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A review on different diseases due to human gut microbiota dysbiosis

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Abstract

Microbes are present everywhere on earth. These are present either inside or outside the body. Microorganisms are found in urinary tract, vagina, gut, nasal cavity, oral cavity and many other parts of body as well. These microbes are beneficial as well as harmful for us. Beneficial microbes can regulate different body mechanisms and sometimes they can convert into pathogenic microbes. Human gut microbiota is necessary in keeping the brain healthy as well as it also maintains the physical health of humans. Microbiota of human gut is made up of complex community of microorganisms that respond in healthy metabolic processes and develop immune responses, but sometimes gut microbiota can be disturbed by different external and internal factors for example antibiotics, more lipid diet, and stress that can cause alteration in gut microbiota. So pathogenic microbes accumulate and release different toxins that cause various diseases such as Alzheimer's Disease, colorectal cancer, cardiovascular diseases, obesity, Clostridium difficile infection, Inflammatory bowel disease, etc. The dysbiosis in human gut microbes is due to release of different toxins from pathogenic bacteria which are converted from beneficial bacteria by internal and external factors. If we will not control these factors it can also change the gene expression and will infect the next generations too. We can prevent these diseases by less use of antibiotics and by taking proper healthier diet it will help in maintenance of normal flora of body.

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Introduction

Microbiota consists of different kinds of microorganisms which include viruses, fungi, bacteria, and single-cell eukaryotes that can be present at a particular habitat such as in animals or humans (Donaldson *et al*., 2016). The microbes which are present on human intestine are more complex, more important in the human immune system's development and maintenance of human health by metabolic responses (Ventura *et al*., 2018). Alteration in gut microbiota secretes bacterial metabolites results in regulation of blood pressure, kidney diseases which can be chronic and can cause cardiovascular diseases (Marques *et al*., 2018). Alteration in human gut microbes due to different circumstances can cause various health issues for example changing in host immune system, inflammatory bowel diseases and allergy (O'Toole *et al*., 2018).

Several microorganisms colonize the human gut these are 10 times more in number as compare to total cells that are found in the human body and the genetic material is more than 150 fold as compared to humans (Qin *et al*., 2010). Microbiota of human gut contains thousands of species of Bacteroidetes and Firmicutes phyla (Falony *et al*., 2016). Gram-negative Bacteroidetes phylum consists of Bacteroides and Prevotella these microorganisms secrete propionate (Reichardt *et al*., 2014). Firmicutes are important in the production of butyrate and leads to degradation of indigestible polysaccharides (Ze *et al*., 2012). Firmicutes include *Ruminococcus, Clostridium, Lactobacillus, Eubacterium, Faecalibacterium,* and *Roseburia* (Eckburg *et al*., 2005). Actinobacteria which include *Bifidobacterium spp*, *Proteobacteria* which includes *Escherichia coli* and *Verrucomicrobia* which include *Akkermansia mucinophila* are in lower numbers in the healthy human gut. 30% of gut microbial species are isolated by culturing and remaining organisms are unable to culture because they require an anaerobic environment (Goodman *et al*., 2011).

There are number of different factors that may lead to dysbiosis in human gut microbial flora which include antibiotics, food additives as well as environment such as depression change in gut microbiota which results in the development of serious diseases (Roca-Saavedra *et al*., 2018). Exposure to toxins, drugs, pathogens and intake of poor diet and antibiotics can change the gut microbiota and cause microbial dysbiosis. Experiments on animal models have shown that foodborne pathogen not only causes local and systemic inflammation but also alters the microbiota composition. These disturbances also change the barrier functions and result in what is known as "leaky gut (Carding *et al*., 2015).

The aim of this review is to consider all the possible factors which are important in dysbiosis of gut microbiota and leads to sever problems. Environmental factors as well as medications can cause mental and physical diseases. In future we can prevent these diseases by less or no use of antibiotics and by taking healthy diet. Less fats and lipids in diet can prevent more accumulation of Low density lipoproteins.

Alteration in human gut microbiota leads to mental diseases

In recent studies, it is stated that there is a bidirectional signaling system among the brain and intestinal microbiota. This kind of interaction leads to change in human physiology or pathological behaviors which include the functions of both the GI tract and central nervous system (CNS). Microbes of the gut communicate with the CNS by different channels which include nervous, endocrine and immune signaling mechanisms. Dysbiosis in the microbial gut-brain leads to the pathogenesis of depression (Du *et al*., 2020). The major cause of depression in humans by dysfunction of the Hypothalamic-Pituitary-Adrenal axis (HPA) (Naseribafrouei *et al*., 2014). HPA is neuroendocrine which is important in the stress response system as well as in mood disorders and functional diseases. The microbiota of intestine is important in the maintenance of the HPA axis, but the alteration in the HPA system can lead to several diseases for example posttraumatic stress disorder, schizophrenia, social anxiety, and depression (Beaton *et al*., 2006). Innate cells of immune system contain Toll-like receptors that

can recognize pathogenic microorganisms (Akira *et al.*, 2003). When TLR recognizes pathogens they will start a cascade of events that can cause the release of cytokines then activation of the HPA and then it leads the activation of the nuclear factor-k-gene binding (NF-kB) signaling system. When there will no gut microbiota due to the usage of antibiotics or improper diet TLR reduces in number which leads to a change in immune and neuroendocrine responses (Barrett *et al.*, 2012). Direct interference with neurotransmitters signaling may lead to depressive disorders (Gosselin & Rivest, 2008).

Alzheimer's Disease (AD) is also known as dementia. It is a neurodegenerative disorder that occurs when amyloid peptide will accumulate in the brain (Chen *et al.*, 2017). Human gut microbes can release lipopolysaccharides (LPSs) and amyloids and it leads to the result of pathogenesis of AD during aging. Because aging will cause permeability in the blood-brain barrier and gastrointestinal tract (A Kohler *et al.*, 2016). Some Bacterial strains of the gut such as *Escherichia coli, Salmonella enterica, Salmonella typhimurium, Bacillus subtilis, Mycobacterium tuberculosis, and Staphylococcus aureus* produce some amount of extracellular amyloid (Pistollato *et al.*, 2016). Drug efficacy can disturb gut microbiota and can affect the blood-brain barrier (Burns *et al.*, 2012). When lipopolysaccharides (LPSs) and amyloids levels will increase it will allow the increase in the level of cytokines such as IL-1, IL-6, TNF-α, and TGF-β start inflammation and leads to different neurological disorders (Bagyinszky *et al.*, 2017).

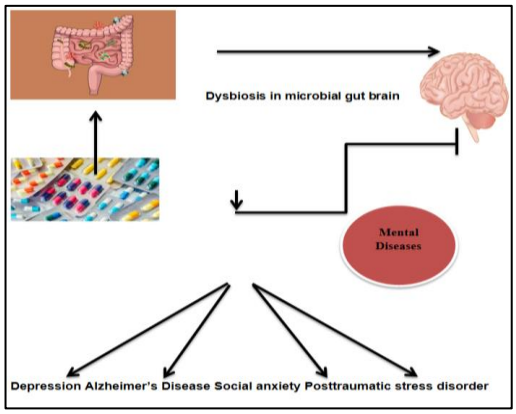

Fig. 1. Dysbiosis in Gut microbiota cause mental diseases.

Alteration in Gut Microbiota leads to Colorectal Cancer

Colorectal cancer is fourth leading disease which can threat life in all over the world. Colorectal cancer is caused by gut micro-organisms promoting tumor growth and spread other parts of the body as well (Brennan & Garrett, 2016). Some bacterial strains that are present in the gut are important in the production of genotoxin virulence factors. For example, bacterial Strains colibactin-producing *Escherichia coli and* enterotoxigenic *Bacteroides fragilis* play role in the induction of colorectal cancer. Sulfidogenic bacteria which include *Fusobacterium*, *Bilophila wadsworthia* and *Desulfovibrio* develop colorectal cancer by the production of hydrogen sulfide. Hydrogen sulfide damages the DNA and cause abnormalities in chromosomes and instability which may lead to mutation in the cell line's genome. Hydrogen sulfide will diffuse into intestinal epithelial cells and enter in mitochondria which leads to dysfunction in mitochondria. Hyperproliferation will be caused by Ras/MAPK pathway. The Ras/MAPK mechanism is important in carcinogenesis of many malignancies, including CRC (Deplancke & Gaskins, 2003). If a diet contains a high amount of fats and protein more amount of sulfidogenic bacteria can cause colorectal cancer (Yazici *et al.*, 2017).

E.coli is considered as gut commensal and can produce intestinal inflammation by secretion of toxins named as colibactin with oncogenic potential (Namavar *et al.*, 1989). *E. coli* which are more associated with mucosal membrane significantly more prevalent in CRC (Bonnet *et al.*, 2014). It is also noted that *E. coli* cause tumorigenesis in $Apc^{Min/+}$;Il10/ mice (Tomkovich *et al.*, 2017).

Bacteroides fragilis is known as anaerobic bacteria present in human gut. It can be non-toxigenic and enterotoxigenic. Enterotoxigenic strain consists of *Enterotoxigenic Bacteroides fragilis* (ETBF) which can cause diarrhea and colorectal cancer in humans (Sears 2009). *Enterotoxigenic Bacteroides fragilis* (ETBF) bacterial strain contain a gene that is known as bft gene and it is important in the production of B.*fragilis* toxins (BFT).

In marine animals, it is stated that ETBF can cause CRC by the production of metalloprotease toxin (Zhang & Weintraub 1998). Metalloprotease binds to colonic epithelial cells and inhibits the function of E.cadrin. E.cadrin is the tumor suppressor protein. It leads to an increase in epithelial cell permeability and leads to colorectal cancer (Chen *et al.*, 2015).

Alteration in Gut Microbiota leads to cardiovascular diseases

Cardiovascular diseases are known as the major cause of death and morbidity in different countries which are developed and developing. There is a strong relationship between gut microorganisms and the development of cardiovascular diseases (Shimokawa *et al.*, 2015). Trimethylamine-N-oxide (TMAO) is secretin which is released from intestinal microorganisms. In various animal-based products and energy drinks different dietary products such as carnitine choline and phosphatidylcholine are used. These metabolites are digested by gut microorganisms to trimethylamine (TMA) and then it will oxidize by flavin monooxidases 3 in the liver to TMAO. TMAO react with platelets and enhances the platelet hyperresponsiveness by increasing the release level of Ca^{2+} from intracellular Ca^{2+} stores which can cause thrombotic risk (Zhu *et al.*, 2016).

An increased level of TMAO causes more adverse cardiovascular events which lead to mortality, myocardial infarction and stroke (Tang *et al.*, 2013). Bacteria that are involved in CVD are *Collinsella Enterobacteriaceae, Lactobacillales, and Streptococcus* spp (Jie *et al.*, 2017). In different studies, it is stated that gut microflora can secrete bile acid which is important in the development of cardiovascular diseases. Bile acid affects cardiac function. Bile acid goes toward cardiac myocytes and interfere with electrical excitation and muscle contractility. Bile acid is also important in plaque formation (Khurana *et al.,* 2011). Bile acid which secretes different metabolites will affect the different types of pathways by FXR-induced signaling (Wahlström, *et al.*, 2016). FXR is known as an endogenous bile acid sensor which is a member of the nuclear receptor family with chenodeoxycholic acid and it is considered as the most potent ligand (Bishop-Bailey *et al.*, 2004). Gut microorganisms also secrete a large amount of short-chain fatty acids (SCFA). When consuming that diet that contains more fats leads to more production of SCFA. SCFA butyrate is important in histone deacetylation, change in gene regulation, immune system modulation, intestinal barrier regulation, oxidative stress reduction, diarrhea control, visceral sensitivity, and intestinal motility modulation and these all participate in the development of ASCVD (Leonel & Aivarez, 2012).

Clostridium difficile infection

Clostridium difficile infection (CDI) cause severe health issues because it is regarded as the most common pathogen for health care infection (Lessa *et al.,* 2015). CDI pathogen is associated with antibiotic diarrhea by causing disturbance through infection and colonization of its pathogens in gut microbiota flora.

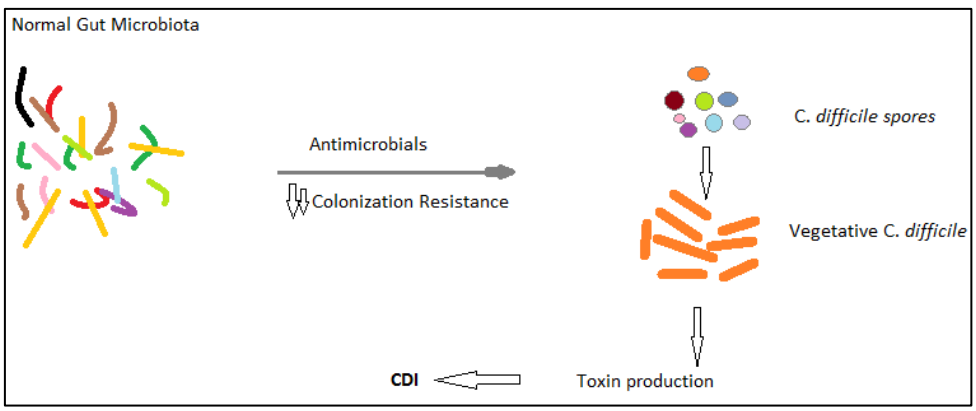

Fig. 2. CDI due to use of Antimicrobials.

C. *difficile* spreads by the fecal-oral route and it may be ingested either as spores or vegetative form which can easily survive for long periods and can penetrate the stomach acid barrier (Underwood *et al.*, 2009). As a result of antibiotic therapy normal gut microbiota changes which act as a barrier against C. *difficile* colonization in the intestine.

After colonization C. difficile releases, the two large clostridial toxins A (TcdA and TcdB) which are exotoxins and attach to the human intestinal epithelial cells which result in tenderness and damage to the intestinal mucosa (Lyerly *et al.*, 1982). TcdA is an enterotoxin and it is important for activation of IL-6 and IL-8 and TcdB is a cytotoxin that is necessary for microorganism pathogenicity (Kachrimanidou *et el.,* 2011). An additional binary toxin (ADP-ribosyl-transferase, CDT) that consists of two components CDTa and CDTb which binds to the host cells and aids in translocation of CDTa into the cytosol.

Studies showed that in CDI's patients characterized by low *Proteobacteria* abundance and more *Bifidobacteria* colony in contrast to healthy persons (Zhang *et al.*, 2015). Besides, decrease population of opportunistic pathogens (*Escherichia* and *Klebsiella*) and a decrease in commensal bacteria (*Barnesiella*, *Alistipes*, *Bacteroides*, *Lachnospira* genera).opulation also observed in CDI's patients (Milani *et al.*,2016). Recent studies also revealed the development of some fungal species during CDI, through which the *Penicillium* genus is much more frequent (Sangster *et al.*, 2016)**.**

Obesity

Obesity can be defined as a multi-factors disease during which the index body mass tend to be increased more than 30kg/m2. Obesity further classified into Gynoid obesity (pear-shaped obesity) that is more ordinary in women and Android obesity (central or apple-shaped obesity) considered as more dangerous than pear-shaped obesity and more ordinary in men. Usually, the obese person is more prone to Diabetic type-II and cardiac diseases. Decreased Bacteroidetes, increased Firmicutes and less diversity in alpha microbes have been observed in obese person's microbiota dysbiosis (Dan Waitzberg *et al,*. 2018).

Development of obesity and role of gut microbiota

The polysaccharide fermentability of micro-organisms that are digested poorly by humans and energy regulation is the basic mechanism that tells the important role of microbiota in obesity. short-chain fatty acids (SCFA) generated as the results of dietary fibers fermentation, which through molecular pathway increase level of triglyceride and induce lipogenesis through activation of sterol regulatory element-binding transcription factor 1 (SREBP1), carbohydrate responsive element-binding protein (ChREBP) and accumulation of triglyceride in adipocyte of a host (Khan *et al.*, 2016)**.**

Decrease oxidation of fatty acid in the liver by suppressed adenosine monophosphate kinase (AMPK) is regarded as another mechanism that explains the relation of obesity with microbiota (Lopez, 2017). Cellular energy indicator (AMPK) normally present in liver and muscle fiber and its inhibition caused a decrease in oxidation of fatty acid which results in fats deposition in muscles (Hardie, 2008). The efficiency of microbiota tends to be increased in obese individuals for more energy extraction from fat storage and dietary fibers. Feces of obese peoples contained a low level of dietary fats and a higher level of SCFA (Aron-Wisnewsky *et al.,* 2012). Gaps are still present regarding the proper knowledge about gut microbiota relation to obesity development and control of this syndrome through its management (Wang *et al.,* 2015)

Inflammatory bowel disease

Ulcerative colitis (UC) and Crohn's diseases (CD) are considered as more prevailing modes of inflammatory bowel disease, which are generally typified by affected intestinal mucosa due to continual relapsing inflammation. The major cause of both these diseases is unknown, however evidence about IBD's pathogenesis due to microbial dysbiosis is supported largely (Baumgart and Carding, 2007). Patients exhibit a decrease in functional diversity, stability and gut microbiota population with decreased Firmicutes and increment of Enterobacteriaceae and Bacteroidetes (Hansen *et al.,* 2010*)*.

Both UC and CD's diseased patients exhibit a significant difference in their gut microbiota population (Darfeuille-Michaud *et al.*, 2004). Moreover, the bacterial population seems to be different in newly CD's diseased persons rather than in both healthy and UC's diseased persons. CD's diseased person exhibit decreased population of Bacteroidales, Clostridiales, bifidobacteria, lactobacilli, and Erysipelotrichales, however, the abundance of Fusobacteriaceae, Enterobacteriaceae, Pasteurellaceae and Veillonellaceae increased as compared to a healthy person (Gevers *et al.,* 2014).

Decreased appearance of lactobacilli and bifidobacteria are considered as major causes for IBD disease, as these two are responsible for the defense of the host intestine by communication with the immunity system (Garcia-Lafuente *et al.,* 1997). The decreased prevalence of Clostridial considered as much worse for IBD disease as Clostridial leads to a reduction in butyrate bacterial group which are responsible for the production of butyrate that acts as an inhibitor of intestinal mucosa inflammation through cytokinesis expression and also a stimulator of mucin and peptide that strengthen then intestinal wall (Geirnaert *et al.,* 2017)

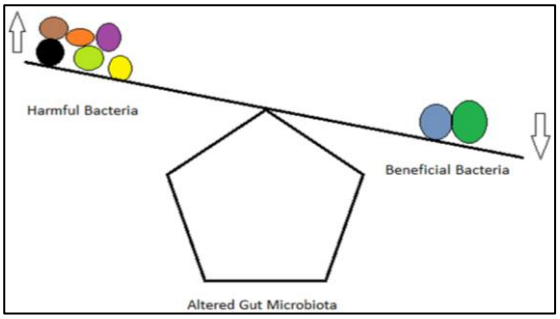

Fig. 3. The gut microbiota of IBD.

Table 1. Bacteria involved in the development of disease.

Diseases	Bacterial Species	Functions	References
Alzheimer's Disease	*Escherichia coli* *Salmonella enterica* *Salmonella typhimurium* *Bacillus subtilis* *Mycobacterium tuberculosis* *Staphylococcus aureus*	Production of lipopolysaccharides (LPSs) and amyloids	(Bagyinszky *et al.*, 2017).
Colorectal Cancer	*Escherichia coli* *Bacteroides fragilis* Sulfidogenic *Fusobacterium* *Bilophila wadsworthia* *Desulfovibrio*	Production of colibactin and hydrogen sulfide	(Yazici *et al.*, 2017)
Cardiovascular Diseases	*Collinsella-Enterobacteriaceae* *Lactobacillales* *Streptococcus* spp	Production of TMAO and Bile acid	(Jie *et al.*, 2017).
CDI	*Clostridium difficile*	Exotoxin (TcdA and TcdB) production	(Lyerly *et al.*, 1982)
Obesity	Bacteroidetes Firmicutes	Decrease oxidation of fatty acid, higher level of SCFA	(Aron-Wisnewsky *et al.*, 2012)
IBD	Firmicutes Lactobacilli, Bifdobacteria Enterobacteriaceae	Inflammation of intestinal mucosa Decrease defense of the host intestine	(Hansen *et al.*, 2010)

Conclusion

Dysbiosis in human gut microbiota can relate to change in metabolic functions which may leads to several diseases. Gut microbes can be altered due to environmental factors. Beneficial microbiota of gut converts into harmful pathogenic microorganisms and release different kinds of toxins which can cause mental stress and other diseases. Pathogenic microbes will compete with beneficial microbes and disturb the immune system cells. Maintaining proper diet and less use of antibiotics can control these situations.

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