

Healthy Gut Microbiome: An Aid to Good Health – A Narrative Review

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Abstract: The human gastrointestinal system works as a complex community that plays a crucial role in the assimilation of food and nutrients. The human gut is well known as the second brain, as it directly influences human physiology by integrating with metabolism and the immune system; thus, it evolves as a developing brain as it ages and adapts to the environment, region, and ethnicity of the individual. When the gut microbial balance is disrupted by a pathogen, it leads to dysbiosis, which affects gut flora and can cause intestinal diseases such as IBD, IBS, celiac disease, and colorectal cancer, and alters the immune system. This review summarizes our current understanding of the human gut system and development, dysbiosis, and associated diseases, and their impact on the immune system.

Keywords: gut microbiome; dysbiosis; vagus nerve; immune system; SCFA.

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1. Introduction

If our digestive system is considered a miniature manufacturing unit, then the microorganisms present in the gut can be called the unit's core workers. These organisms are commonly called the gut microbiota. Recent studies have revealed that the ratio of human to bacterial cells is closer to 1:1. Also, by analyzing ~78 million base pairs of unique DNA sequences found in gut microbiota, it has been found to contain at least 100 times as many genes as our own genome. Leading to enhanced metabolic activity by microbiota than by our cells, making a coalescent habitat of microorganisms and host as 'superorganisms' [1].

Though gut microbial diversity differs by race, ethnicity, and family genetic makeup, the three major phyla that comprise the normal human gut are Bacteroidetes, Proteobacteria, and Firmicutes. Because of this varied differentiation, they aid in integrating gut health to regulate host immunity, playing a crucial role in human health [2].

From the Human Microbiome Project, it was identified that there are 12 phyla, of which 93.5% belong to Proteobacteria, Firmicutes, Bacteroidetes, and Actinobacteria, and Akkermansia muciniphila is the only species in the Verrucomicrobia phylum. This statement may also differ by including more data analysis on various ethnicities. It has been found that nearly 386 identified species are anaerobic, indicating their presence in mucosal regions such as the oral cavity and GI tract [3].

This review summarises our current understanding of the human gut system and development, dysbiosis and associated diseases, and its impact on the immune system.

2. Geomorphology of Gut Microbiota

Even though microbiomes are abundant, their distribution throughout the GI tract is uneven. The main factor is due to the differentiated composition of the gut system and its pH—the chemical, nutritional, and immunological gradients within the gut influence both its composition and population density. The concentration of microbiota increases steadily along the GI tract, from a few in the stomach and duodenum to densely populated microbes in the intestine, as the inhospitable environment, with very few bacteria resistant to gastric acid, bile, or pancreatic enzymes, changes to a basic, alkaline environment [4]. Within the proximal gut, mucosa-associated bacteria such as *Lactobacillus* (Firmicutes), *Veillonella* (Firmicutes), and *Helicobacter* (Proteobacteria) are prevalent. Meanwhile, Bacilli (Firmicutes), Streptococcaceae (Firmicutes), Actinomycinaeae, and Corynebacteriaceae (Actinobacteria) dominate the duodenum, jejunum, and ileum, with elevated levels of Lachnospiraceae (Firmicutes) and Bacteroidetes also reported in this region. [5].

The major contributor to nutrient absorption and active digestion is the small intestine, which results in a high number of acids, oxygen, antimicrobial gradients, and a short transit time; thus, the mucosa-associated bacteria of the phyla Bacteroidetes and Firmicutes are present in minimal amounts [2]. In contrast, the colon region supports a dense and diverse colony of bacteria, labeling it as a place of anaerobes that digest complex carbohydrates not digested in the small intestine; phyla such as Prevotellaceae, Lachnospiraceae, and Rikenellaceae are densely populated [5].

3. Development of Gut Microbiota

The gut microbiota begins only at birth, as the womb is a sterile environment. Hence, the entry of any phyla is a difficult one; the mode of delivery plays a crucial role in the development of gut microbes, with vaginally delivered infants having high colonization of *Bacteroides* and *Lactobacilli* species as these phyla are loaded in vaginal flora [6,7]. Apart from the vaginal and breast milk transfer of microbes, skin also colonizes certain species, mainly *Streptococcus* and *Staphylococcus*, which develop within one week of exposure to the environment [8].

In contrast, infants delivered via C- section has highly colonized facultative anaerobes such as *Clostridium* species and depleted inoculation of *Bacteroides* and *Bifidobacterium* genus, it is also found that infants have similar fecal microbiota as their mother's fecal microbiota, in addition, due to hospital environment exposure they have pathogens such as *Enterococcus*, *Enterobacter*, and *Klebsiella* species which play a complicated role as being an immune booster and disease-causing pathogens [9].

Ethnicity-based diversification and differentiation are major factors in determining a country's future perspective for planning and altering the lifestyle and food habitat, in a study conducted by comparing European and African kids shows sensational results that African kids' lifestyle and diet which is enriched with millet and local vegetable give rise to abundance amount of *Prevotella* and *Xylanibacter* with a low level of *Shigella* and *Escherichia* is found. In contrast, European kids' diets are high in lipids and animal proteins; they have low levels of Proteobacteria and Spirochaetes, with Actinobacteria as the subdominant group, leading to energy production via fermentation, which is not food for the body [10].

During the journey from infancy to pre-toddlerhood, the microbiome develops in ways similar to those of adults, with feeding methods, family physical contact, and the weaning

period playing a major role in diversifying microbial colonization. By the time a child reaches 1 to 2.5 years of age, the gut microbiota is typically enriched with *Akkermansia muciniphila*, *Bacteroides*, *Veillonella*, *Clostridium coccoides*, and *Clostridium botulinum* species [2,11].

Later, it stabilizes as in adults with species population dominated by three phyla, such as Firmicutes (*Lachnospiraceae*, and *Puminococcaceae*), Bacteroidetes (Bacteroidaceae, Prevotellaceae, and Rikenellaceae), and Actinobacteria (Bifidobacteriaceae and Coriobacteriaceae), with density regulated by genetic factors, ethnicity, diet, environmental conditions, lifestyle, and gut physiology. [12].

Overall, microbiome colonies vary across generations, specifically in the population of the late 60s to 70s. Reports indicate that colony composition shifts toward higher abundance of Bacteroidetes and Clostridium cluster IV, whereas in younger individuals, Clostridium cluster XIV is more prevalent. The colon is densely populated with facultative anaerobes such as *Escherichia coli* and self-limiting butyrate producers like *Faecalibacterium prausnitzii*[11].

4. Role of Gut Microbiota for Human Health

The physiology of the intestine is beautifully designed in such a way that the inner lining of the intestine is thickest and the outer layer is loosely adherent to the mucus where this mucus layer acts as the first line of a defense mechanism by producing antimicrobial proteins when pathogens are found in the host, making these pathogens mucus binding and leaving gut microbiota to adhering to the mucus lining, as mucin are rich in glycosylation and contain numerous mono-, di-, trisialylated oligosaccharides. It is found that gut microbes such as *Bacteroides thetaiotaomicron* and *Faecalibacterium prausnitzii* are involved in regulating the thickness of the mucus-adherent lining during a pathogen intervention by inducing small proline-rich protein 2A (*spry2a*) [13]. Also, microbes such as *R.gnavus*E1, *Lactobacillus casei* DN-114 001, and *B. thetaiotaomicron* influence the glycosylation of the mucus lining and modulate glycosyltransferase expression [2].

The gut microbiota contributes to xenobiotic metabolism, with p-cresol reducing hepatic acetaminophen metabolism by competitively inhibiting sulfotransferases [14]. *Eggerthella species of the Actinobacteria phylum seem to be upregulated by cardiac glycosides like digoxin, leading to digoxin inactivation* [15].

Evidence shows that de novo synthesis of essential vitamins is also aided by gut microbiota. Lactic acid bacteria are the primary organisms for the synthesis of vitamin B12 [16]. Other organisms, such as *Bifidobacteria*, are the main producers of folate, which is highly utilized during gestation and the DNA synthesis and repair period. In addition, the gut microbiome is responsible for synthesizing vitamins like vitamin K, riboflavin, biotin, nicotinic acid, pantothenic acid, pyridoxine, and thiamine [17].

Microorganisms, including *Bacteroides*, *Roseburia*, *Bifidobacterium*, *Faecalibacterium*, and *Enterobacteria*, ferment complex carbohydrates and indigestible oligosaccharides, producing short-chain fatty acids (SCFAs) such as butyrate, propionate, and acetate, which serve as important energy sources for the host. They also act as a source of expressing enzymes for the host's needs. It also participates in lipid metabolism by alleviating the inhibition of lipoprotein lipase activity in adipocytes, with *Bacteroides thetaiotaomicron* modulating lipid hydrolysis necessary for pancreatic lipase-mediated digestion. Gut microbes are involved in the breakdown of various polyphenols, and the products are directed to tissues and organs. *Oxalobacterformigenes*, *Lactobacillus species*, and *Bifidobacterium species* reduce the formation of oxalate stones in the kidney [18].

5. Dysbiosis – Contributors to Gut Diseases

Dysbiosis is identified as an imbalance in the beneficial and harmful gut bacteria, which leads to the disruption of the microbe flora in the gut, and adversely affects their functional composition and metabolic activities, among the microbial flora in humans such as skin flora, gut flora, and vaginal flora, dysbiosis is commonly reported as a condition in the gastrointestinal tract [19].

In general, it is normal for harmful gut microbes to be present in the gut flora, but an increased ratio of these microbes to beneficial microbes can lead to this condition as they compete for space, food, and other resources. The key functions of beneficial microbes include facilitating metabolism, suppressing gut pathogens, and producing essential nutrients. Persistent imbalance diminishes the collective beneficial effects of these microbial populations [20].

Dysbiosis can arise from various factors, including excessive antibiotic use, psychological and physical stress, chemotherapy, radiation therapy, exposure to radioactive isotopes, and dietary alterations. These elements have been shown to disrupt the intestinal microbiota [21].

The interplay between gut microbiota and pathogenic microbes is controversial. Metagenomic analyses reveal that in healthy individuals, *Bacteroidetes* and *Firmicutes*, together with *Proteobacteria*, *Actinobacteria*, *Fusobacteria*, *Spirochaetes*, *Verrucomicrobia*, and *Lentisphaerae*, account for roughly 40% of the microbial genes in the colon. Any disturbance in this microbial composition can shift the ratio of commensal to pathogenic microbes, resulting in dysbiosis [22].

Due to wide variation among individuals in genetic makeup, age, and other factors, further investigation is needed to determine the distribution of each non-pathogenic and pathogenic microbe in diseased conditions. In simple terms, dysbiosis is a disruption in gut microbiota balance, which can lead to or arise from health disorders. Sometimes, it may lead to beneficial conditions for the gut, but it mostly contributes to disorders. Dysbiosis causes two types of disorders: intestinal and extra-intestinal.

From the review by [23] the intestinal disorders majorly affect humans includes Irritable bowel syndrome (IBS), Inflammatory bowel disease (IBD), Celiac disease (CD) and Colorectal cancer (CRC); and extra-intestinal disorders includes metabolic disorders (obesity, type 2 diabetes), central nervous system (CNS) – related disorders (Alzheimer's and Parkinson's diseases, hepatic encephalopathy, autism spectrum disorders, stress, and cardiac vascular disorders).

The primary causative factors of dysbiosis are metabolites produced by colonic microbiota as a result of incomplete digestion in the stomach and small intestine. These metabolites include short-chain fatty acids (SCFAs), branched-chain fatty acids, ammonia, amines, phenolic compounds, and gases such as hydrogen, methane, and hydrogen sulfide [24]. Other metabolites, including the SCFAs acetate, propionate, and butyrate, represent the major anions in the colon, generated through bacterial fermentation of undigested carbohydrates. Even plant polyphenols can alter microbial distribution by metabolizing into an active form, and an unhygienic lifestyle is also a contributor to dysbiosis in the intestine [22].

6. Diseases associated with Dysbiosis

6.1. Inflammatory bowel diseases (IBD).

This disease is characterized by recurrent episodes of GI tract inflammation caused by abnormal gut microflora. It consists of two types: Crohn's disease and ulcerative colitis. Where both conditions are characterized by chronic, repetitive inflammation of the GI tract, ulcerative colitis involves diffuse inflammation of the colonic mucosa, and Crohn's disease results in transmural ulceration of a large portion of the GI tract. The causative factor in this disease is dysbiosis in the colon, characterized mainly by a decrease in Firmicutes and an increase in Proteobacteria. In Crohn's disease, a decrease in *Ruminococcaceae* and *Lachnospiraceae* of Firmicutes is found [25]. Reports from microbial analysis reveal that patients affected by IBD have an enormous immunological impact by increased number of neutrophils, macrophages, dendritic cells, and natural killer T cells, along with increased level of tumour necrosis factor- α (TNF- α), interleukin-11b, interferon-gamma, and cytokines of the interleukin-23-TH17 pathway to fight against increased *Proteobacteria taxa* and *Lachnospiraceae* [26]. Mesalamine is the most commonly prescribed medication for both ulcerative colitis and Crohn's disease, as the severity increases. In addition, TNF-alpha monoclonal antibodies (infliximab) are prescribed for ulcerative colitis and Crohn's disease [27].

6.2. Irritable bowel syndrome (IBS).

A mild yet repetitive recurring abdominal pain, altered bowel movement routines, and discomfort are the common characteristics of this syndrome. The root cause of this disease is still unknown, and a harmful lifestyle routine is predicted as its root cause. Microbial dysbiosis in the gut is characterized by reduced levels of *Bifidobacterium* and *Faecalibacterium spp.* An increase in the phylum of Firmicutes, such as *Ruminococcus*, *Clostridium*, and *Dorea*, with a high population of phylum Proteobacteria, family *Enterobacteriaceae* (*Escherichia*, *Shigella*, *Campylobacter*, and *Salmonella*), family *Lactobacillaceae*. The pathophysiology states that IBS affects gut-brain interaction and psychosocial distress. Histological reports show that, in chronic inflammatory conditions, mast cells, enteroendocrine cells, and certain subtypes of IBS exhibit high T-lymphocyte deposition. While no specific treatment exists for this syndrome, management strategies include the use of probiotics and restricting FODMAP-containing foods such as wheat and sorbitol [28,29].

6.3. Celiac disease.

Celiac disease is known as an autoimmune disease due to immune modulation in the expression of the human leukocyte antigen system (HLA-DQ2 and HLA-DQ 8), due to which the presence of metabolite gliadin from gluten damages the small intestine, resulting in reduced intestinal absorption. In patients without medication or dietary restrictions, microbial dysbiosis is characterized by lower levels of *Bifidobacterium spp.*, *B. longum*, *Clostridium histolyticum*, *C. lituseburense*, and *Faecalibacterium prausnitzii*, along with elevated levels of pathogenic bacteria such as *Bacteroides* and *E. coli*, and a decline in beneficial species such as *Lactobacillus* and *Bifidobacterium* [23]. Treatment for this disease involves strictly adhering to a gluten-free diet, as the surface brush border is lactase-deficient, along with taking prolyl-endopeptidase enzyme supplements to reduce the overpopulation of T-cells, and taking probiotics to increase beneficial microbes in the gut [30].

6.4. Colorectal cancer.

This type of cancer is the third most common cancer in the world. Though the cause of this disease is complicated, due to the microbial dysbiosis, the stage and incidence of the disease can be studied. The pathophysiology of this issue lies in metabolic and immunological instability. Analysis of the microbiota showed enrichment of *Bacteroides fragilis*, *Enterococcus*, *Escherichia/Shigella*, *Klebsiella*, *Streptococcus*, and *Peptostreptococcus* in patients, with notable representation of *Roseburia* and Lachnospiraceae butyrate producers. Genomic analysis indicates that colorectal cancer patients exhibit increased abundance of *Dorea* spp., *Faecalibacterium* spp., and *Fusobacterium* spp. compared to the control group [23]. *Fusobacterium* spp causes tumorigenesis through an inflammatory-mediated mechanism. Treatments such as endoscopic resection, adjuvant therapy, neoadjuvant therapy, and systemic therapy are prescribed based on the degree of carcinoma and pathogenic microbial population [31].

7. Complicated Association of Vagus Nerve – Immune System – Gut Microbiota

The vagus nerve is the tenth cranial nerve, which is the longest cranial nerve in the body. It is a bidirectional approach to communication via the afferent and efferent. Connects the entire region of the body, including the tongue, pharynx, heart, and gastrointestinal system, and regulates metabolic homeostasis by controlling heart rate, gastrointestinal motility and secretion, pancreatic endocrine and exocrine secretion, hepatic glucose production, and other visceral functions. And it has been discovered that bidirectional communication linking the gut microbiota-brain axis is achieved through the neuroendocrine system, which is the hypothalamic-pituitary-adrenal axis, the neuroanatomical pathways, cytokines, and via chemical pathways involving microbial metabolites (SCFA) and some specific neurotransmitters.

From the studies conducted by Han and team in the year 2022 [32], it was reported that as the dysbiosis continues and becomes a chronic one, it leads to the destruction of intestinal epithelium, which affects microbiota and their metabolites to communicate with the afferent arm of the vagus nerve via multiple specific receptors. In the case of *Edward siellatarda*, it specifically binds to the receptor transient receptor potential ankyrin A1 (TRPA1), whereas microbial metabolites, such as glutamate and other SCFA, transmit signals to vagal afferents from enteroendocrine cells and affect the neural system.

8. Gut microbiota and Immunity

Gut microbial metabolites play a crucial role in distinguishing between native gut microbiota and parasitic microbes in the mucosal immune system. The metabolites that signal the immune system in the gut are known as SCFAs, which modulate host immune cells and signalling molecules to colonocytes. SCFAs are fatty acids that consist of acetate, propionate, and butyrate. Commensal microbes, including *Faecalibacterium prausnitzii*, *Roseburia intestinalis*, and *Anaerostipes butyraticus*, metabolize complex carbohydrates from opportunistic pathogens via fermentation, producing SCFAs. These signalling SCFAs activate G-protein-coupled receptors (GPCRs) to maintain barrier integrity, reduce intestinal inflammation by regulating pro-inflammatory cytokines, and induce suppressive effects on histone deacetylases (HDACs). SCFAs play a role in controlling the activation, recruitment,

and maturation of immune cells, including neutrophils, macrophages, dendritic cells, and T lymphocytes [33].

In a research study conducted in an immunodeficient strain of mice that lack functional B and T lymphocytes (Rag 1^{-/-}) it has been reported that butyrate leads to differentiation of T-regulatory cells both in in-vitro and in-vivo, by binding to GPR109a receptor on dendritic cells and macrophages results in increased expression of IL-10 and GPR109a lowers IL-6, thereby activating anti-inflammatory pathways, inducing apoptosis, and providing protection from colon cancer formation [34]. Acetate increases gut epithelial barrier function by activating GPR43 and attenuates mutant NOD-like receptors and leucine-rich receptor kinases, such as NOD- and LLR-. Acetate contributes to anti-inflammatory responses in neutrophils by limiting NF-κB activation and downregulating pro-inflammatory mediators, such as lipopolysaccharide-induced TNF-α [35]. Many studies have shown that propionate and butyrate act as potent HDAC inhibitors by altering nucleosome conformation and regulating gene expression [33].

It is believed that the fetal gastrointestinal tract is sterile and that the first exposure to the environment establishes commensal microbiomes in the gut. Also, breast milk contains a mixture of IgA and microbes, which prevents immune activation by the host. In the neonate's innate immune system, these signals are integrated in a unique way to promote healthy microbial colonization, which, in turn, leads to immune cell differentiation of commensal and opportunistic pathogens. In order to bring mucosal immunogenic homeostasis, butyrate activates peroxisome proliferator-activated receptor gamma (PPAR-γ), which is synthesized by intestinal epithelial cells. By promoting mitochondrial β-oxidation of SCFAs and oxidative phosphorylation in colonocytes, this receptor helps maintain a hypoxic environment in the colon, favoring the growth of obligate anaerobic SCFA producers while limiting facultative anaerobic pathogens [36].

9. Conclusion

From the list of evidence and hypotheses, it is evident that dysbiosis should be considered a serious morbidity, and that one must take the necessary precautions to control it to prevent catastrophe. The prominent root cause for this condition is repetitive intake of antibiotics without proper consultation, radiation exposure, and unhealthy lifestyle, leaving its direct impact on the immune system, which is threatened by chronic gastrointestinal disorders such as IBD and IBS, colorectal cancer, and celiac disease; it is counselled to maintain a healthy lifestyle, integrating good physical-psychological wellness also by regular addition of fermented products and removing unhealthy dietary components from the diet result in enhanced gut flora and health.

Author Contributions

Conceptualization, SM; writing—original draft preparation, SM; writing—review and editing, AP; revision, SM. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors confirm that this article has no conflict of interest.

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