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# IMPORTANCE OF GUT MICROFLORA IN HUMAN HOST: DYSBIOSIS AND TREATMENT- A BRIEF REVIEW

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## ABSTRACT

In this review, the interaction between the host and the microbiota present in our gut is highlighted to get an overview of how the microbial population plays a crucial role in Host metabolism as well as immunization.

The consequences of a disbalance of the gut microbiome such as Clostridium difficile infection, chronic diarrhea, inflammatory bowel syndrome, Obesity, etc. have been discussed.

Fecal microbiota transplantation, probiotics, and prebiotics have been discussed as prospects of a new scientific approach toward treating various gut-microbiota related diseases.

Information from different journals and research articles regarding the gut microbiome has been compiled and simplified to understand the importance of the microbial population inside our gut. This is to give a comprehensive understanding of the gut-microbiota interaction and important methods of treatment.

**Keywords:** Gut Microbiome, Microbial Interaction, Dysbiosis, Probiotics, Immunization.

## I. INTRODUCTION

Our gut is habitat to trillions of different kinds of microorganisms, be it bacteria, archaea, protozoa, or even viruses. Most of these are foreign microorganisms that we ingest with food, however many bacteria have evolved to live in a symbiotic relationship with our bodies. Much like how millions of years ago a cyanobacterium was engulfed by a prokaryotic cell but was not killed, instead, it became an endosymbiont which we now know as mitochondria (endosymbiosis theory). The comparison with mitochondria is relevant since the microbiome of our gut is as important to our digestion, absorption, and metabolism as the mitochondria to its cell. With the line of evolution, our body has chosen these bacteria as a tool for helping digestion and absorption of the food we take. Bacteria not only inhabit the gut but also inhabit the oral cavity, respiratory tract, and skin as well as genital organs. The ratio of human cells to microbial cells in our body is roughly 1:1. The microbiota present in the gastrointestinal tract majorly belong to the phyla Firmicutes, Actinobacteria, and Bacteriodetes. [1]

These groups of bacteria play a crucial role in host metabolism and physiology. The balance in the population of these bacteria is of supreme importance for maintaining metabolism, proper digestion, and absorption.

The real importance of the human microbiome was not understood until a few decades ago. However, advancements in technology in the fields of microbiology and biotechnology throughout the world have painted a much clear picture of how the human-microbiota interaction works. Genome sequencing has revolutionized the study of gut microbiota. Projects like HMP (Human Microbiome Project) funded by the United States National Institutes of Health as well as MetaHIT (Metagenomics of the Human Intestinal Tract) funded by the European Commission are large-scale genome sequencing projects which are important to understand the role of the human microbiome.

Although the human microbiome research is at a preliminary stage, understanding the human microbiome's role has opened new horizons for modern medicine and further research is expected to be of great therapeutic importance.

## II. FUNCTIONAL CORE MICROBIOME

We need to understand that the species composition of gut microbiomes differs from person to person. Several innate and environmental factors impact microbial diversity. [2] Hence, it is very difficult to establish which microbes specifically contribute to good health. So to simplify, the concept of Functional Core Microbiome

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(FCM) has emerged. FCM are those microbes that play a fundamental role in maintaining homeostasis. The human Gut Microbiome is an important part of this FCM. [3]

**ROLE OF GUT MICROBIOME IN THE HUMAN BODY**

**1. HOST METABOLISM**

Our Gut microbiota is actively involved in the digestion and absorption of our food. Gut microbiota converts our food to calories we can use. We are capable of digesting simple sugars and a few polysaccharides, but we cannot break down complex fibers (linear or branched chain polysaccharides). Most of the complex fibers are consumed by our microbiota. They break down complex polysaccharides into monomers which in turn are converted to Short Chain Fatty Acids (SCFA) by many bacteria through the process of fermentation. SCFAs include- Butyrate, Propionate, and Acetate. Butyrate provides calories to the intestinal epithelial cells. Propionate inhibits cholesterol synthesis in the liver. Both Butyrate and Propionate Function in maintaining human body weight by increasing the release of hormones that suppress hunger. Acetate is obesogenic, as it acts as the precursor for lipid synthesis in liver and fat cells. [3]

**2. IMMUNITY**

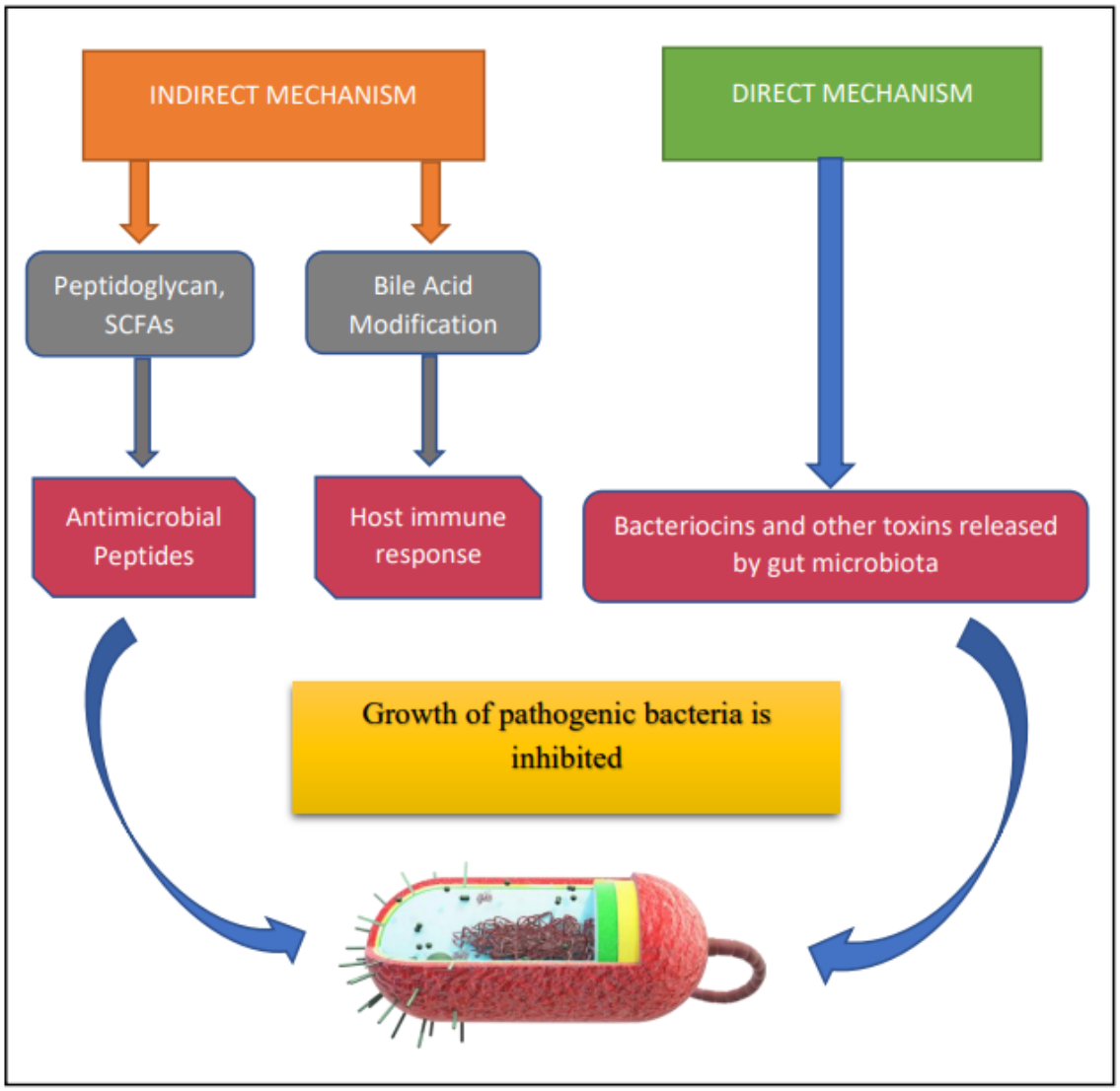


**Fig.** Illustration of Direct and Indirect Mechanism by Flow charts (Copyright belongs to author)

The gut microbiome is crucial for human immunity, it was first hypothesized when it was observed that people who have undergone antibiotic treatment were more susceptible to GI tract infection, diarrhea, Clostridium difficile infection, etc. In normal conditions, the gut microbiome outcompetes the pathogenic strains of bacteria by a mechanism called Colonization Resistance based on the principle of Competitive Exclusion. However, the

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administration of antibiotics disrupts the microbiome and hence leaves the GI tract susceptible to pathogenic infections.

There are two mechanisms by which the gut microbiome provides immunization- Direct Mechanism and Indirect Mechanism.

Direct mechanism refers to the release of toxins by the bacteria present in the gut microbiome which is harmful to the pathogen bacteria. Bacteriocins, Colicins, and Microcins are a few such toxic peptides. These toxins work by the following mechanisms- Cell wall synthesis inhibition, and RNA polymerase inhibition, some toxins are known to have nuclease activity.

The indirect mechanism includes the chemical alteration of bile from primary to secondary bile by the gut microbiota. The secondary bile sends signals to the host to limit inflammation and pathogen infection. Moreover, SCFAs and Peptidoglycans released by the gut microbiota also induce host cell production of C-type lectin (Carbohydrate binding protein). C-type lectin selectively kills Gram-positive bacteria such as C.difficile. [3]

### 3. GUT-BRAIN AXIS

Based on several experiments majorly performed on mice, significant progress has been made in establishing strong grounds for bidirectional interactions between the nervous system, the GI tract, and the gut microbiome. Research suggests that the gut microbiome plays important role in modulating the behavior of the host. Communication between the gut microbiome to the CNS occurs through microbial-derived bi-products as mentioned above example- SCFAs, secondary bile acids, and tryptophan metabolites. It is unclear whether these microbial-derived intermediates reach brain sites directly or not. [4]The vagus nerve connects the brain to the digestive tract. The nerve facilitates the transmission of signals from the brain to the gut and vice versa. The brain and gut are connected through neurotransmitters. The information exchange between neurons occurs through the synaptic cleft. The brain produces neurotransmitters such as Serotonin that creates feelings of happiness. There are different transmitters for different emotions. The digestive tract contains an ample amount of neurotransmitters including serotonin. The gut microbiome produces gamma-aminobutyric acid (GABA), a neurotransmitter that controls feelings of anxiety and fear. [5] The gut microbiota has an influence over our emotions, mood via a neurotransmitter-mediated mechanism.

**Early life events and that influence the development of the infant gut microbiota-**

The gut microbiome is highly responsive to numerous factors which are determined in the infant stage. Genetics, prenatal influences, Delivery (cesarean or normal) early life nutrition, physical environment, physiological influences and antibiotic administration all influence the infant gut microbiome**.** [6] [5]

Gut microbiota and brain development begin during the prenatal period, with the first 3 years of life being particularly important. Disruptions in the development of gut microbiome may influence communication between the brain and the gut which may lead to the pathogenesis of neurodevelopmental disorders such as IBS, autism, and obesity. [6] [5]

## III. DYSBIOSIS

Dysbiosis is a condition associated with the disbalance in human-gut microbiota interaction which may be caused due to host of different reasons- Antibiotic administration, improper diet, underlying pathogen infection, physiological and physical stress, etc. These conditions generally lead to improper digestion, malabsorption, and often diarrhea. Dysbiosis may also lead to a host of different diseases. These diseases are generally caused by selective metabolites or products produced by pathobionts that dominate the microbiota (leading to dysbiosis) potentially harming the host. Some of the diseases caused due to Dysbiosis-

- **Clostridium difficile Infection (CDI)**

Clostridium difficile is the causative agent of CDI. It belongs to the genus Clostridioides. Found in gut microbiota, it is a member of Firmicutes. The toxins damage the intestinal barrier and cytoskeleton, leading to inflammation and cell death. [1]

Diarrhea, inflammation in the colon and sepsis are the common symptoms of CDI. Administration of antibiotics is considered a major cause with diarrhea being a common side effect. Antibiotics having large antibacterial effects were associated with greater instances of diarrhea. At present, it is assumed that C.difficile overgrowth

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is inhibited by the strong gut microbiota through colonization resistance mechanisms. One mechanism is the bio-conversion of primary bile acid(cholate derivatives- act as germinants for spores of C.difficile) to secondary bile acid(deoxycholate- prevents vegetative growth of C.difficile). The administration of antibiotics affects the gut microbial diversity by killing most of the other useful microbiota. This reduces antimicrobial secondary bile production from microbial primary bile, which leads to C.difficile outgrowth, making the host more prone to CDI.

C.difficile has two major toxins TcdA and TcdB which play a major role in the formation of the infection. At present two mechanisms of action of these two toxins are identified -

Both toxins (TcdA and TcdB) are glucosyltransferases, they irreversibly inactivate small Rho GTPases, leading to disruption of the cytoskeleton and tight junctions and subsequent cell rounding, detachment, and cell death.

Another mechanism of action is causing intestinal injuries and inflammation bypassing the intestinal epithelial barrier inducing apoptotic pathways or necrotic pathways leading to cell death and mucosal damage. [7]

Treatment of CDI is mostly done by administration of Prebiotics, Probiotics or Faecal Microbiota Transplant. (Discussed later)

❖ **Inflammatory Bowel Disease(IBD)**

Persistent inflammation of the gastrointestinal tract constitutes IBD. It is of two forms: Ulcerative colitis (UC) and Crohn's disease (CD). UC is characterized by inflammation of the sigmoid, colon, and rectum (large intestine regions) while CD is characterized by transmural ulcers in any part GI tract. The ulcers are penetrative and inflammatory. In some cases, the symptoms and effects are so similar that both diseases can't be distinguished. Also, both these diseases can't be cured and have high mortality as well as colorectal cancer risks. [8] [9]

The main cause of IBD is the dysfunction of the intercellular junctions responsible for the prevention of entry of antigens in circulation. Inflammation or failure of primary barrier function serves as a cause of defective junctions. These inflammations lead to the worsening of the epithelium increasing the risk of exposure to intestinal microbes.

Oedema, ulcers, and electrolyte loss are the symptoms of UC caused due to mucosal inflammation. Inflammation initiates in the rectum and continues till the proximal colon. In chronic cases, the colon is stiff and short with no haustral folds (lead pipe appearance of the colon). Extra-intestinal manifestations include inflammatory arthropathies and scars in bile ducts.

On the other hand, Crohn's disease is associated with inflammation, collection of pus, etc, and can affect any part of the GI tract(mostly the colon and ileum). Extraintestinal involvement includes inflammation of the eyes, arthritis, fusing of spine bones, etc. Less absorption of bile salts and fatty acids can also lead to kidney stones and gallbladder stones. [10]

Various ways like laboratory markers, endoscopic biopsies, etc are utilized to confirm IBD. Microcytic anemia and thrombocytosis fall under hematologic findings. Erythrocyte sedimentation rate (ESR) and high-sensitivity C-reactive protein (hs-CRP) act as inflammatory markers. Anemia and albumin levels are checked through a complete blood count. Intestinal inflammation can be found in fecal calprotectin levels. Ulcerative colitis pointed through lead pipe appearance of the colon is checked through barium studies. It also checks on stricture formation which indicates Crohn's disease. Diagnosis can take place through Ultrasound (evaluate ileal disease), computed tomography (evaluate bowel obstruction), and magnetic resonance imaging (evaluate rectal fistulas). For confirming IBD, obtaining biopsies is essential through endoscopy.

IBD treatment is given based on the seriousness of the disease (mild/ moderate/severe).

UC treatment is based on extraintestinal manifestations. For mild conditions, mesalamine (aminosalicylate agent) is used. It can be given rectally or by oral therapy. In the case of moderate patients, TNF-alpha monoclonal antibodies (immunomodulator) or oral glucocorticoids are used for treatment. For elective cases, proctocolectomy with IPAA (Ileal pouch-anal anastomosis) might be an option.

CD treatment is based on extraintestinal complications and the portion of the GI tract involved. For mild cases, mesalamine further augmented with oral budesonide (steroid) is usually used. As for extensive conditions, systemic steroid therapy with prednisone is important. For moderate disease, anti-TNF (tumor necrosis factor) is applied. A purified protein derivative (PPD) is done before biological therapy, for latent tuberculosis. Also,

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assessment of bone density before steroid administration is necessary as osteoporosis can cause fatality in these patients.

❖ **Obesity**

Recently, the Gut microbiome is being researched as a probable cause of obesity. Obesity is the unhealthy accumulation of fat due to more energy intake and less energy expenditure. This abnormal weight gain leads to various heart-associated diseases, liver problems, and even early death.

Compared to normal cases, metagenomic studies have found that for obese patients, there's an increase in Firmicutes (butyrate-producing) and a decrease in Bacteroidetes in the microbiome of obese patients and obese. An increase in glycoside hydrolase (degrades starch), SCFAs and energy harvest capability in the microbial communities affecting host metabolism, might increase the risk of obesity. A strong link between gut microbiota and host metabolism in glucose homeostasis and lipogenesis can be established by the fact that there's an increase in monosaccharide levels in the liver due to more starch metabolism by gut microbiota. Gut microbiota might also be involved in the storage of triacyl glycerides in adipocytes. All of the above suggests that an increase in saccharolytic gut microbiota leads to greater food digestion facilitating higher energy harvest and more fat deposition, overall leading to obesity. [1]

Further, studies indicate that obesity-associated metabolic problems can also be caused by a rise in endotoxic bacterial lipopolysaccharide (LPS). Like, inulin resistance and low-grade inflammation can be caused by more LPS. Similarly, there was an increase of plasma LPS (metabolic endotoxemia) alongside a decrease of Bifidobacteria (down-regulator of intestinal endotoxin) in high-fat-fed mice. [11] It was found that continuous-LPS-infused mice showed similar phenotypes to high-fat-fed mice like hepatic insulin resistance, glycemia, whole-body fat grains, etc.

The therapeutic approach to obesity (associated with gut microbiota) includes the application of prebiotics/probiotics through diet. In animal models, the use of CLA-producing bacteria

(Lactobacillus rhamnosus) decreased white adipose tissue and plasma cholesterol significantly. Inulin-type fructans (nourish Roseburia) and arabinoxylan (increase Bifidobacterium, Bacteroides) are prebiotics that has shown anti-adipogenic effect in high-fat-induced obese mice. Thus, we can say that prebiotics and probiotics can be used to treat obesity, even though, much research is still needed in this field.

****Other diseases that may be caused by Dysbiosis include**- Autism Spectrum Disorder, Celiac Disease, Colorectal Cancer. [1]

## IV. TREATMENT OF DYSBIOSIS

**PROBIOTICS**

The name probiotic is the polar opposite of the term antibiotic (which means against life). Probiotics can be standardized as microbial cell preparations or components of microbial cells that have a beneficial effect on the health and well-being of the host. So basically they are in favor of life and ironically sometimes they are administered to the human body to reverse the side effects caused by antibiotics. When an antibiotic is administered in the host body more often than not it kills most of the bacteria present inside the gut which causes dysbiosis in the gut microbiome. This causes acute diarrhea.

Diarrhea is not a disease to be overlooked. It is a very common disease that often gets cured on its own, however, prolonged diarrhea (Which can be caused by several reasons from bacterial infection to inflammation of the gut, and many other severe health conditions) could be detrimental to health as it may cause severe dehydration leading to nausea, very weak physical conditions, severe illness and in critical cases even death. In these situations, probiotics can be administered. A standard probiotic (against diarrhea) is nothing but a mixture of different kinds of bacteria present in certain quantities (i.e in millions) which could play a crucial role in restoring the balance in the microbial population inside the gut. [12] [13]

***Important Points to remember**-

- Probiotics are not only manufactured for therapeutic purposes, they are also present in fermented dairy products such as Yogurt, Sauerkraut, Kombucha, Miso, Aged cheese, etc. [14]
- We need to remember that all fermented dairy products are not necessarily probiotics.

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- Although probiotics seemingly do not have any significant side effects they should only be taken when prescribed by a doctor.
- Cases of infection due to the administration of probiotics are pretty low, however, immunocompromised people are advised not to take probiotics.
- For a food to be considered probiotic it must have a sufficient amount of living bacteria that survive food processing, and the bacteria that survive must-have benefits to human health based on clinical research.

Let's have a look at a probiotic capsule composition-

**VIZYLAC® RICH CAP**(TORRENT PHARMACEUTICALS LTD)

**Table:** Showing composition of a probiotic.

| Each hard gelatin capsule contains- | |
|---|---|
| Streptococcus faecalis | 30 Million |
| Clostridium butyricum | 2 Million |
| Bacillus mesentericus | 1 Million |
| Lactobacillus sporogenes | 50 Million |
| Saccharomyces boulardii | 50 Million |

By taking a glance at the composition of the above-mentioned probiotic it is safe to assume that the bacteria present in the composition are close relatives of the bacteria present in our gut (all persons have different bacteria but mostly belong to the same phyla Firmicutes, Actinobacteria, and Bacteriodetes). These bacteria help to restore the balance inside the gut microbiome by either outcompeting a bacteria which was a prime suspect for bacterial infection or by replacing(at least temporarily) the bacteria which were killed by the antibiotics. Probiotics generally work very fast and potently, within 12-24 hours of their administration, normal stool formation is resumed by the bacteria present in it.

**PREBIOTICS**

Prebiotics are special plant fibers that are essential for the maintenance of the gut microbiome. They are food sources for the bacteria present inside our gut. Our digestive enzymes are incapable of digesting the complex fibers so they do not give us any direct health benefit however the bacteria in our gut break them down which in turn nourishes them. The gut bacteria metabolize this prebiotics to form short-chain fatty acids(e.g. butyrate, acetate, and propionate). These short-chain fatty acids nourish the cells which line the gut and act as a food source for the gut microbiome keeping them alive and healthy so that they can execute their job of digesting our food properly, and also enhance calcium absorption which relieves constipation and diarrhea. [15]

Some important sources of prebiotics(natural)- Are chicory root, Dandelion Green, Garlic, Onion, Asparagus, Bananas, Barley, Oats, Apple, etc.

***Important Points to remember**-

- All these foods(Chicory root, Dandelion Green, Garlic, Onion, etc) have different nutritional values however the fiber part of it is only useful for bacterial metabolism.
- Mostly therapeutic prebiotics are in combination with probiotics. Prebiotics in combination with probiotics is known as synbiotics.

**FECAL MICROBIOTA TRANSPLANT**

As the name suggests fecal microbiota transplant is the transfer of fecal matter from a healthy host to an unhealthy host. Most commonly performed as a treatment against digestive disorders or problems like chronic diarrhea, and Clostridium difficile infection caused by disruption of the host microbiome. The principle of action of this therapy is similar to probiotics. The fecal matter of a healthy host is expected to have the bacteria which is important for digestion and maintaining hemostasis(The bacteria present inside the gut of the healthy host naturally gets excreted out with stool however this does not change anything inside that person's gut considering there are millions more bacteria). A stool sample from the healthy host is collected and injected into the patient's gastrointestinal tract. The microbiota in the stool sample helps restore the patient's microbiome, stopping severe diarrhea, Clostridium difficile infection, etc.

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Fecal Microbiota Transplant can be carried out in different ways- by an instrument called Colonoscope. The colonoscope is guided through the entire length of colon. The solution containing faecal microbiota is transferred to the colon. Other ways include ingesting capsules (Presumably having microscopic stool samples or bacteria isolated from a stool sample). [16]

***An ideal fecal donor must maintain the following regulations-**

- The donor shouldn't be immunocompromised.
- The donor should not have any infectious disease.
- The donor must not have administered antibiotics (within at least 6 months).
- The donor should not have any chronic gastrointestinal disorder like inflammatory bowel syndrome.
- The risk of transmission of unknown pathogens cannot be excluded, therefore it is very important to screen and select the donor very carefully (ideally recipients family members).

## V. CONCLUSION

More and more fundamental research is going on in this field of microbiology to understand the importance of gut microbiome to human body, the points established in this review article are based on previous research. These points open up new horizons to not only understand the physical importance of the gut microbiome but also establishes how gut microbiome influences the mental health of a person. Treatment of dysbiosis may also be linked to possibilities of treatment of mental health. With further research there are endless possibilities to be explored.

**ETHICAL STATEMENT**

The material presented in the review article belongs to both the authors. No part of the article has any item which the authors don't own the copyright for. The review article is not under consideration of any other publication at this point of time. The paper contains the authors own research and knowledge from different sources which has been presented in a truthful manner. All the sources which are used in the making of this review article has been listed in the bibliography section. Both authors don't have any conflict of interest of the review article and share equal responsibility.

There are no human subjects in this article hence does not require informed consent.

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