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Literature Review

The role of gut microbiota in health and diseases

Deasy Fetarayani[1*], Handoko Hariyono[2], Gatot Soegiarto[1]

1) Division of Allergy and Clinical Immunology, Department of Internal Medicine, Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
2) Department of Internal Medicine, Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

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Correspondence:
deasyfetarayani@gmail.com

ABSTRACT

Microbiota contributes a crucial part in the human hosts' health and actively provides to the emergence of various diseases. The optimal composition of healthy intestinal microbiota varies from person to person. The more various and abundant of the microbiota, the greater their resistance to outside hazards. Colonization of the microbiota in the human body starts after delivery and develops continuously from infant to adult. The largest microbial colony is constructed in the lower part of the adult human digestive tract. The composition of the human intestinal microbiota alters promptly during the beginning of life and is steady. It has been described the close relationship among dysbiosis of the intestinal microbiota with intestinal and non-intestinal diseases. Nevertheless, it is uncertain whether dysbiosis is the culprit of the disease or only as a result of the disease. Human microbiota's role must be investigated more deeply so that later it can be developed for the prevention, diagnosis of disease, and more effective treatment strategies in the future. In this mwinireview, we will describe the development of the gut microbiota, its interaction with our bodily systems and defense, the multiple causes of dysbiosis, and its impact on several metabolic in inflammatory diseases in humans. With this insight, it is hoped that we can be more cautious about using antibiotics, avoid things that lead to dysbiosis, and handle diseases more holistically, putting the balance of the microbiota into account.

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INTRODUCTION

There are enormous microbiota in the human body, colonized in the epidermis, gastrointestinal tract, urogenital tract, and other tissues that are favorable and implicated in various fundamental functions. Microbiota protects the human body from the entry of pathogens and contributes to the metabolic processes and nutrients essential for human health. Subsequently, it is substantial to sustain a well-balanced microbiota composition to preserve body homeostasis (Toor et al., 2019).

There are over 100 trillion live microorganisms in the human body that have a significant role in healthy and ill conditions. The human gastrointestinal tract comprises of a large and various microbiota colony. Intestinal microbiomes encode over 3 million genes that compose a huge amount of metabolites, whereas the genome of human composed of simply about 23,000 genes (Rinninella et al., 2019). Some important reports revealed that intestinal microbiota is implicated in many fundamental human biological processes, such as regulating metabolism, controlling epithelial growth, and affecting natural immunity (Wang et al., 2017).

In the last few decades, the knowledge of intestinal microbiota has changed from the previous of combating bad microbes in the intestine with antibiotics to efforts to protect good microbes in the intestine that function as the first layer of defense for the body and contribute to overall health (Eppinga et al., 2016).

This paper will discuss microbiota's role, primarily intestinal microbiota in a healthy state, conditions that arise if there is a disturbance in the balance of intestinal microbiota, and clinical interventions that can be used to overcome microbiota imbalance (dysbiosis).

GUT MICROBIOTA

The human intestine is an elaborate ecosystem where microbiota, host cells, and nutrients collaborate thoroughly (Azad *et al*., 2018). Intestinal microbiota (intestinal normal flora or gut microbiota) is an intricate population consisting of live microorganisms that exist in the digestive tract of a human. It contains the highest amount of bacteria and the most various species in the entire human organs (approximately 400 to 500 species of bacteria form intestinal microbiota) (Round & Mazmanian, 2009; Shi et a*l*., 2016; Feng et al., 2018). Metagenome or a collection of all DNA from all microorganisms that colonize in the human body is collectively called microbiomes (Levy et al., 2017).

Intestinal microbiota consists of bacteria, viruses, protozoa, and fungi, and is roughly calculated to be more than 100 trillion (Toor et al., 2019). These microbiotas have extraordinary potential to influence human physiology, both in a healthy and illness state. Its contributions include metabolic functions, protecting against pathogens, educating and maturing the immune system, and, along with these fundamental functions, affecting the majority of human physiological functions directly or indirectly (Shreiner et *al*., 2015).

Bacteroidetes, *Firmicutes, Actinobacteria*, *Fusobacteria, Proteobacteria*, and *Verrucomicrobia* are the predominant microbiota phyla in the intestine. The dual main phyla namely *Bacteroidetes* and *Firmicutes* constitute 90 % of intestinal microbiota (Figure 1). Phylum *Bacteroidetes* comprised of dominant genera like *Prevotella* and *Bacteroides*. Phylum *Actinobacteria* is lower in proportion and predominantly constituted by the *Bifidobacterium* genera. Phylum *Firmicutes* consists of over 200 diverse genera namely *Clostridium, Bacillus*, *Lactobacillus*, *Ruminicoccus*, and *Enterococcus*. The *Clostridium* genera constitutes 95 % of the phylum *Firmicutes* (Azad et al., 2018; Feng et al., 2018; Rinninella et al., 2019).

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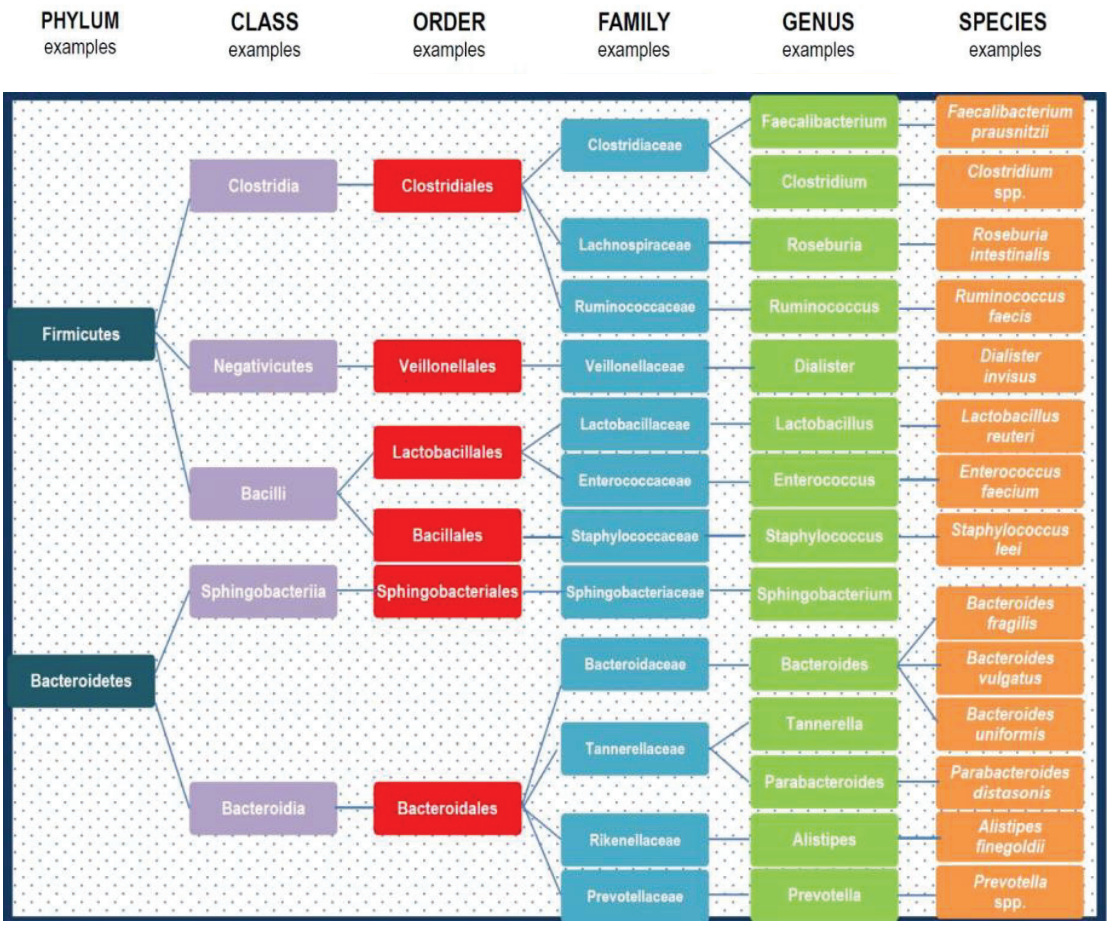

Figure 1. Two main phylum of intestinal microbiota (Rinninella et al., 2019)

DEVELOPMENT OF GUT MICROBIOTA

The colonization of microbiota in the human body commenced postpartum and progresses gradually from infant to adult, with the greatest microbial colony constructed in the lower part of the adult human digestive tract (Iebba et al., 2016). Microbial diversity in the intestine of infants increases over time. Intestinal microbiota of babies delivered by cesarean section becomes less heterogeneous during the first two years of life than babies delivered in vaginal mode (McBurney et al., 2019).

Bifidobacterium and *Bacteroides* species predominate early intestinal microbiota of breast-fed infants and vaginal-delivered infants. These genera can be regarded as characteristics of healthy baby microbiota, and they are largely decreased in babies born by cesarean section and receive milk formula. Aside from the delivery mode and the type of milk taken, intestinal microbiota evolution in infants is also affected by the utilization of antibiotics and probiotics, the initiation of food substances in the weaning period, and the possible maternal types microbiomes during pregnancy. The human gut microbiota configuration alters promptly during the beginning of life and then is quite steady (McBurney et al., 2019).

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ROLE OF GUT MICROBIOTA

The human intestinal microbiota is competent to affect the host physiology by controlling various processes namely absorption of nutrients, inflammatory processes, immunologic function, generation of oxidative stress, and balanced anabolic processes (Ticinesi et al., 2019). Together with the host defense system, the microbiota serves to protect the host from colonization and invading pathogens. Finally, the number of fundamental functions in host is influenced by the gut microbiota, and therefore the gut microbiota contributes to maintaining the host health (Carding et al., 2015; Toor et al., 2019).

Intestinal microbiota works as "a metabolic organ" that interrelates with the human host and conducts numerous important activities to keep the human's healthy state (Schippa & Conte, 2014). The intestinal microbiota is the main regulator of the digestive process along the digestive tract, with an essential function in the extraction, synthesis, and absorption of plenty metabolites and nutrients in food, for instance, lipids, short-chain fatty acids (SCFA), vitamins, bile acids, and amino acids (Rinninella et al., 2019).

Carbohydrates and undigested protein are the main substrates that are ready for use by microbiota. Fermentation of these substrates produces various metabolites, namely branched-chain fatty acids, SCFA, ammonia, amines, phenolic compounds, and gases such as methane, hydrogen, and hydrogen sulfide (Carding et al., 2015). SCFA products, particularly acetate, propionate, and butyrate, are important for microbiota functions. SCFA is an essential root of energy for the mucosa of the intestine and is crucial for immunologic responses modulation and tumor formation in the intestine (Shreiner et al., 2015). Butyrate is utilized as a substrate of energy and capable of substantiating the colon's defensive barrier by promoting antimicrobial peptides and mucin secretion (Schippa & Conte, 2014).

Intestinal microbiota prevents pathogenic colonization through various competitive processes such as metabolism of nutrients, modification of pH, secretion of the antimicrobial peptide, and affecting intracellular signal delivery pathways (Rinninella et al., 2019). The microbiota ability to preclude colonization of pathogens by contending for attachment and nutrition, production and secretion of antimicrobial peptides is called "colonization resistance." The provision of antibiotics in humans greatly reduces colonization resistance (Schippa & Conte, 2014).

Microbiota is very important for the functional immune system development, which influences natural and adaptive immunity, and can also improve the control of mucosal immunity on the intestinal surface (Schippa & Conte, 2014). Recent research has identified the important role of normal flora bacteria and their products in controlling natural and adaptive immune cell development, homeostasis, and function (Rinninella et al., 2019).

The interplay among gut microbiota and the host immune system is very complicated and goes both ways. The host immune system should ascertain to tolerate commensal microbiota and make a response to pathogens appropriately. By turns, the microbiota is a fundamental part of maturing the immune system to be appropriately functional (Figure 2) (Shreiner et al., 2015).

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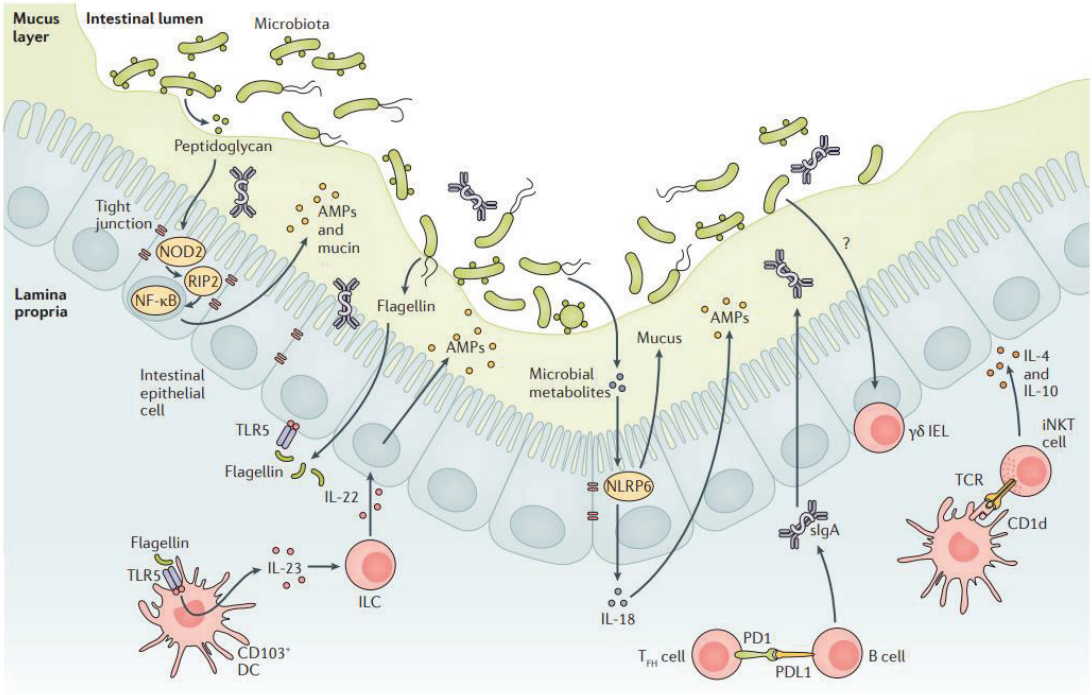

Figure 2. The role of natural and adaptive immunity in microbiota homeostasis (Levy et al., 2017)

DYSBIOSIS

The balance of the gut microbiota ecosystem is called eubiosis. Intestinal microbiota in eubiosis status is characterized by the predominance of possibly beneficial species, owned by *Bacteroidetes* and *Firmicutes* as the main two phyla bacteria. For instance, those included in the *Proteobacteria* (*Enterobacteriaceae*) phylum do exist as certainly pathogenic species, but in extremely low percentages. In the dysbiosis condition, the "good bacteria" is no more capable of managing "bad bacteria," and "bad bacteria" eventually take control (Iebba et al., 2016; Zhang et a*l*., 2015).

The general definition of dysbiosis is the composition and functional changes in microbiota determined by a range of factors related to host and environment that disrupt the microbiota ecosystem to a level that surpasses its resiliency (Levy et al. 2017). A reduced microbiota diversity and the excessive growth of *Proteobacteria* are the main characteristics of dysbiosis (Weiss & Hennet, 2017). Currently, there are several substantial diseases in humans linked to dysbiosis, comprising autoinflammatory and autoimmune diseases, inflammatory bowel disease, obesity, and allergic diseases (Schippa & Conte, 2014).

A lifestyle that lacks physical activity and consumption of foods high in carbohydrates and processed salts and low in fiber is associated with an imbalance of intestinal microbiomes. Also, it increased the prevalence of chronic diseases associated with intestinal microbiomes (McBurney et al., 2019).

Causes of dysbiosis include (1) infection or inflammation, (2) composition and diversity of the diet, (3) use of antibiotics (xenobiotics), (4) personal and community hygiene habits (hygiene), and (5) genetic factors (Figure 3) (Levy et al., 2017). Diet and antibiotic use may have a temporary or sustainable effect on gut

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microbiota composition. Genetic factors and microbial transmission from mother to child, which is the initial succession of intestinal colonization, is influenced by the mother's microbiota composition and delivery mode (Levy et al., 2017).

The illness state can cause changes in microbiota composition over various mechanisms, comprising alteration in dietary habits and intestinal function due to the drug administration in particular antibiotics (Shreiner et al., 2015). At present, in most diseases, the association between dysbiosis and disease pathogenesis is still unclear. It is vague about dysbiosis as the culprit of the disease or its impact (McBurney et al., 2019).

Dysbiosis does not merely affect the response of inflammation but also the digestive process and other substantial intestinal functions. Impaired tolerance mechanisms caused by dysbiosis often cause chronic intestinal inflammation. Commensal bacteria are replaced by pathogenic bacteria complemented by Th17 immune responses that increase pathological inflammation, as demonstrated in colorectal cancer (Toor et al., 2019).

Diet is the main element that affects intestinal microbiota. The lack of nutrition in the intestine that occurs in parenteral alimentary enhances Proteobacteria's extent, which induces the mucosal wall inflammation and ultimately elicits the disruption of the epithelial defense. An oversupply of nutrients results in obesity-related to dysbiosis and inflammatory, metabolic complications (Weiss & Hennet, 2017). According to the literature, current "western" lifestyles and infectious agents are regarded as the pivotal eliciting factors for developing intestinal dysbiosis. In hosts with a genetic predisposition, changing the microbiota composition might greatly influence chronic disorder's evolution (Figure 4) (Schippa & Conte, 2014).

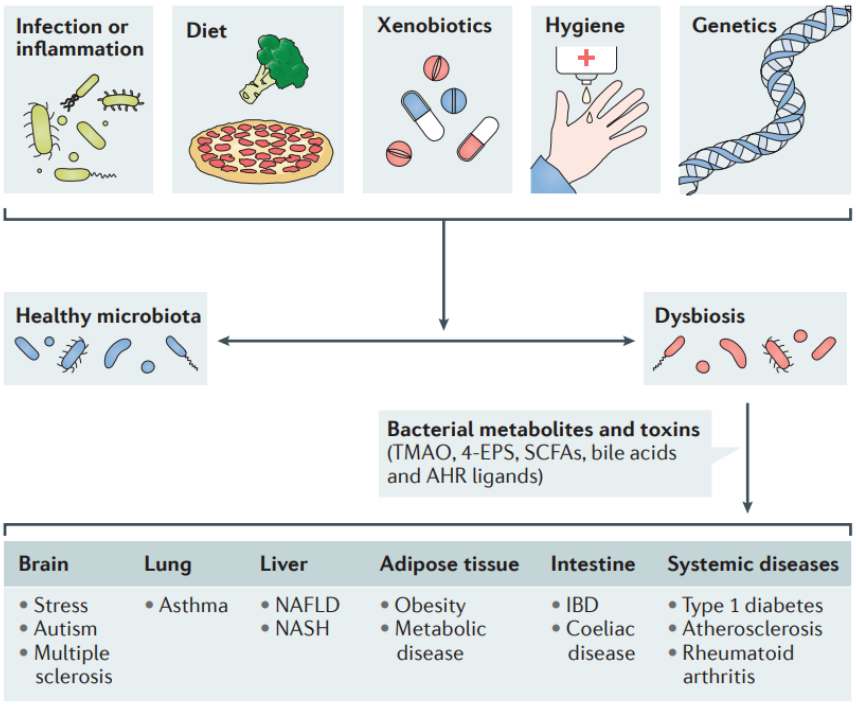

Figure 3. Causes of dysbiosis and its medical implications (Levy et al., 2017)

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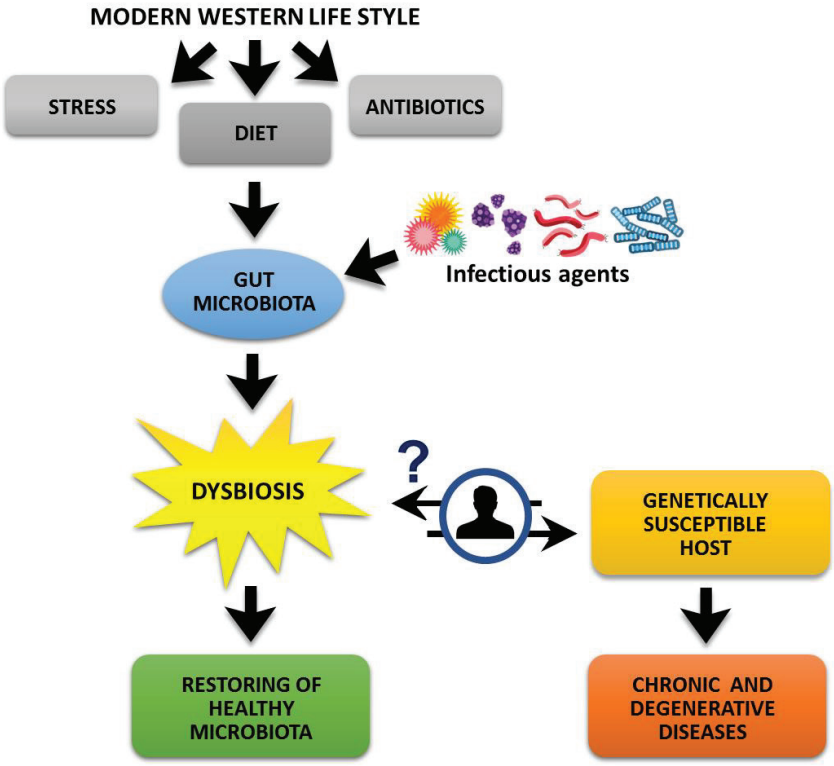

Figure 4. Factors triggering dysbiosis and degenerative chronic disease (Schippa & Conte, 2014)

GUT MICROBIOTA AND HEALTH

Although numerous reports indicate that alterations in microbiota composition are related to some diseases, it is still vague in defining the healthy intestinal microbiota. Although over a hundred phyla of bacteria have already been identified, the gut microbiota in an adult human is only predominated by two bacterial phyla, namely *Firmicutes* and *Bacteroidetes*, and a limited range of *Proteobacteria*, *Actinobacteria*, *Verrucomicrobia, Cyanobacteria*, and *Fusobacteria* (Schippa & Conte, 2014; Shreiner et al., 2015).

Healthy intestinal flora is essential to improve host health, but excessive bacterial population growth causes various dangerous conditions. In order to avoid this result, humans have implemented various strategies. The mucosal immune system must fulfill two functions: (1) can control intestinal microbiota and prevent excessive growth and translocation to systemic locations (Sekirov et al., 2010), (2) can tolerate harmless microbes, and prevent the induction of an excessive and harmful systemic immune response (Iebba et al., 2016).

Researchers in intestinal microbiomes are faced with the complexity of defining the interplay of healthy intestinal microbiomes. As an ecological colony, the microbiome is composed of a multitude of genetic, environmental, and clinical factors, causing wide variations between individuals and biogeographical variance in human populations. All these things make identifying the microbiome characteristics that define health more complicated. Furthermore, the microbiome's characteristics and nature can influence the risk of a disease many years before the pathological state arises (McBurney et al., 2019).

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Because the variability of human microbiomes between individuals is high, there is very difficult and unconceivable to identify and validate the human microbiomes characteristics and the standard range that enables the presence of the human host's health risk of the disease. Thus, it seems impossible to determine the characteristics of universally healthy microbiomes (healthful microbiome) by an individual or community of humans. It may be unhealthful in a particular condition. For instance, microbiomes that lead to excess weight will be unfavorable in the environment contributing to obesity. On the other hand, it will be useful in the context of food shortages (McBurney et al., 2019).

GUT MICROBIOTA AND DISEASES

Microbiota in the gastrointestinal tract can provide to and be influenced by the disease in different forms. For example, increased growth in some bacterial phyla can cause inflammatory conditions, in particular inflammatory bowel disease (IBD) (Feng et al., 2018). Generally, high microbiota heterogeneity is regarded to be related to healthy intestinal microbiota, whereas the loss of dissimilarity appears to be correlated with a disease (Scott et al., 2015).

Chronic disorders like type 2 diabetes mellitus, obesity, metabolic syndrome, IBD, colorectal carcinoma, atherosclerosis, alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), liver cirrhosis, liver cancer, and allergic diseases such as asthma and food allergy have been related to human gut microbiota (Wang et al., 2017).

Type 2 Diabetes Mellitus

Obesity and concomitant metabolic complications, for instance, type 2 diabetes mellitus (T2DM) as well as cardiovascular disease, turned into worldwide health problems and are regarded as a consequence of complex multidirectional interactions between host genetics, environment, diet, and intestinal microbiota (Wang et al., 2017). Some reports revealed that the intestinal microbiota composition changed in T2DM patients; nevertheless, it is unclear whether this change is a culprit or an effect of the disease (Rinninella et al., 2019).

A study by Larsen *et al*. (2010) revealed a significant reduction in the proportions of the class *Clostridia* and phylum *Firmicutes,* whereas the amount of *Bacteriodetes* and *Proteobacteria* were significantly increased in patients with T2DM compared with the healthy control group. Additionally, the ratio of *Bacteroidetes* to *Firmicutes*, also the *Bacteroides-Prevotella* group to *C. coccoides-E. rectale* group ratio, and class *Betaproteobacteria* have a significant positive correlation with plasma glucose levels.

Obesity

Obesity is illustrated by reduced microbial heterogeneity and over-growth of microbiota phylum *Firmicutes*. A lower ratio of *Bacteroidetes* to *Firmicutes* leads to a greater lipopolysaccharides (LPS) release into the circulation. Elevated LPS levels provide to the chronic low-level inflammatory conditions in obesity (Weiss & Hennet, 2017).

A higher relative number of microbial *Firmicutes* phylum and a lesser number of the microbial *Bacteroidetes* phylum were found in obese rats and humans. The quantity of SCFA provided by intestinal microbiota is a more substantial factor for obesity development than changes in the microbiota composition. It is unclear whether gut microbiota dysbiosis directly induces some metabolic-related disorder or whether the gut microbiota alterations in affected and obese persons are a form of adjustment to host dietary changes (Carding et al., 2015).

Inflammatory Bowel Disease (IBD)

The most common inflammatory bowel disease (IBD) types are Crohn's disease (CD) and ulcerative colitis (UC) which marked by

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chronic inflammation that affects the mucosa of intestine and the extra-intestinal organs. Despite the etiology of those diseases is not clearly known, there is raising evidences that dysbiosis of intestinal microbiota takes a part in the IBD pathogenesis (Carding et al., 2015). Dysbiosis of gut microbiota in IBD involves a decrease in the amount of butyrate-producing bacteria and a higher sulfate depletion, which leads to a decrease in the levels of butyrate and an increase in permeability of the intestinal epithelia and translocation of bacteria (Levy et al., 2017).

In general, there is a reduction in overall microbial heterogeneity and gut microbiota stability in patients with IBD. Particular bacterial species, such as *Faecalibacterium prausnitzii*, which possess anti-inflammatory products, are plenty reduced in IBD patients (Scott *et al*., 2015). Frank et al. (2007) revealed a reduction in the microbial population of *Lachnospiraceae* (a member of the phylum *Firmicutes*) and *Bacteroidetes* but a higher composition of the *Proteobacteria* family in IBD patients compared with intestinal microbiota of the control group.

Nearly all studies regarding the identification of intestinal microbiota in IBD patients show a significant increment in the profusion of *Enterobacteriaceae* species, particularly *Escherichia*/*Shigella* bacteria. *Escherichia coli* is the largest facultative anaerobic bacteria in the mammals gut flora (Round & Mazmanian, 2009; Schippa & Conte, 2014). It is uncertain whether gut microbiota dysbiosis leads to inflammation in IBD directly or is only a consequence of a disrupted environment in the gastrointestinal system (Carding et al., 2015).

Variations in the gut microbiota differ among UC and CD. A relative decrease in the number of the prominent butyrate-producing bacteria species *Faecalibacterium prausnitzii* and *Roseburia hominis* demonstrated in patients with UC compared to healthy controls (Machiels *et al*., 2013). Conversely, in CD patients, there is an increment in the amount of *Faecalibacterium prausnitzii* (Hansen et al., 2012). These study results do not show a causative relation among gut microbiota dysbiosis and the IBD pathogenesis. Nevertheless, they relatively indicate that the imbalance of intestinal microbiota probably contributes to the severity of the disease (Rinninella et al., 2019).

Colorectal cancer

All over the world, colorectal cancer is the second most frequently diagnosed cancer in females and the third in males and also the third leading cause of death from cancer in females and the fourth in males (Jemal et al., 2011). There was an increase of *Enterococcus*, *Bacteroides fragilis*, *Escherichia*/*Shigella*, *Streptococcus*, *Peptostreptococcus*, and *Klebsiella* and a decrease of *Roseburia* and another butyrate-producing bacteria from *Lachnospiraceae* family in the intestinal microbiota of colorectal cancer patients. Nevertheless, in healthy volunteers, the intestinal microbiota was enriched with *Bacteroides vulgatus* and *Bacteroides uniformis* (Wang et al., 2012).

A study by Shen et al. (2010) showed a high number of *Proteobacteria* and a declined number of *Bacteroidetes* in colorectal adenoma patients compared to non-adenoma subjects. Patients with colorectal adenoma revealed a higher amount of *Faecalibacterium* spp. and *Dorea* spp. and a lower amount of *Coprococcus* spp. and *Bacteroides* spp. at the genus level of gut microbiota, compared to controls.

Utilizing analysis of genome, Kostic et al. (2012) reported an association of *Fusobacterium* spp. with the mucosa of the colon in colorectal cancer. They have identified a significant enhancement of *Fusobacterium* spp. and a reduction of *Bacteroidetes* and *Firmicutes* phyla in the microbiome of colorectal cancer. Additionally, *Fusobacterium* spp. may contribute to the generation of the tumor through the inflammatory mechanism,

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but the definite role of *Fusobacteria* spp. in the colorectal cancer pathogenesis remains to be elucidated by further exploration.

Apart from varying results from several different studies, the characteristics of microbiota in adenoma or colorectal cancer cases are defined by a higher amount of potential pathogens, like *Acinetobacter*, *Pseudomonas*, and *Helicobacter*, and reduced numbers of beneficial bacteria, like butyrate-producing bacteria (Wang et al., 2017). Changes in microbiota may have a contribution to the colorectal cancer etiology. The expansion of these study results may be used to identify high-risk individuals and provide as a base for establishing interventions to manipulate intestinal microbiota to prevent colorectal cancer (Rinninella et al., 2019).

Allergic diseases

Evidence showed a reduction of gut microbiota diversity in infancy periods associated with a higher risk of allergic sensitization, eosinophilia, and allergic rhinitis at the age of 6 years (Bisgaard et al., 2011). A systematic review by Murk et al. (2011) revealed that exposure to antibiotics in prenatal or early in life vaguely enhances the risk of suffering asthma in childhood. Evidence from an experimental study in murine with allergic asthma demonstrated that the administration of antibiotics particularly vancomycin decreased microbiota diversity, altered the composition of the bacterial community, and increased severity of asthma in newborn mice, but had no significant effects on older mice (Russell et al., 2012). Moreover, method and location of labor influence the composition of infant intestinal microbiota mainly if dominated by *Clostridium difficile* colonization, consequently increase the risk of developing atopic diseases (van Nimwegen et al., 2011). A study Bunyavanich et al. (2016) observed that intestinal microbiota of infants at age 3-6 months that enriching with Firmicutes and Clostridia are associated with cow's milk allergy (CMA) resolution at the age of 8 years. Since the infant gut microbiota develops promptly during its first year, the composition of intestinal microbiota early in life possibly leads to CMA outcomes during childhood.

Central nervous system disorder

The brain-gut axis entity has been known for decades. This axis has an important part in preserving normal brain function and digestive tract. Lately, intestinal microbiota has appeared as a crucial regulator of the brain-gut axis (Wang et al., 2017). Intestinal microbiota impacts brain alterations through gamma-aminobutyric acid (GABA), which instantly affect several receptors in both the immune system and the nervous system, including the central nervous system and enteric nervous system (Carding et al., 2015). GABA is the principal central nervous system inhibitory neurotransmitter and is implicated in controlling physiological and psychological activities. Expression changing of GABA receptors in the central nervous system involves anxiety and depression pathogenesis (Bravo et al., 2011). The latest research revealed that intestinal permeability and translocation of bacteria could trigger the immune-mediated inflammatory and oxidative stress pathways in depressed patients (Carding et al., 2015).

Hepatic encephalopathy (HE) is one form of liver cirrhosis complications and described as a spectrum of abnormalities in neuropsychiatry that occurred in liver disorder patients (Rinninella et al., 2019). Bajaj et al. (2012) revealed an association of the intestinal microbiota composition with impaired cognition and inflammation in HE. The stools of liver cirrhosis patients, particularly with HE complication, showed a significant increase of *Fusobacteriaceae*, *Enterobacteriaceae*, and *Alcaligenaceae*, and a decrease of

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Lachnospiraceae and *Ruminococcaceae* compared to healthy controls. They found a strong association between particular bacterial families such as *Alcaligenaceae*, *Porphyromonadaceae*, and *Enterobacteriaceae*, with cognitive impairment and inflammation in HE patients.

In 2015, it was estimated that 46.8 million persons had dementia in the whole world, and mostly, this count will be twofold every twelve years, and it will be assumed to be 74,7 million in 2030 (Prince et al., 2015). The most typical forms of dementia in older people are Alzheimer's disease and Parkinson's disease.

The definition of Alzheimer's disease (AD) is a rapidly progressive chronic neurodegenerative disorder related to cognitive impairment and accumulation of amyloid-beta peptide in the cerebral (Rinninella et al., 2019). A study by Cattaneo et al. (2017) revealed an increment plenty of a pro-inflammatory intestinal microbiota *Escherichia/Shigella* and a decrement plenty of an anti-inflammatory gut microbiota *Eubacterium rectale* may be related to a state of inflammatory in periphery that occurred in patients with impaired cognitive function and brain amyloidosis. Another report from Vogt et al. (2017) identified the composition of intestinal microbiota from fecal samples of patients with and without AD. Their analysis demonstrated that in AD patients have a reduced gut microbiota diversity and different in composition from age- and sex-matched controls, with a less amount of *Bifidobacterium* and *Firmicutes* and a greater amount of *Bacteroidetes* in the microbiome of AD patients.

Changes in intestinal microbiota also contribute to the Parkinson disease (PD) pathogenesis (Rinninella et al., 2019). A study by Hopfner et al. (2017) found an enhancement of the abundant *Lactobacillaceae* in patients with PD compared to age-matched healthy controls. PD is related to intestinal microbiota alterations and this dysbiosis probably can be considered as the neuro-inflammation mechanism that contributes to the pathology of PD.

Clostridium difficile infection

Infection caused by *Clostridium difficile* is the best representation of a disease in human arising as a consequence of crucial alterations in intestinal microbiota. This disease can adequately be treated with therapy which based on microbiota (Britton et al., 2014). A meta-analysis by Kassam et al. (2013) reviewed the success of fecal microbiota transplants (FMT) to prevent recurrent infections of *Clostridium difficile* analyzed 11 studies involving 273 patients until March 2012. In general, success rate was around 90% and no side effects associated with FMT were revealed. Seekatz *et al*. (2014) investigated alterations in stool microbiota structure after FMT in relapsing *Clostridium difficile* infection patients. Following FMT, there were a rise in diversity and several microbes from the Firmicutes and Bacteroidetes phyla and a reduction in the plenty of *Proteobacteria*. The composition of fecal microbiota of recipients after FMT was more identical to the donor's microbiota profile than the microbiota before FMT.

CONCLUSION

In the human host, microbiota plays a substantial part in the health and, otherwise, the emergence of various diseases. There is a variation of the optimal composition of healthy intestinal microbiota in each person. The more diverse and abundant the microbiota, the greater their resistance to outside hazards. The colonization and composition of the human microbiota starts and alters promptly after delivery and develops continuously from infant to adult with a quite stable composition in adults.

The close relationship among dysbiosis and intestinal or non-intestinal diseases has been demonstrated although it is still uncertain

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whether dysbiosis is a culprit or a result of the disease. The role of human microbiota must be thoroughly investigated in order to be developed for the prevention, diagnosis of disease, and more effective treatment strategies in the future.

REFERENCES

Azad, M.A.K., Sarker, M., Li, T., & Yin, J (2018). Probiotic species in the modulation of gut microbiota: an overview. *BioMed Research International*, 2018: 9478630. doi:10.1155/2018/9478630.

Bajaj, J.S., Ridlon, J.M., Hylemon, P.B., Thacker, L.R., Heuman, D.M., Smith, S., Sikaroodi, M., & Gillevet, P.M (2012). Linkage of gut microbiome with cognition in hepatic encephalopathy. *American Journal of Physiology Gastrointestinal and Liver Physiology*, 302(1): G168-G175. doi:10.1152/ajpgi.00190.2011.

Bisgaard, H., Li, N., Bonnelykke, K., Chawes, B.L., Skov, T., Paludan-Muller, G., Stokholm, J., Smith, B., & Krogfelt, K.A (2011). Reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age. *The Journal of Allergy and Clinical Immunology*, 128(3): 646-652. doi:10.1016/j.jaci.2011.04.060.

Bravo, J.A., Forsythe, P., Chew, M.V., Escaravage, E., Savignac, H.M., Dinan, T.G., Bienenstock, J., & Cryan, J.F (2011). Ingestion of *Lactobacillus* strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proceeding of the National Academy of Sciences of the United States of America*, 108(38): 16050-16055. doi:10.1073/pnas.1102999108.

Britton, R.A. & Young, V.B (2014). Role of the intestinal microbiota in resistance to colonization by Clostridium difficile. *Gastroenterology*, 146(6): 1547-1553. doi:10.1053/j.gastro.2014.01.059.

Bunyavanich, S., Shen, N., Grishin, A., Wood, R., Burks, W., Dawson, P., Jones, S.M., Leung, D.Y.M., Sampson, H., Sicherer, S., & Clemente, J.C (2016). Early- life gut microbiome composition and milk allergy resolution. *The Journal of Allergy and Clinical Immunology*, 138(4): 1122-1130. doi:10.1016/j.jaci.2016.03.041.

Carding, S., Verbeke, K., Vipond, D.T., Corfe, B.M., & Owen, L.J (2015). Dysbiosis of the gut microbiota in disease. *Microbial Ecology in Health and Disease*, 26: 26191. doi:10.3402/mehd.v26.26191.

Cattaneo, A., Cattane, N., Galluzzi, S., Provasi, S., Lopizzo, N., Festari, C., Ferrari, C., Guerra, U.P., Paghera, B., Muscio, C., Bianchetti , A., Volta, G.D., Turla, M., Cotelli , M.S., Gennuso, M., Prelle, A., Zanetti, O., Lussignoli, G., Mirabile, D., Bellandi, D., Gentile, S., Belotti, G., Villani, D., Harach, T., Bolmont, T., Padovani, A., Boccardi, M., & Frisoni, G.B (2017). Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. *Neurobiology of Aging*, 49: 60-68. doi:10.1016/j.neurobiolaging.2016.08.019.

Eppinga, H., Fuhler, G.M., Peppelenbosch, M.P., & Hecht, G.A (2016). Gut microbiota developments with emphasis on inflammatory bowel disease: report from the Gut Microbiota for Health World Summit 2016. *Gastroenterology*, 151(2): e1-e4. doi:10.1053/j.gastro.2016.06.024.

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Frank, D.N., St Amand, A.L., Feldman, R.A., Boedeker, E.C., Harpaz, N., & Norman, R.P (2007). Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proceeding of the National Academy of Sciences of the United States of America*, 104(34): 13780-13785. doi:10.1073/pnas.0706625104.

Feng, X.W., Ding, W.P., Xiong, L.Y., Guo, L., Sun, J.M., & Xiao, P (2018). Recent advancements in intestinal microbiota analyses: a review for non-microbiologists. *Current Medical Science*, 38(6): 949-961. doi:10.1007/s11596-018-1969-z.

Hansen, R., Russell, R.K., Reiff, C., Louis, P., McIntosh, F., Berry, S.H., Mukhopadhya, I., Bisset, W.M., Barclay, A.R., Bishop, J., Flynn, D.M., McGrogan, P., Loganathan, S., Mahdi, G., Flint, H.J., El-Omar, E.M., & Hold, G.L (2012). Microbiota of de-novo pediatric IBD: Increased *Faecalibacterium prausnitzii* and reduced bacterial diversity in Crohn's but not in ulcerative colitis. *The American Journal of Gastroenterology*, 107(12): 1913-1922. doi:10.1038/ajg.2012.335.

Hopfner, F., Künstner, A., Müller, S.H., Künzel, S., Zeuner, K.E., Margraf, N.G., Deuschl, G., Baines, J.F., & Kuhlenbäumer, G (2017). Gut microbiota in Parkinson disease in a northern German cohort. *Brain Research*, 1667: 41-45. doi: 10.1016/j.brainres.2017.04.019.

Iebba, V., Totino, V., Gagliardi, A., Santangelo, F., Cacciotti, F., Trancassini, M., Mancini, C., Cicero, C., Pantanella, F., & Schippa, S (2016). Eubiosis and dysbiosis: the two sides of the microbiota. *New Microbiologica*, 39(1): 1-12. PMID: 26922981.

Jemal, A., Bray, F., Center, M.M., Ferlay, J., Ward, E., & Forman, D (2011). Global cancer statistics. *CA: A Cancer Journal for Clinicians*, 61(2): 69-90. doi:10.3322/caac.20107.

Kassam, Z., Lee, C.H., Yuan, Y., & Hunt, R.H (2013). Fecal microbiota transplantation for *Clostridium difficile* infection: systematic review and meta-analysis. *The American Journal of Gastroenterology*, 108(4): 500-508. doi:10.1038/ajg.2013.59.

Kostic, A.D., Gevers, D., Pedamallu, C.S., Michaud, M., Duke, F., Earl, A.M., Ojesina, A.I., Jung, J., Bass, A.J., Tabernero, J., Baselga , J., Liu, C., Shivdasani, R.A., Ogino, S., Birren, B.W., Huttenhower, C., Garrett, W.S., & Meyerson, M (2012). Genomic analysis identifies association of *Fusobacterium* with colorectal carcinoma. *Genome Research*, 22(2): 292-298. doi:10.1101/gr.126573.111.

Larsen, N., Vogensen, F.K., van den Berg, F.W., Nielsen, D.S., Andreasen, A.S., Pedersen, B.K., Al-Soud, W.A., Sorensen, S.J., Hansen, L.H., & Jakobsen, M (2010). Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. *PLoS ONE*, 5(2): e9085. doi:10.1371/journal.pone.0009085.

Levy, M., Kolodziejczyk, A.A., Thaiss, C.A., & Elinav, E (2017). Dysbiosis and the immune system. *Nature Reviews Immunology*, 17(4): 219-232. doi:10.1038/nri.2017.7.

Machiels, K., Joossens, M., Sabino, J., De Preter, V, Arijs, I., Eeckhaut, V., Ballet, V., Claes, K., van Immerseel, F., Verbeke, K., Ferrante, M., Verhaegen, J., Rutgeerts, P (2014). A decrease of the butyrate-producing species *Roseburia hominis* and *Faecalibacterium prausnitzii* defines

QANUN MEDIKA
JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

dysbiosis in patients with ulcerative colitis. *Gut*, 63(8): 1275-1283. doi:10.1136/gutjnl-2013-304833.

McBurney, M.I., Davis, C., Fraser, C.M., Schneeman, B.O., Huttenhower, C., Verbeke, K., Walter, J., & Latulippe, M.E (2019). Establishing what constitutes a healthy human gut microbiome: state of the science, regulatory considerations, and future directions. *Journal of Nutrition*, 149(11): 1882-1895. doi:10.1093/jn/nxz154.

Murk, W., Risnes, K.R., Bracken, M.B (2011). Prenatal or early-life exposure to antibotics and risk of childhood asthma : a systematic review. *Pediatrics*, 127(6): 1125-1138. doi:10.1542/peds.2010-2092.

Oliphant, K. & Allen-Vercoe, E (2019). Macronutrient metabolism by the human gut microbiome: major fermentation by-products and their impact on host health. *Microbiome*, 7(1): 1-15. doi:10.1186/s40168-019-0704-8.

Prince, M., Wimo, A., Guerchet, M., Ali, G.C., Wu, Y.T., Prina, M (2015). Alzheimer Report 2015: The Global Impact of Dementia: An Analysis of Prevalence, Incidence, Cost and Trends. Available online: https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf (accessed on 18 September 2020).

Rinninella, E., Raoul, P., Cintoni, M., Franceschi, F., Miggiano, G.A.D., Gasbarrini, A., & Mele, M.C (2019). What is the healthy gut microbiota composition? A changing ecosystem across age, environment, diet, and diseases. *Microorganisms*, 7(1): 14. doi:10.3390/microorganisms701001.

Round, J.L. & Mazmanian, S.K (2009). The gut microbiota shapes intestinal immune responses during health and disease. *Nature Reviews Immunology*, 9(5): 313-323. doi:10.1038/nri2515.

Russell, S.L., Gold, M.J., Hartmann, M., Willing, B.P., Thorson, L., Wlodarska, M., Gill, N., Blanchet, M., Mohn, W.W., McNagny, K.M., & Finlay, B.B (2012). Early life antibiotic-driven changes in microbiota enhance susceptibility to allergic asthma. *EMBO Reports*, 13(5): 440-447. doi:10.1038/embor.2012.32.

Schippa, S. & Conte, M.P (2014). Dysbiotic events in gut microbiota: impact on human health. *Nutrients*, 6(12): 5786-5805. doi:10.3390/nu6125786.

Scott, K.P., Antoine, J.M., Midtvedt, T., & van Hemert, S (2015). Manipulating the gut microbiota to maintain health and treat disease. *Microbial Ecology in Health & Disease*, 26: 25877. doi:10.3402/mehd.v26.25877.

Seekatz, A.M., Aas, J., Gessert, C.E., Rubin, T.A., Saman, D.M., Bakken, J.S., & Young, V.B (2017). Recovery of the gut microbiome following fecal microbiota transplantation. *mBio*, 5(3): e00893 - e00914. doi:10.1128/mBio.00893-14.

Shen, X.J., Rawls, J.F., Randall, T., Burcal, L., Mpande, C.N., Jenkins, N., Jovov, B., Abdo, Z., Sandler, R.S., & Keku, T.O (2010). Molecular characterization of mucosal adherent bacteria and associations with colorectal adenomas. *Gut Microbes*, 1(3): 138-147. doi:10.4161/gmic.1.3.12360.

Shi, Y., Dong, Y., Huang, W., Zhu, D., Mao, H., & Su, P (2016). Fecal microbiota transplantation for ulcerative colitis: a systematic review and meta-analysis.

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JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

PLoS ONE, 11(6): 1-18. doi:10.1371/journal.pone.0157259.

Shreiner, A.B., Kao, J.Y., & Young, V.B (2015). The gut microbiome in health and in disease. *Current Opinion in Gastroenterology*, 31(1): 69-75. doi:10.1097/MOG.0000000000000139.

Sovner, R. (1989). The use of valproate in the treatment of mentally retarded persons with typical and atypical bipolar disorders. *Journal of Clinical Psychiatry*, 50(3 Suppl.): 40-43. PMID: 2494159.

Su, X., Xue, Y., Wei, J., Huo, X., Gong, Y., Zhang, H., Han, R., Chen, Y., Chen, H., & Chen, J (2018). Establishment and characterization of gc-006-03, a novel human signet ring cell gastric cancer cell line derived from metastatic ascites. *Journal of Cancer*, 9(18): 3236-3246. doi:10.7150/jca.26051.

Ticinesi, A., Nouvenne, A., Cerundolo, N., Catania, P., Prati, B., Tana, C., & Meschi, T (2019). Gut microbiota, muscle mass and function in aging: a focus on physical frailty and sarcopenia. *Nutrients*, 11(7): 1-21. doi:10.3390/nu11071633.

Toor, D., Wasson, M.K., Kumar, P., Karthikeyan, G., Kaushik, N.K., Goel, C., Singh, S., Kumar, A., & Prakash, H (2019). Dysbiosis disrupts gut immune homeostasis and promotes gastric diseases. *International Journal of Molecular Sciences*, 20(10):1-14. doi:10.3390/ijms20102432.

van Nimwegen, F.A., Penders, J., Stobberingh, E.E., Postma, D.S., Koppelman, G.H., Kerkhof, M., Reijmerink, N.E., Dompeling, E., van den Brandt, P.A., Ferreira, N.E., Mommers, M., & Thijs, C (2011). Mode and place of delivery, gastrointestinal microbiota, and their influence on asthma and atopy. *The Journal of Allergy and Clinical Immunology*, 28(5): 948-955. doi:10.1016/j.jaci.2011.07.027.

Vogt, N.M., Kerby, R.L., Dill-McFarland, K.A., Harding, S.J., Merluzzi, A.P., Johnson, S.C., Carlsson, C.M., Asthana, S., Zetterberg, H., Blennow, K., Bendlin, B.B., & Rey, F.E (2017). Gut microbiome alterations in Alzheimer's disease. *Scientific Reports*, 7: 13537. doi:10.1038/s41598-017-13601-y.

Wang, T., Cai, G., Qiu, Y., Fei, N., Zhang, M., Pang, X., Jia, W., Cai, S., & Zhao, L (2012). Structural segregation of gut microbiota between colorectal cancer patients and healthy volunteers. *The International Society for Microbial Ecology Journal,* 6: 320-329. doi:10.1038/ismej.2011.109.

Wang, B., Yao, M., Lv, L., Ling, Z., & Li, L (2017). The human microbiota in health and disease. *Engineering*, 3(1): 71-82. doi:10.1016/J.ENG.2017.01.008.

Weiss, G.A. & Hennet, T (2017). Mechanisms and consequences of intestinal dysbiosis. *Cellular and Molecular Life Sciences*, 74(16): 2959-2977. doi:10.1007/s00018-017-2509-x.

Zhang, W., Li, J., Lu, S., Han, N., Miao, J., Zhang, T., Qiang, Y., Kong, Y., Wang, H., Gao, T., Liu, Y., Li, X., Peng, X., Chen, X., Zhao, X., Che, J., Zhang, L., Chen, X., Zhang, Q., Hu, M., Li, Q., & Kan, B (2019). Gut microbiota community characteristics and disease-related microorganism pattern in a population of healthy Chinese people. *Scientific Reports*, 9(1): 1-10. doi:10.1038/s41598-018-36318-y.