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Health Benefits, Associated Disorders and Influencing Factors of Gut Microbiota: A Comprehensive Review

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ABSTRACT

The gut microbiota considered as the diverse community of the microorganisms that found within the gastrointestinal tract. It plays a significant role and provides health benefits to the body in various processes including mental, digestive and metabolic health. This review article highlighted and elaborated the gut microbiota composition, factors affecting on the gut microbiota essential for the metabolic health of body and its brief beneficial role for the human body and also discussed the diseases associated with the gut microbiota in detail. It is also considered that gut microbiome plays a beneficial role in maintaining and improving the overall health of body by employing various mechanisms such as synthesis of vitamins, development and production of short chain fatty acids (i.e., SCFA) and breakdown of the carbohydrates considered as complex. These all factors exhibit healthy role maintenance and regulation of gut associated barriers, improving immunity and fat metabolism system. The disturbance in microbial community of gut leads to gastrointestinal, metabolic and neurological disorders. Different factors such as life style, diet and exercise significantly shapes the gut microbiota which helps in designing personalized therapeutic strategies to prevent life threatening diseases. This review depicts detailed literature on the relation of gut microbiome with the body health.

INTRODUCTION

Introduction to gut microbiota

The gut microbiota is a vital organ of the human body that is accompanied by other organs of body. In 1900s microbiota was first recognized by a Russian scientist named Élie Metchnikoff. It was discovered that different body parts of humans like gut, skin, lungs and oral cavity are colonized by the diversity of different numbers of bacteria, viruses, archaea and many other unicellular microbes (Ursell et al., 2014). The microbiota of human packs 150 times more genetic information as compared to the genome of the entire human combine. This is due to the trillions of microbes which are present inside the human body. They play a vital role in maintenance of human health and in disease (Wang et al., 2017). It was also assumed that gut microbiota has a huge impact in overall condition of human body. Recent researches has manifested the association of gut microbiota with different diseases, which includes metabolic disorders like obesity and type 2 diabetes (Hur & Lee, 2015), gastrointestinal disorders like irritable bowel syndrome (IBD), inflammatory bowel disease (IBD) and celiac disease (Johnson et al., 2016), neurological disorders like autism, anxiety and depression (Lee et al., 2017), and in last place the immunological disorders including autoimmune diseases and different allergies (Brown et al., 2018). In optimum conditions, the gut microbiota also contributes significantly in important functions of human body like digestion, vitamins synthesis, and protection against invading pathogens. It also plays an important role in the breakage of complex carbohydrates and fibers which is difficult to process for human digestive system by its own and also supply energy to body by transforming then into short-chain fatty (Flint et al., 2012). These microbes also participate in the synthesis of essential vitamins (LeBlanc et al., 2013).

Composition of Gut Microbial Ecosystem

Every individual carries a distinctive profile of gut microbiota. Factors such as route of birth, feeding process, lifestyle, diet, usage of antibiotics and many more influence gut microbiota heavily. Recent studies have demonstrated the presence of over 35,000 species of microbes in the human gut (Lozupone et al., 2012). Bacteria in the gut are classified taxonomically into phyla, classes, orders, families, genera, and species. The 90% of the gut microbiota is dominated by only two phyla which are Firmicutes and Bacteroidetes. The other 10% are member of phyla Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia. Phyla Firmicutes contain more than 200 genera, but 95% of this phylum is represented by only 5 genera including Bacillus, Lactobacillus, Clostridium, Enterococcus and Ruminococcus (Shin et al., 2014). the pH of the different parts of the human gut influences the presence of different genera of bacteria which are able to survive that particular pH.

The Distribution of different Bacterial genera according to the pH in various parts of human gut flora is summarized in Table 1.

Table 1

Microbial Distribution in Different Parts of Gut

Esophagus pH < 4.0	Stomach pH 2	Colon pH 5-5.7	Small intestine pH 5-7	Cecum pH 5.7
Bacteroides Gemella Megasphaera Rothiasps Streptococcus Veillonella Pseudomonas Prevotella	Enterococcus, Helicobacterpylori Streptococcus, Lactobacillus, Prevotella,	Bacteroides, Clostridium, Prevotella, Porphyromonas, Eubacterium, Ruminococcus, Streptococcus, Enterobacterium, Enterococcus, Lactobacillus, Peptostreptococcus, Fusobacteria	Bacteroides, Clostridium, Streptococcus, Lactobacillus, g-Proteobacteria, Enterococcus	Lachnospira, Roseburia, Butyrivibrio, Ruminococcus, Fecalibacterium, Fusobacteria

Role in Health

The Humans gut microbiota play an important contribution in number of physiological processes to maintain normal body condition. This process involved cognitive function, metabolism, digestion, immunity and more. The microbial community of gut contributes in health in following ways.

Breakage of Complex Carbohydrates

The unique metabolic ability of the dense microbial community of gut makes it easy to break down complex carbohydrates into simple molecules. These molecules can easily be utilized by human body for different purposes and functions. The gut microbiota releases a variety of enzymes that disintegrate complex carbohydrates which includes resistant starches, dietary fibers, and oligosaccharides. These complex carbohydrates are difficult to digest by enzyme released in small intestine. These enzymes include polysaccharide lyase (PL), glycoside hydrolase (GH), and carbohydrate esterase (CE). They are all carbohydrate-active enzymes that take part in the degradation of polysaccharides into simple molecules like monosaccharides and disaccharides (Rios-Covian et al., 2017).

Production of Short-Chain Fatty Acids (SCFAs)

The fermentation and breakdown of complex carbohydrates are done on their arrival in colon by gut microbiota. This process leads to the production of several useful molecules for the human body. One of the most important results of this fermentation process of complex carbohydrates is the production of short-chain fatty acids (SCFAs), like propionate, acetate and butyrate. These SCFAs serve as a crucial energy source for epithelial cell line of colon called colonocytes. Moreover, butyrate is one of the important SCFA due to its role in inflammation reduction, instigating apoptosis in colon cancer cells and maintaining the integrity of the gut barrier (Louis & Flint, 2017). On the other side, acetate is utilized for the energy production by peripheral tissues and acts as a substrate for lipogenesis (den Besten et al., 2015). Propionate, at the end of the line, is consumed by the liver to inhibit cholesterol formation (Canfora et al., 2015).

Vitamin Synthesis

The different types of vitamins crucial for overall healthy human body can be synthesized by gut microbiota. One of them is vitamin B12, which is produced by the members of genera Lactobacillus and Bifidobacterium, and is essential for different body functions like DNA synthesis, RBC formation and many more. The deficiency of vitamin B12 leads to conditions like anemia which can be lethal (Degnan et al., 2014). Moreover, folate and biotin is also very essential product of gut microbiota. Folate is synthesized by gut bacteria like Lactobacillus reuteri and Bifidobacterium adolescents, useful in processes like DNA synthesis, repair, methylation and amino acid metabolism. On the other hand, Biotin, another key vitamin, is essential for amino acid metabolism, fatty acid synthesis and glucose production. Biotin is produced by the species of genera Bacteroides and bifidobacterium, helps to meet the daily intake when dietary supply is not enough. Biotin is very important for skin, hair and nails (Said, 2011).

Impact on Fat Metabolism

Through mechanism such as regulation of dietary fat absorption, production of short-chain fatty acids, and regulation of lipid storage, gut microbiota strongly influences the fat metabolism. The community of microbes present in the gastrointestinal tract plays a crucial role in fat metabolism. They also have strong impact on digestion and absorption of dietary fats. In small intestine these fats are broken down by pancreatic lipase into fatty acids and monoglycerides, which then combine with bile acids to form micelles. This process helps in the absorption of fatty acid and monoglycerides into cells which line our small intestine called enterocytes. Moreover, this whole process is facilitated by the production of bile salt hydrolase enzyme produced by the gut bacteria like *Bacteroides fragilis*, *Clostridium butyricum*, and *Lactobacillus acidophilus.* These enzymes change the structure of bile acids, impacting micelle formation and efficient absorption of fatty acids and monoglycerides (Ridlon et al., 2014). Furthermore, Short-chain fatty acids like acetate and propionate, which are produced by gut microbiota through the fermentation of dietary fibers, had a strong influence on the regulation of lipid metabolism (Canfora et al., 2015).

Impact on Immune System

The relationship between gut microbiota and immune system has a strong influence on body immunity. This relationship affects the body's response to different invading pathogens and allergens. At the time of birth, the initial exposure and colonization of gut microbiota shape the neonatal immune system. This immune system is strongly influenced by the mode of delivery such as vaginal birth or cesarean section and also the early feeding practices of neonates (Korpela & de Vos, 2018). Research has shown that children with less microbial diversity or different composition of gut microbiota in early life due to various reasons are most likely to develop different allergies and diseases due to compromised immunity (West et al., 2015).

Feeding practices influence the growth of beneficial bacteria like *Bifidobacterium* and *Lactobacillus* in neonatal gut due to the presence of oligosaccharides in the breast milk of mother (Ballard & Morrow, 2013). These bacteria are essential for the balanced immune system because they stimulate the development of gut-associated lymphoid tissue (GALT). The interaction of gut microbiota with immune cells in intestinal mucosa plays a critical role in distinguishing between harmless antigens like food and harmful pathogenic antigens. The excessive immune response is also suppressed the certain gut bacteria like *clostridium* species because these bacteria induce the production of regulatory T cells which produce anti-inflammatory cytokines like IL-10 and TGF- β (Geuking et al., 2014). The gut microbiota also protects against invading pathogens by different ways like lactic acid produced by *Lactobacillus* and *Bifidobacterium* species inhibit the growth of pathogens such as *Salmonella* and *Clostridium difficile* (Gareau et al., 2010). These different roles show the critical importance of gut microbiota in maintaining a balanced immune system.

Gut Barrier Integrity

The gut microbiota helps in maintaining the gut barrier which prevents toxins, pathogens and other harmful substances from diving into the bloodstream from the digestive system. The intestinal barrier is consists of epithelial cell layers that are held together by tight junctions. The permeability of the gut is remarkably affected by these junctions, which allow only nutrients to pass through it. Short-chain fatty acids (SCFAs) produced by gut microbiota maintain the integrity of these junctions like butyrate which has a significant effect on strengthening the gut barrier (Peng et al., 2009). The intestinal damage repair is also a crucial aspect in maintaining gut barrier integrity. Gut microbes produce certain growth factors and cytokines which stimulate the differentiation and proliferation of epithelial cell lining of the gut (Matsumoto et al., 2018). Moreover, the microbiota is also helpful in regulation of the immune response in the gut. The neutralization and translocation of harmful pathogens across the gut barrier is done by the antimicrobial peptides and secretory IgA, produced by gut microbes. Gut microbiota helps prevent inflammation through these responses which inhibit damage to gut lining (Hooper et al., 2012). The increased gut permeability due to the disruption of gut microbiota leads to a condition called "leaky gut". Due to these pathogens and toxin can easily pass the gut barrier and enter into bloodstream, leads to many chronic diseases and systemic inflammation (Camilleri et al., 2012).

Role in Xenobiotic Metabolism

Over the last decades, the ability of gut microbiota to metabolize xenobiotics and drugs has received significant attention. Researchers are taking substantial interest due to its potential effect on personalized medicines and therapies. The engagement between gut microbiota and pharmaceutical drugs can significantly influence drug efficacy, metabolism and toxicity. The xenobiotic metabolism is influenced by various enzymatic processes that include reactions like hydrolysis, reduction and conjugation. These reactions convert drugs into active, inactive or toxic metabolites. Gut microbes produce enzymes such as β-glucuronidases, azoreductases, and sulfatases that target a broad range of xenobiotics. Deconjugation of drugs by β-glucuronidases enzyme is a well-known process of microbial xenobiotic metabolism. Irinotecan is a chemotherapy drug which is commonly used to treat colon cancer. This drug is processed into an active form by the liver and then sent to the gut. In the gut, β-glucuronidases produced by the gut microbiota can reactivate this drug within the intestine. This can cause serious side effects like diarrhea and inflammation of the colon (Wallace et al., 2010). Moreover, the gut microbiota also influences the host's overall response to drugs. For example, the adsorption of certain drugs is affected by gut microbiota either by directly altering gut permeability or pH (Spanogiannopoulos et al., 2016).

Gut-Brain Axis

The Brain and Gut communicate through a two-way communication network where central nervous system (CNS) and enteric nervous system (ENS) are interconnected. This communication is facilitated by various pathways such as hormonal response, nervous system signals, chemical signaling and immune system interaction. Neurotransmitters such as dopamine, serotonin and gamma-aminobutyric acid (GABA) are produced by the certain gut bacteria of gut. Through these neurotransmitters gut microbiota primarily impact brain. Serotonin, a neurotransmitter essential for regulating mood and emotions is majorly produced by the gut bacteria like *Enterococcus* and *Streptococcus* in the body (Clarke et al., 2013). Moreover, GABA which can influence the anxiety and stress is also produced by the gut bacteria like *Lactobacillus* and *Bifidobacterium* (Barrett et al., 2012). The brain is also influenced by the gut microbiota through systemic immune response by releasing cytokines which have strong impact on brain function. For example, inflammatory cytokines can cross the blood-brain barrier and have a significant effect on neuroendocrine function, neurotransmitter metabolism and neuronal plasticity (Cryan & Dinan, 2012). Short-chain fatty acids specially butyrate produced by the gut bacteria through the fermentation of dietary fibers, have been shown to affect brain-derived neurotrophic factor (BDNF) expression. That supports neural growth and synaptic plasticity which have positive effects on learning and memory (Stilling et al., 2016).

Disorders Related to Gut Microbiota Imbalance

Dysbiosis refers to the disturbance of microbial composition which occurs when in the gut there is decrease in the number of beneficial microbes and deposition of harmful bacteria. This imbalance leads to the development of various disorders like Inflammatory Bowel Disease (IBD), type 2 diabetes, obesity, anxiety and depression. These disorders can also be life-threatening as well.

Gastrointestinal Disorders

Dysbiosis can leads to various gastrointestinal disorders like inflammatory Bowel Disease (IBD), irritable bowel syndrome (IBS), and Celiac disease. This disorder can cause serious issues for body's normal functioning.

Inflammatory Bowel Disease (IBD)

The exact cause of IBD isn't fully understood till date. It is thought to be a combination of factors such as genetics, immune system issues, environmental factors and also imbalance in gut microbiota. Chronic inflammation of gastrointestinal tract give rise to IBD which also includes conditions like Ulcerative Colitis and Crohn's Disease as well. Researchers have seen the reduction of the beneficial bacteria like *Frimicutes* and *Bacteroidetes* and increased population of harmful ones like *Proteobacteria* and *Actinobacteria* in the IBD patients (Frank et al., 2007). This disruption weakens the gut barrier which allows pathogens and toxins to easily pass through it and reach the internal lining. That invasion triggers the immune response and leads to the chronic inflammation (Kostic et al., 2014).

Irritable Bowel Syndrome (IBS)

IBS is a very common digestive disorder which shows symptoms like bloating, frequent abdominal pain, diarrhea and constipation. Unlike in the case of IBD, IBS does not cause inflammation or any notable tissue damage but it can still have a significant impact on patient's daily routine. The fundamental cause of IBD includes increased sensitivity of the digestive tract, disturbance in the gut brain axis and alteration in gut motility. The reduced population of bacteria like *Lactobacillus* and *Bifidobacterium* and increased in number of harmful one like *Enterobacteriaceae* and *Clostridia* is found in the IBD patients (Salonen et al., 2010). Moreover, Probiotics and prebiotics have shown helpful in treating IBS by restoring healthy balance of gut bacteria. Probiotic strains like *Bifidobacterium infantis* are helpful in reducing symptoms of IBS like bloating and abdominal pain (Whorwell et al., 2006).

Celiac Disease

Celiac disease is generally an autoimmune disorder caused by the consumption of gluten which is a type of protein present in foods like wheat, rye and barley. When patients with celiac disease ingest gluten-rich food like wheat their immune system unintentionally attacks the intestinal lining which leads to nutrient depletion and symptoms like stomach pain and diarrhea. Dysbiosis is observed in celiac disease patients that involves a reduced population of beneficial bacteria like *Bifidobacterium* and *Lactobacillus* and increased in number of inflammatory bacteria like *Bacteroides* and *Enterobacteriaceae* (Collado et al., 2009).

Metabolic Disorders

The metabolic homeostasis of body is heavily influenced by the gut microbiota. Dysbiosis can result in various metabolic disorders like obesity and type 2 diabetes mellitus (T2DM). The gut microbiota has a significant effect on the energy balance, glucose metabolism and insulin sensitivity which contributes to the development and progress of following metabolic disorders.

Obesity

Obesity is a complex condition often characterized by excessive fat accumulation in the body. The composition of gut microbiota has a strong effect on obesity. Generally, an obese individual has a less diverse microbiota and a different ratio of two major gut bacteria like *Firmicutes* and *Bacteroidetes* (Cani & Delzenne, 2009). As compared to lean person, an obese person has a higher proportion of *Firmicutes* and less proportion of *Bacteriodetes*. This imbalance contributes efficiently in the body's ability to extract energy from food which possibly leads to increased fat storage in different body parts (Turnbaugh et al., 2006). Additionally, Metabolism is also affected by the gut bacteria by the production of short-chain fatty acids (SCFAs). These SCFAs helps in fat storage and energy balance in the body (Canfora, Jocken, & Blaak, 2015). In obese people, more energy is being stored in the form of fat due to the increased SCFA production (Schwiertz et al., 2010).

Type 2 Diabetes Mellitus (T2DM)

T2DM is also very closely related to gut microbial dysbiosis. It mainly involves insulin resistance, low grade chronic inflammation and high blood sugar levels. Studies have shown the distinct gut microbiota of individuals with T2DM as compared to healthy individuals (Qin et al., 2012). Qin et al. (2012) proved this by conducting a metagenomic analysis on large scale and concluded that patients with T2DM had a significant less population of butyrate producing bacteria in the gut. Butyrate helps in maintaining intestinal barrier and reducing inflammation. Butyrate deficiency can contribute to the chronic inflammation and leaky gut (Vrieze et al., 2012). Moreover, gut microbiota also affects glucose metabolism by bile acids. Bile acids are produced by the liver which helps in fat digestion and glucose regulation. Gut bacteria modify primary bile acids into secondary bile acids. These secondary bile acids act as signals to manage metabolism via different receptors like FXR and TGR5. Dysbiosis leads to the disruption of bile acid modification which potentially leads to insulin resistance in the body (Joyce &

Gahan, 2014) (Tilg & Moschen, 2014).

Neurological Disorders

The connection between gut microbiota and neurological disorders has gained significant attention in last few years. The gut-brain axis is a bidirectional communication system which connects CNS and GIT. Gut microbial imbalance can significantly impact this system and leads to the various neurological disorders like autism, depression and anxiety.

Autism Spectrum Disorders (ASD)

ASD is a group of neurological conditions that defined by difficulties in communication, social interaction and behavior. Studies have found the difference in the microbial composition of gut of ASD children from children without them. Finegold et al. (2010) had seen the high number of pathogenic bacteria like *Clostridia* and *Sutterella* but on the other hand bacteria like *Bifidobacterium* and *Lactobacillus* were found in less number. This dysbiosis contributes to common gastrointestinal issues in patients such as constipation, diarrhea and abdominal discomfort which leads to the serious behavioral problems. Moreover, Particular gut microbes can produce SCFAs which are able to cross the blood-brain barrier and strongly influence brain development and its functions (Mulle et al., 2013). Additionally, some other issues like leaky gut and immune system disturbance have been also linked to ASD (de Theije et al., 2014).

Depression

Depression is another neurological disorder that has been strongly influenced by gut microbiota. It is a very common brain disorder which is identified by lasting sadness, hopelessness and lack of interest in routine activities. The gut-brain axis is believed to influence the effect of gut microbiota on mood and behavior leads to disorders like depression. Zheng et al. (2016) conducted a study and seen that people who are struggling with depression have a different gut microbial profile from those of healthy individuals. Particularly the study found a notable reduction in beneficial bacteria like *Lactobacillus* and *Bifidobacterium* on the other hand the presence of pro-inflammatory bacteria like *Enterobacteriaceae* is sharply increased in depress parsons. This dysbiosis leads to the inflammation which often observed in people with depression. This inflammation can negatively impact brain functions and emotions. The production of key neurotransmitters such as serotonin and dopamine is also influenced by gut microbiota which plays a vital role in mood stability. Serotonin is closely related with feelings of happiness. About 90% of body's serotonin is produced in gut by the influence of gut bacteria. Low serotonin level leads to depressive symptoms (Yano et al., 2015).

Anxiety

Anxiety is another neurological disorder related to dysbiosis. Anxiety is a very common disorder of mental health which is defined by fear, unease and excessive worry. Sudo et al. (2004) conducted an animal study on mice and found that germ free mice which have week gut microbiota shows high stress level and anxiety as compared to the regular mice. Additionally, when these germ-free mice were exposed to microbiota from healthy ones their stress and anxiety like behaviors is noticeably reduced. Moreover, Liang et al. (2018) conduct a study on humans which have shown the disrupted gut microbiota in individuals with anxiety issues. This disruption usually involves an increase in harmful bacteria like *Proteobacteria.* Such Imbalance can lead to inflammation and also interrupt in the production of neurotransmitters which play a vital role in modulating stress and mood.

Factors Affecting Gut Microbiota

The composition of the gut microbiota is affected by the factors like diet, lifestyle and antibiotics. By understanding such factors can be helpful in keeping overall gut health.

Diet

Diet has a significant effect on the composition of gut microbiota. High fiber diet more importantly which contain complex carbohydrates is very good for our gut bacteria. Complex carbohydrates enhance the growth of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus* (Flint et al., 2012). These bacteria are helpful in fermentation of fibers which turn out to be Short-chain fatty acids which have anti-inflammatory properties and also support overall body's health. Moreover, the high protein food can affect gut microbiota because some by-products of protein rich foods such as ammonia and hydrogen sulfide can be harmful for gut lining and also promote the growth of harmful bacteria as well (Canfora et al., 2015). Vitamins and minerals rich diets especially that rich in vitamin D and zinc is also very important for shaping gut microbiota (Singh et al., 2017).

Antibiotics

Antibiotics are one of the most used treatments to reduce bacterial infections but their over-use can also negatively impact the gut by altering the composition of gut microbiota. Antibiotics often decrease the microbial diversity in the gut which can leads to an overgrowth of pathogenic bacteria like Clostridium difficile over there (Francino, 2016). Antibiotics can also cause permanent changes in the gut microbial composition. The gut microbial shift due to the early exposure to antibiotic in life may increase the risk of developing conditions like asthma and obesity (Francino, 2016) (Blaser, 2016).

Lifestyle Factors

Lifestyle factors such as stress, lack of sleep and minimum to low physical activity also play a vital role in shaping gut microbiota and overall health of the body. Chronic stress can affect negatively the gut by decreasing the population of beneficial bacteria like *Lactobacillus* which leads to increased gut permeability (Foster et al., 2017). Regular exercise and physical activity can also support gut health because it support the growth of beneficial bacteria like *Akkermansia muciniphila* which helps in maintaining gut barrier function (Barton et al., 2018). Moreover, the sleep patterns and deficiency have a direct impact on gut heath. Lack of sleep can lead to the alteration in gut microbial composition (Thaiss et al., 2016).

CONCLUSION

Gut microbiota plays a vital role in our overall body's health. It also affects processes like digestion, immunity and mental health. Balanced community of gut microbes is very important for overall health. The disturbance in microbial composition of gut leads to several disorders like obesity, diabetes and depression. We can improve our gut health by understanding those factors which influence gut microbiota like our daily eating habits, lifestyle and use to antibiotics. Our future research should be focus on personalized treatments based on microbiome of person. We should also focus on therapies like prebiotics, probiotics and microbiota transplant which can be helpful in maintaining microbial balance and improve overall health of human body.

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