infections as *Helicobacter pylori* (*H. pylori*) management. Lately, increased resistance to key antibiotics of *H. pylori* triple therapy so its efficacy decreased lower than 70%. So Many trials were done to investigate the effect of probiotics on *H. pylori* gastritis. The probiotic strain most frequently used is *L. johnsonii* La1, either in a fermented milk preparation containing live bacteria or as a free-cell culture supernatant. Other strains used are *L. brevis*, *L. casei*, and *L. gasseri* OLL2716. While two other studies used yogurts containing mixtures of live probiotic bacteria, some studies showed a statistically favorable effect of probiotic treatment on *H. pylori* gastritis but unfortunately no study proclaimed the cure of *H. pylori* infection by probiotics alone [16]. The addition of probiotics to standard antibiotic treatment improved *H. pylori* cure rates to 81%. Probiotics use also decreases the adverse effects of current medication therapy [17].

Many studies done proved the antagonistic effect of probiotics against multi-drug resistance

(MDR) pathogens [18]. **Ibraheem et al.** [19] tested the effect of *Lactobacillus acidophilus* and *Saccharomyces cerevisiae* against MDR isolates of *S. typhimurium* in vitro and in vivo by using the mouse as an animal model of the infection. They found that increased concentration of probiotic filtrate could increase the inhibition zone. Mouse oral administration of both probiotic isolates could decrease the counts of *S. typhimurium* in liver and spleen of infected mouse.

**Moghadam et al.** [20] investigated the effect of combination of probiotics with different antibiotics against Thirty burn MDR isolates of *P. aeruginosa*. The probiotics tested were *L. plantarum* 299 (DSM9843), *L. reuteri* (DSM17938), *B. coagulans* (DSM1), *L. acidophilus* (DSM), and *B. bifidum* (DSM20456). They reported that combination of probiotic strains with antibiotics was synergistic against MDR isolates of *P. aeruginosa*.

### Prebiotics

Prebiotic was described as “a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health”. Later on, the definition was modified as “a selectively fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health” [21]. A substance to be considered a prebiotic, it should be resistant to gastric conditions, and selectively fermented by beneficial microbes especially probiotics. Finally, it should improve health of the host [22].

Examples of prebiotics include Fructans, Galacto-Oligosaccharides (GOS), Starch and pectins. Lactic acid bacteria can be selectively simulated by Fructans while Bifidobacteria and *Lactobacilli* flourish in the presence of GOSs [21]. The source of prebiotics can be natural as food stuffs whether vegetables as garlic and onion, fruits as banana; whole grains as wheat, honey, and seaweeds. They can also be artificially manufactured on large scale as GOS. Prebiotics affect the microbiota by providing them with energy thus affecting its growth, function and even composition. A prebiotic may be either degraded by few microbial species as inulin or by many species as FOS [23].

Prebiotics stimulate the proliferation of the gut microbes. Prebiotics metabolism by microbiota

produce broken down products that have anti-inflammatory effect as short chain fatty acids (SCFAs) as acetate and butyrate [24]. They promote the regeneration of the intestinal epithelium; boost mucus secretion; preserve the normal intestinal pH. They also compete with other bacteria for cell receptors thus prevent their adherence and invasion of enterocytes. Acetate is a source of energy that nourishes and builds the colonic epithelium. Butyric acid improves cell metabolism, augments the gut immune cells, in addition to reducing inflammation. Prebiotics can be used to treat local GIT conditions and other distant organ systems due to the SCFAs' capacity to diffuse to the circulation. So prebiotics can have an anti-inflammatory influence on the management of many human illnesses [25].

Oral administration  $\beta$ -fructans was proved to significantly reduce the severity of biochemical relapse of ulcerative colitis (UC) patients compared to placebo. It further increases the level of anti-inflammatory fecal metabolites as arabinose, but unfortunately it has no relation to relapse of symptoms and signs in these patients [26].

In ulcerative colitis (UC), high dose Fructans has a good clinical effect with significant reduction of colitis. The effect of Fructans was attributed to increased colonic butyrate formation. As regard to microbiota, it stimulates luxuriant growth of Bifidobacteriaceae and Lachnospiraceae. These findings encourage further studies for its use as an add therapy in management of UC [27].

Prebiotics are effective treatments for patients of chronic idiopathic constipation. These patients showed improvement in symptoms as the stool consistency, number of bowel moments and bloating. The use of prebiotics as lactulose, Lactose, fructans as inulin, psyllium, and GOS encourage the growth of *bifidobacteria*, *lactobacilli* and *bacteroides* that produce SCFAs which decrease intestinal inflammation, regulate gut motility, and increase energy for colonic epithelium. All these effect ameliorate constipation [28].

Many studies showed that prebiotics have a good effect on constipation in animals as the defecation frequency/day improves. Among humans, inulin intake increased the defecation frequency. This good effect is due to supporting good gut microbiota as *Bifidobacterium* species, and decreasing bad microbiota as the *Bilophila* [29].

Prebiotics was proved to have an effect in the prevention of colo-rectal cancer (CRC) at high

risk patients, whether taken alone or in combination with probiotics. The previous effect was claimed by its good impact on the modulation of the immune system by colon microbiota. The preventable effect of the combined intake of the prebiotic fructans and probiotics (*lactobacilli* and *bifidobacteria*) on azoxymethane -induced cancer in rats could be explained by the down-regulation of expression of NO-synthetase and cyclooxygenase-2 genes. Prebiotics consumption is advised to enhance the immune system in CRC patients [30].

Prebiotics intake has favorable effects on several behavioral paradigms including anxiety, learning, and memory. It can help patients with neurological diseases as Huntington's disease and neuropsychiatric illnesses, including autism and depression through modulating the gut-brain axis when used outside of the gastrointestinal tract [31].

### Synbiotics

Synbiotics is the term used when a product contains both probiotics and prebiotics thus obtaining a synergism to improve the host health. Synbiotics can be complementary or synergistic. Complementary Synbiotics is called when the used probiotic in the product has good effects on the host, while the used prebiotic independently acts to stimulate the good microbiota components of that host. Synergistic synbiotics, if the used probiotic in the product is chosen on with a particularly good effect on the host, and the prebiotic used in the product boosts the proliferation and activity of the used probiotic [32].

Synbiotics provide the joint action of probiotics and prebiotics, which is considered functional dietary ingredients that stimulate growth of probiotics while it passes through the upper gastrointestinal tract, and its specific substrate available for fermentation. The use of synbiotics may improve blood sugar level, blood lipid profile and enhance the good intestinal flora as *bifidobacteria*. These effects lead to improving bowel habit, decreasing intestinal permeability and enhancing immune response [33].

A study done using a synbiotic formed of the probiotics; *Enterococcus faecium*, *Lactobacillus plantarum*, *Streptococcus thermophilus*, *Bifidobacterium lactis*, *Lactobacillus acidophilus*, *Bifidobacterium longum* plus the prebiotic; fructo-oligo-saccharide on 40 UC patients for 8-week. The patients improved showing statistically significant improvement of CRP and ESR. The clinical and

endoscopic manifestations also significantly improved in patients treated with the synbiotic [34].

A study that investigated effect of synbiotics on colitis in mice showed improved pathology scores of the colonic mucosa, improvement of mucus secretion, decreased inflammation and improvement of colonic integrity with good alterations of gut microbiome. The level of the pro-inflammatory cytokine IL-6 significantly decreased while the IL-10 increase with its anti-inflammatory effects [25].

### Psychobiotics

Psychobiotics are probiotics or prebiotics that affect bacteria–brain relationship. Psychobiotics have different mood effects on the host. They can have anxiolytic and antidepressant effects. They can change the cognitive, emotional, and neural indices. Psychobiotics perform these effects on bacteria–brain communication channels through the enteric nervous system and the immune system [35].

The effects of the gut flora on the mental state of the host lead to the development of the term microbiota–gut–brain axis (MGBA). Gut microbiota can produce many neurotransmitters and hormones, such as melatonin, serotonin, acetylcholine,  $\gamma$ -aminobutyric acid (GABA), histamine, and catecholamines. The previous hormones and transmitters mediate the effect of the microbiota on the brain and behavior [36].

The expression of GABA receptors in the CNS was reported to be modulated by the probiotic *L. rhamnosus* (JB-1) in the mouse model of depression. This effect was mediated through the vagus nerve. These mice showed less anxiety and depressive behavior that was explained by the decreased level of corticosterone in response to stress [35].

Steenbergen et al, [37] investigated the effects of probiotics on mood in humans. They gave the participants a mixture of several probiotics (*Lactobacillus casei* W56, *Lactobacillus salivarius* W24, *Lactococcus lactis* W19 and W58, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Bifidobacterium bifidum* W23, and *Bifidobacterium lactis* W52) over a period of 4 weeks. The probiotics treated subjects showed lower reactivity to sad mood in comparison to subjects given placebo.

### Metabolites

According to the theory that the healthy effect of the good microbiome is due to production of certain metabolites that affect the health of the host, then many of these metabolites were used as a novel therapeutic tool.

Many investigators reported a positive impact of butyric acid in IBD as it decreases inflammation of the GIT. Use of oral butyric acid as an add therapy decreases gut dysbiosis in UC patients. The explanation may be due to modulation of the immune cells by butyrate. Its use increases Th1 cells and regulatory T cells while down-expression of Th17 cells and IL-17, thus improving colitis [38]. On the contrary, a multicentric study done in Poland on IBD patients showed no significant change in either disease remission or disease activity in patients whether taking sodium butyrate twice daily or not [39]. In another study, colonic inflammation was not significantly affected after intake of SCFAs, however modulation of immune cells occurred in the form of over expression of regulatory T cell and TH-17 cell DSS-induced murine colitis model [40]. Also, four patients with diversion colitis receiving a solution of SCFAs two times a day showed cure of symptoms and decrease of the endoscopic inflammatory changes [41].

### Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) means introducing preprocessed, liquefied, or capsuled feces from a healthy donor into the colon of a recipient. Historically speaking as mentioned by Fe Hong, food poisoning and severe diarrhea was treated in the Chinese medicine in the fourth century using human fecal suspension introduced by mouth. In the 1500s, the “Yellow soup” which is really a fermented fecal solution was used to treat severe diarrhea, constipation, and other abdominal infections. Also, dysentery patients were given camel feces as a line of treatment by Bedouins people centuries ago [42].

In modern medicine, the 1st publication on fecal microbiota transplantation (FMT) was done in 1958 in which FMT used in a patient with recurrent *C. difficile* and it was introduced by enema. In 2013, the Food and Drug Administration approved human feces as a “new drug”. This happened after the publication of the first study that proved the more effectiveness of the FMT using duodenal infusion as a treatment for this infection than antibiotics [42].

FMT can be introduced to recipient through the upper or the lower GIT. By the upper GIT, suspension of healthy donor stool is administered using oral intake of capsules, or by gastric, duodenal or jejunal tube. By the lower GIT, FMT is introduced directly via the endoscope channel into the terminal ileum, cecum, or sigmoid, or through rectal enema [43].

**Russell et al.**, [44] treated 10 children with recurrent *C.difficile* using one time FMT. They mentioned that 9 patients showed a better response with no recurrence for 4 years. Also, multicenter study done on 372 pediatric patients with recurrent pseudo-membranous colitis who were managed with FMT showed that favorable outcome in 86.6% following single or repeated FMT [45].

FMT was also used in the treatment of other disease states as obesity and diabetes, recurrent d-lactic acidosis and metabolic syndrome. Many previously published case reports found post-FMT clinical improvement and even remission in extra-gastrointestinal conditions like multiple sclerosis, Parkinson, idiopathic thrombocytopenic purpura and chronic fatigue [46, 47].

#### Other therapeutic strategies

Other novel strategies that affect the human microbiome and thus affecting human health are under research. MicroRNAs (miRNA) are brief non-coding RNA molecules that control post-transcriptional gene expression. Commensal, pathogenic, and probiotic bacteria have an effect on intestinal miRNAs [24]. *Fusobacterium nucleatum* could suppress miR-18a and miR-4802 expression, which has a role in autophagy-related pathways, possibly resulting in chemotherapy failure of colorectal cancer [48]. Thus, manipulating gut microbiome may be a strategy to enhance human health through miRNA [24].

#### Conclusion

The human microbiome can affect the health and disease states of the human beings. Many therapeutics can improve the human microbiome, so it can indirectly improve the human health and can be used as an add therapy in many disease states.

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