


Microbiome and Its Roles in Gut-Brain Axis

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ABSTRACT

Among the trillions of microbes that live in our intestinal tract, scientists have found groups of species that play a key role in our health and disease conditions. These microbes harbored on our mucosal and skin surfaces with the bulk of it in the colon of our lower gut system. It is commonly referred to as gut commensal. In this review we summarized briefly our current knowledge of these microbiota or microbiome, and how they work to affect our functions in different organs and systems including our brain and immune system, either directly or indirectly through their metabolites. Technical advances in genetic sequencing such as metagenomic and 16S rRNA (ribosomal RNA) sequencing had greatly facilitated researches on microbiome. Our review will be focused mainly on the roles of microbiome in the gut-brain axis. The use of probiotics and prebiotics for intervention of dysbiosis or altered microbiome will also be discussed.

Keywords: Gut-brain axis, microbiome, prebiotic, probiotic

ABSTRAK

Di antara jutaan mikroba di dalam usus, beberapa kelompok di antaranya dapat berperan dalam kesehatan manusia; secara umum dikelompokkan sebagai *gut commensal*. Tulisan ini meninjau peranan kelompok tersebut, cara kerjanya dalam mempengaruhi metabolisme manusia, termasuk otak dan sistem imun, baik secara langsung maupun dengan perantaraan metabolitnya. Kemajuan teknologi seperti *metagenomic* dan *16S rRNA (ribosomal RNA) sequencing* sangat membantu penelitian mikrobiom. Tulisan ini terutama meninjau peranan mikrobiom pada *gut-brain axis*; juga akan dibicarakan peranan probiotik dan prebiotik untuk intervensi disbiosis. Khing S. Ong, Zack ST. Lim, Boenjamin Setiawan. *Microbiome* dan Peranannya pada *Gut-Brain Axis*

Kata kunci: *Gut-brain axis*, mikrobiom, prebiotik, probiotik

INTRODUCTION

The gut microbiota has been considered as an "essential organ" in our body,[1] carried over 100 trillions of synbiotic microbes, outnumber the human cells by about 10 to 1, and approximately have 150 times more genes than the entire human genome.[2] Progress made over the last decade characterized by the interaction between central nervous system (CNS), enteric nervous system (ENS) and gastrointestinal (GI) tract.[3] Although ENS works autonomously, it also communicates with CNS through parasympathetic and sympathetic nervous system, and is susceptible to neuro-modulating signaling, supporting the notion that our gut is a "second brain",[3] and the term "gut – brain axis" or "gut-microbiome-brain axis" indicates the important role of the microbiota not only in the gut but in the whole body through the brain.[4] It also reflect the slang 'gut instinct' that denotes the cognitive functions such as decision- making and other behavioral traits are originated from our gut.

The exploded research works and publications from 2013 to 2017 alone resulted more than 12,900 papers devoted to the study of gut microbiota,[5] emphasizing that microbiomie are at the forefront of medical sciences. Up to recently, the tally revealed there are more than 100 disease entities linked to changes in the gut microbiota, spreading not just in the gut and brain, but also include liver, heart and lung, skin and vagina.[6] Accumulating data indicate that gut microbiota also communicates with the brain through neural, endocrine and immune pathways, thereby influencing host behavior and brain functions.[7] Knowing the vast and diverse influence of our gut microbes in our health and diseases, it is essential to also look for ways to avoid or intervene any deleterious effects that may be caused or associated with altered communities of the gut microbes. First come to mind is to replace the faulty of microbiota with proper healthy microbial composition, such as by fecal microbial transplant (FMT),[8] or administration of probiotics currently commercialized as supplement for preventive and maintenance purposes.[9] Prebiotics and a healthy diet for our nutritional requirements are also necessary to complement our effort in maintaining a healthy gut microbiota.[9]

HUMAN MICROBIOTA/MICROBIOME

Definition[10]

Microbiota: a term refers to a collection of all taxa constituting microbial communities, such as bacteria, archeae, fungi, and protista.

Microbiome: this term was initially used to refer to the genes of the microbes, currently however is also used to refer to the

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microorganisms themselves or microbiota.
Eubiosis: Normal healthy microbial composition.
Dysbiosis: Deviation in composition or functions from usual normal microbiome

Sites of Microbiota in Our Body

The bulk of the microbiota harbored in our mucosal and skin surfaces is in the colon – our lower gastrointestinal systems. Microbial distribution by body sites:[11] GI tract 29%, oral 26%, skin 21%, airway 14%, urogenital 9%, blood 1%, eyes 0% (excluding conjunctiva).

Gut Microbiome[12]

Stomach: with its acidic environment and transient stay, there are about 10^3 microbes per ml stomach content, and the main inhabitants are: *Lactobacilli, Enterococci, Helicobacter,* and *Bacilli*.

Duodenum: still an acidic environment, and with added pancreas secretion and bile, it became a hostile environment for the microbes. Predominant bacteria are: *Lactobacilli* and *Streptococci* with a total of 10^2 - 10^4/mL content.

Jejunum and ileum: the numbers and diversity of bacteria are increasing in the lumen of these areas. Germ-free (GF) mouse are resistant to diet-induced obesity and malabsorb fat in the food. However administration of specific pathogen free microbes along with high fat diet induced weight gain and boosts the abundance of *Clostridiaceae* and *Peptostreptococcaceae* in the small intestine with a decrease in leanness-associated *Bifidobacteriaceae* and *Bacteroidaceae*.[13]

Colon: contained the majority of our gut microbes with estimated 10^{11}/mL content. A healthy human colon microbiota are very diverse, containing over 1000 species.

There may be shared 'core microbiota' which in healthy people dominated by phyla *Firmicutes, Bacteroidetes, Actinobacteria,* and *Verrucomicrobia*.[14] The relative proportions and species within individual microbial community may varied dramatically. Studies of microbial gene profile suggest there is a shared common functional pathway across individuals (a "functional core microbiome"), however, different communities of bacteria may be found in different people.[15] Gut microbiota also regulates gut motility, intestinal barrier homeostasis, absorption of nutrients and fat distribution.[16]

MICROBIOME EFFECT ON BRAIN FUNCTION

1. **Altered microbial composition:**[17]
   Administration of probiotic bacterial or infectious pathogens can affect the composition of gut microbiota in multiple ways, e.g. compete for dietary nutrients as growth substrates, fermentation of sugar, produce growth substrates and vitamins for other bacteria, produce bacteriocins (proteinaceous toxin produced to inhibit the growth of similar or related bacteria), compete for binding sites on enteric wall, improve gut barrier, reduce inflammation and stimulate innate immune responses.

   By and large, our gut microbiota works through communicating with the immune system of the host and or the metabolites from nutrients, and resulted in a bi-directional communication among the brain and the gut, the gut microbiome-brain axis, which also involved immune system and nutritional intake.

2. **Microbiome and immune system:**
   Our gut microbiome and immune system co-evolve during our lifespan, and the components of microbiota impact the immune system and vice versa, resulted in the maintenance of a synbiotic relationship between the host and highly diverse microbiota, a microbiome-immune system axis.[18] Since immune system also exerts a bi-directional communication with the brain, it is a prime target for transducing the effects of microbiota to the brain. In addition, indirect effects of microbiota on innate immune system can result in changes of the circulating levels of pro-inflammatory and anti-nflammatory cytokines that directly affect brain functions.[19]

3. **Microbiome and Oxidative Stress:**
   The presence of microbiota on gut epithelial lining induces physiological level of oxidative stress (OS). This in turn interfere with both the composition and functions of microbiota (e.g. anaerobes thrive in the presence of electron acceptors), and directly with the permeability of the intestine, increasing chances of foreign molecules reaching the circulation and the brain. The oxidative reduction (gaining electron) potential of microbiota also influences the homeostasis of intestinal barrier as well, suggesting that dysbiosis may be both a cause and a consequence of increase OS level of the brain.[20]

4. **Gut-microbiota-brain axis (GMB axis):**
   GMB-axis consists of bi-directional communication between central and enteric nervous systems, linking emotional and cognitive centers in the brain and peripheral intestinal functions, immune activation, intestinal permeability, enteric reflex, and entero-endocrine signaling.[21]

   a. Vagus nerve as modulator of GMB-Axis:
   Vagus is the major parasympathetic nervous system that regulates much organ function, including bronchial constriction, heart rate and gut motility. Many effects of gut microbiota on brain function have been shown to be dependent on vagus activation. However, vagus-independent mechanisms are also involved in microbiota-brain interactions, as vagotomy failed to affect the effect of antimicrobial treatments on brain or behavior.[22]

   b. Tryptophan metabolism:
   Tryptophan is a precursor of many biologicall active agents including serotonin and nicotinamide adenine dinucleotide (NAD+), metabolized through kynurenine pathway.
   Dysregulation of this pathway can lead to immune system activation and accumulation of neurotoxic compounds as in many disorders of both brain and GI tract.[23] There is evidence that probiotic Bifidobacterium infantis can alter concentration of kynurenine, however it is not a universal property of all strain of *Bifidobacterium*.[24]

   c. Microbial metabolites:
   Microbial metabolites play a central role in the host immune responses and brain functions.
   SCFAs are the most abundance molecules produced by gut commensal anaerobic bacteria fermentation of dietary fibers


in the colon. It consists of acetate, propionates, and butyrate, which are recognized by the host via intracellular receptors PPAR (peroxisome proliferator-activated receptor)-gamma. Acetate and propionate produced mainly by *Bacteroidetes*, and butyrate primarily produced by *Firmicutes*.[25]

Acetate: the most abundant SCFA and an essential metabolite for the growth of other bacteria.[26]

Propionate: transferred to the liver and regulates gluconeogenesis and satiety signaling through interaction with the gut fatty acid receptors.[27]

Butyrate: the main energy source for colon epithelium, can induce apoptosis of colon cancer cells, and activate intestinal gluconeogenesis, a beneficial effect on glucose and energy homeostasis.[27] Butyrate also consume oxygen via beta oxidation; essential for epithelial cells to generate a state of hypoxia that maintain oxygen balance in the gut to prevent dysbiosis.[28]

d. Microbial neuro-metabolites:

Microbes have the capacity to generate neurotransmitters and neuromodulators. *Lactobacillus spp* (spp refer to all species in a given genus) and *Bifidobacterium spp* produce GABA (gamma aminobutyric acid), Escherichia spp, Bacillus spp and *Saccharomyces spp* produce noradrenalin, *Candida spp, Streptococcus spp, Escherichia spp,* and *Enterococcus spp* produce serotonin, *Bacillus spp* produce dopamine, and *Lactobacillus spp* produce acetylcholine.[29]

e. Bacterial wall:

The outer exocellular polysaccharide (EP) of bacteria is largely responsible for many of their health promoting effects. EP of *Bifidobacterium breve* protects the bacteria from acid and bile in the gut. and shields the bacterial from host immune response.[30]

f. Calbindin:

Expression of calbindin (calcium binding protein) in the enteric neuron is dependent on vitamin D concentration in the nerve and intestinal cells, and has a critical role in preventing neuronal death, beside maintaining calcium homeostasis.[31]

5. Microbiota and psychiatric disorders

a. Stress:

Stress and the associated activity of the hypothalamus-pituitary-adrenal (HPA) axis can influence the composition of gut microbiota.[32] Maternal separation in early life can results in long term increases in HPA axis activity. Chronic stress in adulthood also affects composition of gut microbiota with relative abundance of *Bacteroides spp* and *Clostridium spp.*[33)] Chronic stress also disrupts the intestinal barrier lead to increasing circulatory levels of bacteria cell wall components lipopolysaccharides.[34]

b. Depression and anxiety:

Anxiety and depression often are co-morbid condition in patients with irritable bowel syndrome (IBS). Studies with depressed human fecal microbial transplants induced depressive behavior in the rodent suggest the causality of implanted microbes.[35]

c. Behavior and Cognition:

Studies with germ-free animal indicates that at neuronal level showed a decreased brain-derived neurotrophic factor (BDNF), a key factor in neuronal survival and growth, and a decreased expression of NMDA (N-methyl-D-aspartate) receptor subunit 2A (NR2A) in the cortex and hippocampus as compared to controls. At the cognitive level, germ-free mice displayed deficit in simple non-spatial and working memory tasks.[36]

d. Autism spectrum disorders (ASD):

Core symptoms of ASD are difficulty in social and communicative behavior, and repetitive behavior; however, GI symptoms are common and contribute significantly to the morbidity of affected patients. GI symptom severity is strongly correlated to severity of ASD symptoms, as well as anxiety and sensory over-responsive conditions are modulated by gut microbiota.[37] Autism symptom severity rather than GI symptom is associated with decreased microbial diversity with decrease of *Prevotella, Coprococcus*, and *Veillonellaceae* which involved in carbohydrate degradation and fermentation.[38] Intake of probiotic *Lactobacillus reuteri*, a gut commensal has been reported associated with up-regulation of oxytocin level and reversed autism behavior.[39]

e. Bipolar disorders/Schizophrenia:

Analysis of microbiota in schizophrenic patients was done with oropharyngeal swab due to difficulty in obtaining fecal samples. At the phylum level schizophrenia samples showed higher proportion of *Firmicutes* compared to controls, whereas in controls higher proportion of *Bacteroide* and *Actinobacteria* are found.[40]

Toxoplasma gondii has been associated repeatedly with higher incidence of schizophrenia and bipolar disorders [(41)], indicating disruption of gut microbiota that normally would

detect the infection and mount a defensive immune response.

6. Microbiota in neurological disorders:

a. Multiple Sclerosis (MS):

MS is an autoimmune disease with demyelination of CNS nerves. Study suggest that there is imbalance of gut microbiota composition in MS patients in specific taxa, some of which associated with promotion of inflammatory cytokine and overall inflammation.[42] There is increased *Akkermansia, Ruminococcus*, and *Methanobrevibacter* related to pro-inflammatory pathway, and decreased in anti- inflammatory bacteria including *Bacteroidacea, Faecalibacterium* and *Butyrimonas.*[42]

b. Parkinson's disease (PD):

A neurodegenerative disorder characterized by aggregation of misfolded peptides alpha- synuclein (aSyn) in the gut and brain. A recent study have shown that appendix acts as major reservoir for aSyn linked to the onset and progression of PD.[43] Examination of fecal microbiome revealed that on average PD patients have a 77.6% decrease of *Retovellaceae* as compared to control, and the relative abundance of the *Enterobacteriaceae* is positively associated with the severity of the motor symptoms.[44]

Escherichia coli and other enteric bacteria (members of human microbiome) are capable of producing extracellular functional amyloid: Curli.[45] Rat exposed orally to Curli were found to have


enhanced aSyn production in the gut, and increased aggregation of aSyn in the brain.[45] In addition, there is association between bacteriophage community with PD. A shift of phage/bacteria ratio in lactic acid bacteria known to produced dopamine and regulate intestinal permeability has been identified in PD, and depletion of Lactococcus spp is most likely due to lytic-c2 type and 936 like lactococcal-phages frequently present in the dairy products.[46]

c. Alzheimer's disease (AD):
A neuro-degenerative disease characterized by extra-cellular aggregation of amyloid-beta (Ab) plaques and intracellular tau tangles.
Gut_microbiome of AD patients has decreased in diversity and is compositionally distinct compared to matched control without AD.[47] Study has identified decreased abundance of_*Firmicutes* and *Bifidobacterium*, and increased in *Bacteroide*.[47] There is also correlation between levels of genera abundance and cerebrospinal fluid biomarkers of AD (including phosphorylated tau (ptau), Ab42/Ab40 and ptau/Ab42 ratios).[47]

d. Amyotrophic lateral sclerosis (ALS):
An alteration in gut microbiome has been shown in the mouse model of ALS, with reduced abundance of *Butyrivibrio fibrisolvens*, *Escherichia coli,* and *Fermicus* as compare to in d-type mice.[48]

7. **Functional gastrointestinal disorders (FGID)**
Dysbiosis also occurs in FGID that are highly associated with mood disorders and are linked to disruption of gut-brain axis. Both gut to brain and brain to gut dysfunctions occur with the former being dominant particularly in IBS. This disruption of the gut- brain axis lead to changes in intestinal motility and secretion, causes visceral hypersensitivity, and cellular alteration in entero-endocrine and immune system.[49]

BRAIN AFFECTS ON GUT-MICROBIOTA

1. **Stressors:**
Psychological stressors modulate composition and total biomass of gut microbiota independent of duration. Exposure for as short as 2 hours could significantly change the composition profile and reduce relative proportion of the main microbial phyla.[50] These effects may be mediated through efferent of ANS and HPA-axis, both directly via host microbiota or indirectly by changes in intestinal environment.[21]

2. **Brain effects on bowel functions:**
Brain has a prominent role in the modulation of gut functions, such as motility, secretion of acid, bicarbonates and mucus, intestinal fluid handling and mucosal immune response, all are important for the maintenance of mucus layer and biofilm for the growth of individual group of bacteria.[51]

3. **Gut alteration and virulence expression:**
Gut alteration associated to stress facilitates the expression of virulent bacteria. Norepinephrine released during surgery induced the expression of *Pseudomonas aeruginosa* which may results in gut sepsis.[52] Norepinephrine can also stimulate proliferation of several strains of eneteric pathogens, and increase the virulent properties of *Campylobacter jejuni*, and might favor over-growth of non-pathogenic as well as pathogenic *Eschericia coli*.[53]

INTERVENTIONS OF MICROBIOME DYSBIOSIS

1. **Engineered bacteria/gene therapy:**
Several companies are testing whether engineered bacterial can be used to kill harmful bacteria or treat conditions that affect the brain, gut or other organs.[54] US regulators have approved trials of several engineered bacteria as a 'form of gene therapy'.[54] Researchers from National University of Singapore engineered the gut bacteria *Escherichia coli* and *Lactobacillus* to recognize and kill the harmful microbes.[54]

2. **Vaccine:**
Another group of researchers had developed a carbohydrate based vaccine for the gut microbe *Clostridia bolteae* to treat autism spectrum disorders.[55]

3. **Probiotics:**
Definition of probiotic by FAO/WHO (food and agricultural organization of WHO) according to an expert consensus panel is 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host'.[56] Our limited review found a scarcity in randomized control studies. A meta-analysis of 7 published peer-review papers on randomized controlled trials of probiotics, no effects were observed on the fecal microbiota composition in alpha diversity species richness in any of these 7 studies when compared to placebo, except one study showed probiotic modified the overall structure of beta diversity (a measure of how different is the microbial composition in one situation compare to another) of microbial community.[57]

A review by Cochrane – an independent network of experts – however, did found probiotics may be useful in neonatal intensive care unit that seems to reduce the likelihood of developing necrotizing enterocolitis.[58] Recent advances in engineered probiotics: A recent study led by researchers from Washington University, School of Medicine, reported that a strain of *E. coli* known as *E. coli Nissle* (EcN)-1917 marketed in Europe as anti-diarrhea probiotics, when tested on mice, could evolved in mice's bowels just within a few weeks.[59] Depending on the diet and composition of the gut microbiota – the probiotic EcN strain gained ability to damage protective layer of the intestine. Destruction of this layer has been linked to IBS.

Microbes are not immune to evolution, they change and adapt, and subjecting their genomes and therapeutic property to natural selection. In transit within the bowel system, EcN accumulate genetic mutations that modulate carbohydrate utilization, stress response, and adhesion to gain fitness.[59] With this insight, researchers generate a therapeutic strain of EcN by genetic engineering for specific drug synthesis or enzyme synthesis - in this case - for phenylketonuria (PKU).

4. **Prebiotics:**
Prebiotic as defined by a panel of expert


consensus is a substrate that is selectively utilized by host microorganisms conferring a health benefit.[60]

This definition expands the concept of prebiotics to include non-carbohydrate substances, applications to body sites other than the GI tract, and diverse category other than food.[60] Prebiotics dietary fibers acts as carbon sources for primary and secondary fermentation in the colon. Two class of compounds, fructants (fructooligosaccharides or FOS and inulin) and galactants (galactooligosaccharides or GOS) are prebiotics with ability to alter microbiota to the benefit of the host by promoting *Bifidobacteria*.[61] Not all fibers are prebiotics.To be a prebiotic it requires to be:[62]

- Resistance to gastric acidity, hydrolysis by enzymes and absorption from the upper GI tract.
- Fermentation by gut microbiota.
- Selectively stimulate the growth and or activity of gut microbiota associated with health and well being.

CONCLUSION

Microbiota play a significant role that contributes to our health and well-being. So far, despite of advances in sequencing and genetic engineering technologies like metagenomics and CRISPR Cas9 gene editing, we still seems to be limited only with describing the correlations or association of microbiota with disease conditions. Although randomized control studies were mostly disappointed, it could be due to variety of reasons, e.g. colonization restriction, genetically based interpersonal differences (precision medicine) etc. Recent progress in engineered probiotics open a new 'platform' for treatment of genetic diseases such as PKU, and pave the way for future 'new drug' discoveries.

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