International Journal of Bioinformatics and Biological Sciences
Citation: IJBBS: **11**(1&2): 43-51, June & December 2023
DOI: 10.30954/2319-5169.1.2023.5
Peer Reviewed Journal

REVIEW PAPER

Gut Dysbiosis and Its Potential Impact on Immunomodulation

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Received: 19-03-2023 **Revised:** 26-05-2023 **Accepted:** 04-06-2023

ABSTRACT

Past decades have witnessed an increasing trend of various types of metabolic disorders in young adults all over the world. Majority of these ailments have been found to be connected with unhealthy dietary habits which seriously disturbs the consortia of microbes that inhabit in our gut. The microorganisms naturally present in human digestive tract are referred to as the gut microbiota and collective form of their genome constitute the gut microbiome. These microorganisms play crucial role in maintaining normal nutrition, metabolism and immune function in our body; hence, has attracted substantial attention of researchers. The gut microbiome always remains in symbiotic association with the host. Any kind of imbalance in the composition of the gut microbiome leads to dysbiosis causing various types of gastrointestinal disorders like inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), diabetes, obesity, atopy and even mental illness. It is therefore, of utmost importance to take care of the gut microbiota for getting a healthy mind and a healthy life as well. This review is intended to investigate and establish the risk of immune dysfunction affected by gut dysbiosis.

Keywords: Gut microbiome, Dysbiosis, Inflammatory bowel disease (IBD), Irritable bowel syndrome (IBS), Immunomodulation, Short Chain Fatty acids (SCFAs)

The human gut is inhabited by trillions of microorganisms which overcount the total number of cells in human body. This gut associated microorganisms are often referred to as gut microbiota and their genomes comprise the gut microbiome (Carding *et al*. 2015). Amongst various types of microorganisms, the gut microbiota are mainly comprised of three phyla which include *Firmicutes*, *Bacteroidetes* and *Actinobacteria* (Tap *et al*. 2009). The composition of intestinal microbiota may vary with individual; however, *Proteobacteria*, *Actinobacteria*, *Fusobacteria*, *Spirochaetes, Lactobacilli, Streptococci, Enterobacteria* etc. have been known to be the predominant types as revealed in DNA sequencing studies (Carding *et al*. 2015; Hou *et al*. 2022). These microorganisms play significant role in overall wellbeing of human health and therefore; have occupied the core area of present research. Several studies have reported multifaceted roles of intestinal microorganisms in our body that cover metabolic homoeostasis, maintaining the structural integrity of gut mucosal lining, immunomodulation, protection against pathogens, production of vitamins and amino acids and many more (Hou *et al*. 2022). In other way, it can be said that the intestinal microorganisms always

How to cite this article: Ghatak, A. and Ghosh, S.T. (2023). Gut Dysbiosis and Its Potential Impact on Immunomodulation. *International Journal of Bioinformatics and Biological Sciences (IJBBS),* **11**(1&2): 43-51.

Source of Support: None; **Conflict of Interest:** None

maintain a symbiotic relationship with the host. Any impairment in the composition and quality of these beneficial microorganisms leads to a condition known as dysbiosis (Carding *et al*. 2015; Choden and Cohen, 2022). The ultimate result of dysbiosis is the development of metabolic disorders like diabetes, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), pathogenic invasion, celiac disease, colorectal cancer, immune dysfunction and even mental illness (Clapp *et al.* 2017; Kho and Lal, 2018). In a recent study, a new concept, "gut flora-centric theory", has been proposed by a group of researchers which clearly described that the incitement of human hunger actually comes from the gut flora and not from the cerebral signalling (Zhang *et al*. 2019). Majority of the gut microorganisms are non-pathogenic and are best known for their immense influence in good health. They serve as the source of various essential nutrients and vitamins in our body which ultimately contribute to healthy state of body and mind (Fujimura *et al*. 2010; Zhang *et al*. 2019). Therefore, taking care of gut microbiota is of prime importance for avoiding unnecessary health issues. Other than genetic predisposition, unhealthy diet regime, over usage of drugs and antibiotics, physical damage to mucosal lining, environmental factors, age etc. cause serious perturbation in normal activity of the intestinal microorganisms and thus, play crucial role in gut dysbiosis (Jandhyala *et al*. 2015; Yoo *et al*. 2020; Choden and Cohen, 2022).The purpose of the current review is to provide a comprehensive understanding regarding the contribution of intestinal microorganisms in immunomodulation.

Development of Microbiota in Our Gut

The development of microbial community in the gastrointestinal (GI) tract of human being has long been thought to provide essential benefit to a healthy life. Though the fetal GI tract is considered to be sterile, the first exposure to microorganisms begins at birth during the passage through the birth canal (Moles *et al*. 2013). The GI tract gets progressively enriched with these commensals when the neonate gets exposed to vaginal, fecal and skin microbiota of the mother. Hence, it is believed that the newborn delivered through caesarean section often carry low number of normal flora as compared to them, delivered through vaginal canal (Bull and Plummer, 2014). The most striking fact, reported in a study, is the effect of mode of delivery in differences of microbial composition which may last up to seven years of age. However, maximum variation in microbial composition is predominantly shown up to three years of age (Choden and Cohen, 2022). Moreover, this period is critical for developing a balanced ensemble of beneficial microorganisms to achieve good health and boosted immunity. In this context, it should be mentioned that our immune system is equipped with an exceptional feature of immune tolerance to a variety of harmless microbes which aid in preserving the commensals in our body (Zheng *et al*. 2020). In spite of having considerable similarity in composition of gut flora between mother and neonate, the microbial consortia may get changed due to various intrinsic and extrinsic factors. The intrinsic factors presumably include pH of the gut, health status of the newborn, drug usage etc.; while the microbial composition of the immediate environment, dietary and feeding habits serve as the external determinants in shaping the gut microbiota. The impact of gut microbiome is not only restricted to the intestinal tract only, rather extended throughout the body (Kho and Lal, 2018).

Gut Microbiota and its Influence on Health

Gut microbiota play pivotal role in restoration of good health by providing several health benefits which is mediated by a precise interaction between host and the microbes. The interaction is imposed chiefly by the metabolites synthesized by these commensals which regulate various physiological and metabolic activities of the host. The versatile activities displayed by intestinal microorganisms are presented here in a nutshell; however, the current discussion is exclusively aimed at shedding light on the interaction between gut flora and immunomodulation.

Metabolism

Human digestive tract is heavily populated by different microbial phyla, all of which confer assistance in different physiological and metabolic activities. The most important contribution portrayed by these symbionts is helping in fermentation of undigested foods, carbohydrates and dietary fibers. The fermentation results in the production of short chain fatty acids (SCFAs) that include acetate,

butyrate, propionate etc. All these SCFAs impart several key benefits to the host and contribute to 70% of the total ATP production in colon (Bull and Plummer, 2014). Butyrate, one of the SCFAs is known to inhibit the accumulation of metabolic toxic by products and act as energy source for colonocytes (Jandhyala *et al*. 2015; Valdes *et al*. 2018). SCFAs can serve as ligands for G-protein coupled receptors and therefore, help to mediate various cellular signalling processes (Kho and Lal, 2018). Current understanding of gut microbial association and host metabolism also depicted their importance in lipid and amino acid metabolism. It has been documented that gut microbes can produce various essential, non-essential amino acids and vitamins. These microorganisms are befitted with several key enzymes including proteinases and peptidases which help in protein breakdown and formation of amino acids. They also facilitate the entry of these amino acids through intestinal epithelial lining (Portune *et al*. 2016). Substantial effort has been made to explore the underlying mechanism of microbial colipases in lipid metabolism and this unveiled their vital role in lipid hydrolysis. Other than these, gut bacteria also employ machinery for metabolic degradation of various polyphenolic compounds consumed through diet (Jandhyala *et al*. 2015; Jia *et al*. 2021).

The intestinal microbiota possesses a remarkable ability of biotransformation of bile acids using bile salt hydrolases secreted by a wide variety of gut bacteria like *Clostridium perfringens* and other *Clostridia*. *Bacteroides*, *Enterobacter*, *Enterococcus* these intestinal bacteria are known to produce substantial amount of vitamin K whereas many others synthesize vitamin B, especially B5 and B12 which are utilized by the host cells (Bull and Plummer, 2014; Kho and Lal, 2018).

Colonization of microorganisms in the gut is also involved in xenobiotic metabolism and thus converts them into a non-toxic form. This ability of the gut microbiota protects the host cells from possible potential damage caused by xenobiotic compounds and pharmaceuticals. This is achieved either through inactivation of the xenobiotic compound or through bioactivation of the same. The alteration may be carried out by the addition of different functional groups or reduction of reactive species. Microbes presumably secrete many enzymes which neutralizes the toxic effect of the xenobiotics (Collins and Patterson, 2020). As discussed long ago in a study, *Actinobacteria* are able to reduce cardiac glycoside digoxin into non-toxic derivates (Saha *et al*. 1983). All these findings successfully established the impact of gastrointestinal microbes and need of harnessing their power for a healthy wellbeing.

Gut-brain axis

The gut-brain axis is suggested to be the bidirectional interaction between central nervous system and the gut microbiota. This aids in communication among neural cells, hormones, immunological factors and help to suppress various neurodegenerative disorders (Loh *et al*. 2024). The SCFAs, produced by gut microbiota has been reported to help in maturation of neural glial cells and microglial homeostasis. This interaction is crucial for perpetuating the normal activities of the neural cells (Kho and Lal, 2018). It is evident from the studies on germ-free mice that gut microbiota pose significant role in neural signalling involving neurotransmitters, hormones, cytokines and hence, any impairment in the quality and composition of gut flora leads to anxiety disorder, mental illness and other serious consequences (Clapp *et al*. 2017).

Gut microbiota and their role in host immunity

The crosstalk between gut microbiota and host's immune system is the indispensable route of homeostasis in physiologic, metabolic and immune response. It all starts from early developmental stages of the fetus. Gut microbes present in the newborn help in defining and shaping human's overall health status. Although, microbial colonization starts from early pregnancy period and progresses consecutively with further exposure, but their affirmative role can only be achieved with a healthy diet and well sanitized surroundings. Every organ and tissue of our body harbours normal biota which coexists with the host and benefit in a variety of ways. Hence, a clear correlation always sustain between the activity of the gut flora and the host's immune system (Pola and Padi, 2021).

The immune system-microbiota alliance is extremely dynamic and is thought to be the key modulator in regulating both innate and adaptive branches of immunity; but this dependence often

causes inappropriate immune response leading to inflammatory and autoimmune disorders. All these ailments arise due to loss of central or peripheral tolerance to self, microbiota-derived or environmental antigens (Belkaid and Hand, 2014).

From the very first day of life human body starts to get exposure of various types of microorganisms but it strategically prevents unwanted invasion with the development of anatomic, physiologic, phagocytic and inflammatory barriers. These barriers include mucus, epithelial cells, secretory immunoglobulins like IgA, numerous antimicrobial peptides (AMPs) and phagocytic cells (Macpherson *et al*. 2009) which limits contact, translocation and thereby facilitating commensal gene expression to prevent bacterial adhesion (Fig. 1).

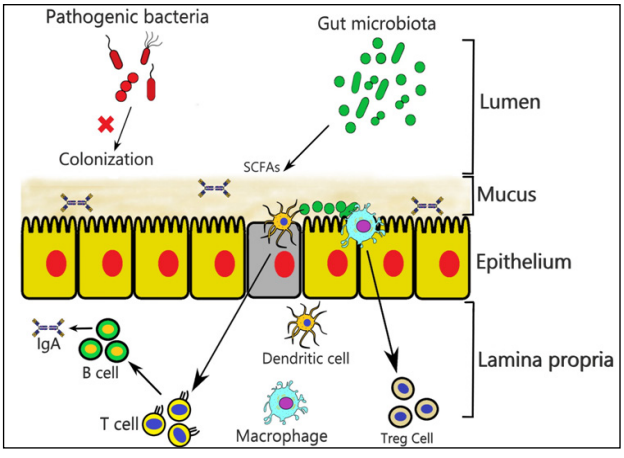

Fig. 1: Overview of the interaction between gut microbiota and host immunity

❍ Gut microbiota in immune homeostasis

Gut mictobiota are of paramount importance in regulating immune homeostasis. In a healthy state, the host's immune response to the intestinal microbiota is strictly localized to the mucosal surface. Innumerable mechanisms are employed to achieve microbiota compartmentalization. The mucus acts as the physiologic barrier and restrict pathogen adherence and gut colonization. Healthy gut synthesizes an arsenal of antimicrobial peptides (AMPs) which are composed of 5 to 100 amino acids carrying basic and hydrophobic residues. The classic cationic AMPs include defensins, histatins and cathelicidin. These, along with few lytic enzymes are involved in elimination of pathogens with the production of cytokines and chemokines (Guryanova and Ovchinnikova, 2022). Impairment in good microbes may exert adverse effect on production and functionality of AMPs. Gut microorganisms themselves produce certain AMPs, popularly known as bacteriocins which exhibit bactericidal properties by interfering with DNA, RNA and protein metabolism or by disrupting bacterial membrane. All these, selectively impose quality for competing with the pathogenic microbes for binding site in the gut epithelium and challenge their entry into the cell (Zong *et al*. 2020). Secretory IgA antibodies and AMPs maintain the mucosal barrier function and they, together with the mucus producing goblet cells, lubricate and protect the gut epithelial lining from potential damage (Guryanova and Ovchinnikova, 2022). The importance of the immune system barriers in maintaining homeostasis and their interaction with commensal and pathogenic microbes are therefore noteworthy for both healthy and diseased state.

❍ Function of microbiota-derived SCFAs and other metabolites

As discussed in the earlier section, fermentation of complex carbohydrates by some bacteria, such as *Faecalibacterium prausnitzii*, *Roseburia intestinalis* and *Anaerostipes butyraticus*, produce short chain fatty acids (SCFAs) like butyrate, propionate, acetate that regulate host immune cells in many ways (Kaiser *et al*. 2017; Yoo *et al*. 2020). These SCFAs get absorbed by the colonocytes and are used as carbon and energy source for the gut epithelial cells (Sanna *et al*. 2019). Even during gestation, SCFAs are translocated from gut to mammary gland and help the neonate to acquire in born immunity. There have been increasing evidences which conveyed the efficiency of microbe-derived SCFAs in protecting host cells from local inflammation and pathogen colonization. Their role in maintaining the integrity of the mucosal lining of the gut can be better explained by the ability of binding to a specific G-protein coupled receptor (GPCR) and altering the gene expression pattern via reducing the activity of histone deacetylases (HDACs). Acetate, produced in excess by *Bifidobacteria*, exactly performs the same duty in controlling localized inflammation in gut tissue by manipulating the activity of a GPCR (Yoo *et al*. 2020). Apart from carrying out multiple functions

in gut epithelium, SCFAs also regulate expression of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-12 (IL-12), interleukin-6 (IL-6) etc. through activation of macrophages and dendritic cells (Vinolo *et al*., 2011). Microorganisms such as *Ruminococcus bromii*, *Faecalibacterium prausnitzii*, *Eubacterium rectale*, *Eubacterium hallii* are especially known for producing butyrate by breaking down resistant starch. Butyrate reduces mucosal level oxidative stress by consuming oxygen and thus stabilizes hypoxia-inducible factor which is also important for barrier protection (Kelly and Colgan, 2016). Notably, a decrease in butyrate, stimulates pro-inflammatory cascades in immune cells that in turn, activate downstream signalling elements such as nuclear factor kappa-β (NF-β), mitogen activated protein kinase (MAPK) and cytokine production like tumor necrosis factor-α (TNF-α) and IL-6 (Prause *et al*. 2021). This results in many gastrointestinal and neurological diseases (Parada Venegas *et al*. 2020; Silva *et al*. 2020). A striking observation has been documented in a study which showed decreased number of certain commensals like *Escherichia*, *Shigella*, *Enterobacter* in patients with lung cancer; on the contrary, healthy individuals carried these microbes in good number. This result is in agreement with the anti-cancer property of microbe-derived SCFAs as they promote killing of altered self cells through apoptosis (Shim *et al*. 2023).

❍ Gut microbiota in T cell response

The signals derived from gut microbiome are found to be responsible for modulation of host immune system in a precise manner, although a decisive step to establish the cumulative effect of all factors involved is underway. Several reports elucidate contributory role of the gut microbiota in regulating the development of antigen presenting cell (APCs). Experiments with germ-free (GF) mice reportedly showed a marked reduction in number of intestinal APCs and recruitment of dendritic cells (DCs) in intestine due to *Escherichia coli* infection (Haverson *et al*. 2007).

The chief component of the adaptive immune system is $CD4^+$T cells. There are four major subpopulations of $CD4^+$T cells (T_H1, T_H2, T_H17 and regulatory T cells) which generate upon differentiation of the naive $CD4^+$T cells. Gut microbiota influence the differentiation of these T cell subtypes which in turn, determines health status of an individual. All four T cell subtypes have characteristic functions in host's immune system. For example, T_H1 cells provide protection to the host against intracellular microbial infection; while T_H2 cells play important role in clearing parasitic infection. T regulatory cells (T_{reg}) are the main proponent of immune tolerance whose malfunction leads to autoimmune diseases. *Bacteroides fragilis* has been shown to induce the development of a systemic T_H1 response through its polysaccharide A (PSA) molecule. In contrast, segmented filamentous bacteria (SFB) have been found to be potent inducers of T_H17 cells (Wu and Wu, 2012). Common gut bacteria *Lactobacillus plantarum* and *L. salivarius* are reported to stimulate the production of T_H1 cytokines namely TNF-α, and interferon-γ (IFN-γ) in mucosal associated tissues (Shim *et al*. 2023). Studies have also revealed that *Candidatus arthromitusis*, a gram positive bacterium, promotes T_H17 cell differentiation and secretion of several cytokines like IL-17 and IL-22 (Atarashi *et al*. 2008; Ivanov *et al*. 2015). In a recent investigation, it has been observed that microbial by products can influence $CD8^+$T cell functions. Butyrate and propionate, two major SCFAs, inhibit $CD8^+$T cell activation by regulating IL-12 production in APCs (Nastashi *et al*. 2017); whereas pentanoate, produced by the gram negative bacteria *Megasphaera massiliensis*, promotes effector $CD8^+$T cell activity (Luu *et al*. 2021). $CD8^+$T cell response has also been reported to be affected by commensal-derived SCFAs and holds significant importance during cancer immunotherapy (Shim *et al*. 2023).

❍ Pattern recognition receptors and gut microbiota

Pattern recognition receptors (PRRs) are specific transmembrane proteins which identify motifs or patterns present in microorganisms. Toll like receptors (TLRs) are one the best example of PRRs. The interplay between PRR and normal biota of gut is essential to sense and transduce the signal in pathogen detection, regulation of composition of commensals and maintaining the integrity of mucosal lining (Chu and Mazmanian, 2013). Diversity of TLRs can influence immune system regulation in a profound manner. PSA of *B. fragilis* can be efficiently recognized by TLR-1 and TLR-2 and result in the downstream expression of many

anti-inflammatory genes (Erturk-Hasdemir *et al*. 2019). This proves the efficacy of PRRs in identifying subtle differences in an array of microbial patterns present in different microbes. These interactions ultimately activate the APCs and DCs which subsequently help in priming of B and T cells. Other PRRs such as nucleotide-binding oligomerization domain receptors (NOD-1 and NOD-2) also impact on intestinal homeostasis. Both NOD1 and NOD2 act as sensors and help to promote regeneration of gut epithelial cells (Ramanan *et al*. 2014). Another important cell type is mucosal associated invariant T cell (MAIT). These are MHC-1b restricted lymphoycytes which possess antimicrobial function. Several studies corroborated that *Francisella tularensis*, *Mycobacteroides abscessus*, *Escherichia coli*, *Salmonella typhimurium* and *Lactococcus lactis* act as MAIT cell activators. Activated MAIT cells recognize various bacterial antigens presented by MHC class-1b and secrete various cytokines and ultimately controlling several aspects of immune system homeostasis (Meierovics *et al*., 2014).

Concept of Gut Dysbiosis and its Implications

Gut dysbiosis is the state of imbalance in composition of gut microflora which promotes various diseases. Gut dysbiosis leads to dysfunction and disruption of the normal activities of the intestinal commensals. The gut microbial niche is extremely dynamic and constantly altering with changing internal and external environment of the host (Fig. 2).

A proper balance of normal gut microbiota can be the ultimate saviour from life threatening diseases. The divergent activities of intestinal microorganisms may get hampered due to enumerable factors some of which are unhealthy and sedentary lifestyle, consumption of high-sugar and high-fat diet, irregular dietary habits, excess use of antibiotics and other drugs, stress, mode of delivery, hereditary predispositions and even ageing (Bull and Plummer, 2014; Hou *et al*. 2022). Hence, it is believed that a healthy life starts with a healthy gut. The diseases associated with gut dysbiosis are listed below, however, emphasis is mainly given on immunity related diseases (Table 1).

- Diabetes and chronic renal malfunction
- Heart diseases
- Immune diseases
- Neurological disorders
- Cancer

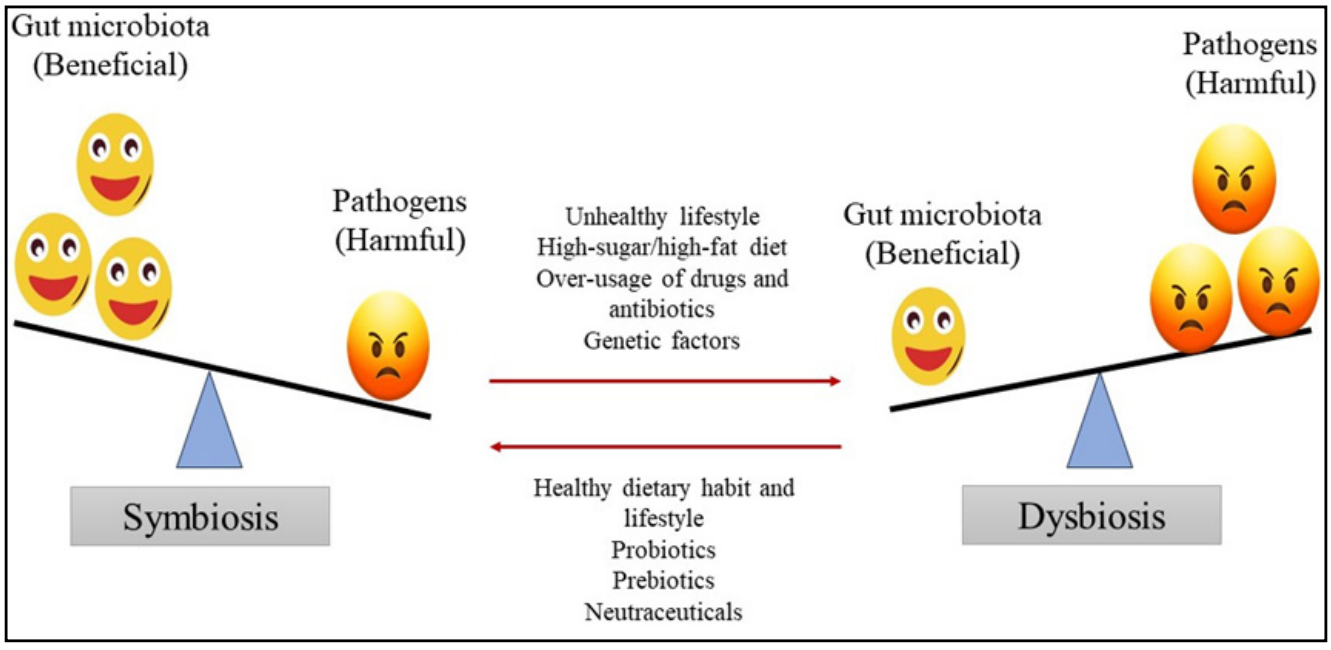

Fig. 2: Concept of dysbiosis and its probable causes

Table 1: Gut dysbiosis and its effect on immune dysfunction

Disease	Proposed Cause	Major Consequences	Reference
Irritable Bowel Syndrome (IBS)	Gut microbial imbalance promotes adherence of pathogenic bacteria	Abdominal pain and discomfort accompanied by diarrhea or constipation	Bull and Plummer, 2014; DeGruttola *et al*. 2016
Inflammatory Bowel Disease (IBD)	Reduction in the number of *Firmicutes* and *Bacteroides* Decrease in SCFA and subsequent entry of pathogens	Inflammation of the gut, ulceration, Crohn's disease Decreased rate of bile acid bioconversion	Duboc *et al*., 2012
Type-1 Diabetes	Alteration in gut microbial composition affects both innate and adaptive branch of immunity	Increased intestinal permeability leading to susceptibility to pathogen invasion followed by destruction of pancreatic beta cells	Zhou *et al*. 2020
Autoimmune diseases	Alteration in gut microbial diversity	**Rheumatoid arthritis-** generation of autoreactive antibodies against self-antigens resulting in Chronic inflammation of bone joints and cartilages **Systemic lupus erythematosus-** loss of self-tolerance, antibody response to self antigens leading to systemic inflammation in skin, glomerulus, neural cells **Multiple sclerosis-** disintegration of the myelin sheath of neuron by autoreactive immune cells	Wu and Wu, 2012; Chang and Choi, 2023
Atopy	Alteration in gut microbiome attracts fecal organisms	Skin rashes, rhinitis, eczema, asthma	Kho and Lal, 2018
Celiac disease	Alteration in colon bacteria like *Lactobacillus*, *Enterococcus*, *Bifidobacteria*	Gluten intolerance	Kho and Lal, 2018
Colorectal cancer	Decrease in *Enterobacter* and other gut associated microbes	Activate beta-catenin which induce transcription of various oncogenes	Shim *et al*. 2023

CONCLUSION

The human body carries innumerable microorganisms, some of which constitute the normal biota and some are transient biota. All these microbes reside in symbiotic relationship with the host. Amongst all organs and tissues the gut provides the largest area for microbial colonization. Different phyla of microorganisms could be found in human digestive tract all of which exhibit potential benefit to the host. These microbes produce various important metabolites including SCFAs, vitamins and amino acids which significantly regulate the activities of gastrointestinal tract, immune system and neural system. The gut microbiota associated metabolites are known to have antimicrobial, anticancer effects and they play substantial role in regulation of our immune function. Any kind of disturbance in the composition of gut microbes lead to a condition called dysbiosis which exert serious detrimental effect on health. It is worthy of mention that imbalance in gut microbiota has been proved to be connected with various ailments like gastric disorders, immunological malfunction, neurological complications and metabolic diseases. Hence, it is believed that a healthy gut contribute to a healthy wellbeing. Care should be taken to restore the normal activities of the gut microbiota. Now a days, people are more focused to establish the fact that a healthy lifestyle means, proper dietary habits, avoidance of excess drug usage etc. can only conserve proper functioning of intestinal microorganisms. It is therefore advised to include prebiotics in diet for enriching the beneficial activities of these commensals. As gut microbiota display several health benefits hence, their application could be carefully exploited in therapies related to

critical illnesses. Research on gut microbiota needs to be significantly concentrated to manipulate the activities of these organisms and exploit their beneficial aspects for treatment of various diseases.

ACKNOWLEDGEMENTS

The authors are grateful to Sri S.M. Kankaria, President Shree S.S. Jain Sabha and the members of the governing body for their constant support and financial assistance.

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