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Microbiome Modulation-Based Therapeutic Interventions to Target Enhanced Human Health

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A B S T R A C T

The potential of gut microbiome in health and diseases has emerged as an area of profound scientific research and clinical exploration that elucidates the correlation of human immune system homeostasis, and metabolic functions with altered diversity of gut microbiota. This further validates the underlying causes and consequences of variability in gut microbiome profiles in the development of autoimmune and inflammatory diseases such as rheumatoid arthritis, cardiovascular and respiratory illnesses, neurological disorders such as neurodevelopment disorders, autism spectrum disorders, attention deficit hyperactivity disorder, stroke, Parkinson's disease, schizophrenia, Alzheimer's disease, depression, gastrointestinal inflammations including irritable bowel syndrome, inflammatory bowel disease, ulcerative colitis, Crohn's disease, *Clostridium difficile* infection, metabolic diseases including type 1 and type 2 diabetes mellitus, non-alcoholic fatty liver disease, liver cirrhosis, immunomodulation and certain types of cancers. Dietary interventions, fasting regimens, nutritional supplements, antibiotics, probiotics, prebiotics, synbiotics, postbiotics psychobiotics, bacteriophage, and fecal microbiota transplantation are the possible interventions that open avenues in the near future to exploit individual microbiota profiles in clinical practice as a biomarker for gut health of the patients who are at the risk of developing certain abnormalities and ailments attributed to dysbiosis. The knowledge of the present review on microbiome modulation-based therapeutic interventions to target enhanced human health comprehensively sheds light on how this upcoming field unveils the opportunities for improving human health and for preventing, treating and managing certain autoimmune diseases.

Introduction

The human body is home to trillions of microbes especially the intestinal compartment, where these are prevalent in maximum density to form the gut microbiota. Gut microbiota encompasses the cells of all the microbes whereas microbiome includes their genetic materials too. Gut microbiota is a dynamic and ever-changing organ that is the most forgotten part of the body including trillions of bacteria, viruses, parasites, archaea, and fungi that make humans a superorganism. It varies with sex, age, race, and lifestyle habits such as smoking,

exercise, alcohol consumption, dietary habits, medications, geographical location, and temperature of the person. The microbial community starts to colonize at birth and is altered further during the life span of an individual based on the mode of delivery of the child, gestational age, breastfeeding, and infections.Exposure to xenobiotics and certain environmental factors such as level of oxygen, redox state, pH, temperature, and dietary nutrients in the gut additionally contribute to variations in gut microbiota (Spor *et al.,* 2011; Milani *et al.,* 2017). Besides these, sex hormones (Fransen *et al.,* 2017), pharmaceuticals like proton pump inhibitors (PPIs) (Imhann *et al.,* 2016) environmental intoxicants, treatment with antifungal and antibacterial agents (Wheeler *et al.,* 2016) and consuming several prescribed drugs (Ticinesi *et al.,* 2017) contribute to dysbiosis. The evolution of microbiota is through Proteobacteria,Actinobacteria and then to a stage where *Bacteroides, Bifidobacterium,*and Enterobacteriaceae are dominant to a group of Lachnospiraceae and Ruminococcaceae families of phyla *Firmicutes, proteobacteria, Bacteroidetes, Actinobacteria* and *Verrucomicrobis* with family Akkermansia and eventually to a more personalized microbiota as found in adults (Heiman and Greenway, 2016; Wu *et al.,* 2011).

These factors during pregnancy modulate the microbiome of offspring by regulating neurotransmitter pathways, signal transduction, and synaptic transmission (Lindsay *et al.,* 2019). The study of microbiomes is important, concerning associated and correlated diseases, what are the causes, effects, and consequences of manipulations of gut microbiomes and how these interventions can be exploited for the possible development of novel, diagnostic, prognostic, and therapeutic strategies. Even the stage of the disease, risk assessment, and early diagnosis of the disease can be elucidated with the knowledge of these modulations (Fig.1).

The gut microbiome not only contributes to the well-being and diseases of the gut but also regulates the health of extra enteric organs such as the liver, pancreas, heart, brain, skin, bones, muscles, etc. It leads to the construction of the gut epithelium, its maintenance, and metabolism affecting energy balance, digestion of food, and development of the immune system and protecting against physiologic stress (Visconti *et al.,* 2019; Adak and Khan, 2019). The gut microbiome plays a role in angiotensin II-induced vascular dysfunction and hypertension (Karbach *et al.,* 2016).

Gut microbiota plays a key role in the nutritional and metabolic functions of the host and determines immune homeostasis. It modulates the level of various neurotransmitters and neuromodulators, which induce intestinal epithelial cells to release molecules such as cytokines and hormones for modulating signaling pathways within the enteric nervous system thereby controlling cognitive abilities, brain function, and behavior of the person. The brain in turn can alter the composition and functioning of microbiota via the release of hormones and neurotransmitters to influence gut physiology and environment, where certain types of microbial population can thrive. This is mediated through the gut-brain axis. Some strains of these microbial populations mediate their impact on the brain via the vagus nerve. For example, gut microbiota controls the metabolism of precursors of the kynurenine pathway which along with serotonin can be derived from tryptophan. The metabolites of the pathway can modulate neurotransmission serving themselves as neuroactive molecules (Cryan and Dinan, 2012). Signals from the gut microbiome to the brain are mediated by several bacterial neuroactive metabolites like short-chain fatty acids (SCFAs), acetate, butyrate, and propionate (MacFabe *et al.,* 2011). Non-digestible carbohydrates serve as a source of carbon and energy for SCFA production to influence body homeostasis (Cani and Jordan, 2018; Chambers *et al.,* 2018).

Dysbiosis is also correlated with irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis, colon cancer, non-alcoholic fatty liver disease (NAFLD), liver cirrhosis, cardiovascular disease (CVD), neurological disorders, neurodegeneration, metabolic disorders such as diabetes type1 and type 2 (T1DM, T2DM), obesity and more chances of hepatitis B virus infections with complications related to liver cirrhosis, hepatic encephalopathy, bacterial peritonitis, and renal failure (Cohen, 2016; Ling *et al.,* 2016; Lakshmi *et al.,* 2010). Gutdysbiosis is also associated with chronic liver failure, hepatocarcinoma, fibrosis and mortalities due to specific inflammatory cytokines from specific bacterial families which lead to reduced pancreaticobiliary secretions, reduced intestinal motility, impaired intestinal barrier, increased intestinal permeability, decreased gastric acidity and activation of Toll-like receptors (TLRs) (Dapito *et al.,* 2012). Gut dysbiosis can lead to endotoxemia that may induce immune dysfunctions leading to cell necrosis and hepatic failure (Boursier *et al.,* 2016).

Besides playing a central role in immunomodulation, gut microbiota also regulates oxidative stress which brings about homeostasis of inflammations, and macrophage cell population in the central nervous system (Angoorani *et al.,* 2021; Li *et al.,* 2017; Baek *et al.,* 2013; Sampson *et al.,* 2016). Even increased abundance of *Enterobacteriaceae, Fusibacteriaceae, Pasteurellacea, and Veillonellaceae* and decreased levels of *Bacteroidales, Clostridiales,* and *Erysipelotrichales* during the analysis of IBD patient samples show a correlation with the status of the disease which paves the way for easy diagnosis and offers an opportunity for early treatment (Gevers *et al.,* 2014).

Microbiome-based therapies are still in the early stages of development due to the challenge of an undefined healthy microbiome, standardized microbiome sampling and analysis, safety and efficiency, undefined pharmacodynamics and pharmacokinetics, variability from individual to individual, less understood long-term side effects and less explored and less understood microbiome –host-environment cross-talk for health and disease management (Fig 2).

The present review aims to elucidate the data correlated with possible interventions at one place to provide deep insight into strategies attributing to the modulation of gut microbiota composition for the health of the host and to understand the existing gaps in knowledge and to explore the possibilities of future therapeutics based upon personalized plans.

Mechanism of Action of Gut Microbiota

Bifidobacterium has been known as a key modulator of G1T helper 17 (Th17) cells besides maintaining barrier function to check the entry of pathogenic microbes. The role of gut microbiota in tumorigenesis is in addition to genetic factors. The possible mechanism includes the promotion of inflammations due to more expression of pro-inflammatory genes such as COX2, IL-6, IL-8, TNF-α, and MMP3. However, *Helicobacter pylori* are known to play a protective role in the development of esophageal adenocarcinoma (Hamada *et al.,* 2000).

Enterotoxigenic *Bacteroides fragilis* leads to activation of Wnt/β-catenin signaling pathway and NF-κB producing inflammatory mediators via the release of a toxin known as fragilysin which causes cells to proliferate excessively (Sokol, 1999; Shiryaev *et al.,* 2013). *Enterococcus faecalis* and *E.coli* induce DNA damage by producing superoxides (Huycke *et al.,* 2002). Gut microbiota also influences the circadian clock (Leone *et al.,* 2015). *Firmicutes* and *Clostridia* abundance can resolve the issues of cow milk allergy if made present at the age of 3 to 6 months old. *Clostridium sensu strict*is responsible for IgE levels in serum (Ling *et al.,* 2014; Atarashi *et al.,* 2011).

Clostridium species that belong to clusters IV, XIVa, and XVIII produce SCFAs and thereby induce $Foxp3^{+}$, $CD4^{+}$, and Treg cells (Atarashi *et al.,* 2013) while *Bacteroides fragilis* binds to TLR2 (Toll-like receptor 2) of dendritic cells (DCs) to enhance immuno-tolerance through the production of cytokine IL-10 by regulatory T cells (Das Gupta *et al.,* 2014). Short-chain Fatty Acids (SCFAs) produced by beneficial microbiota mediate their functions by activation of G-protein coupled receptors (GPCRs) such as GPR41 and GPR43. These also block the action of histone deacetylase (HDAC) (Zaibi *et al.,* 2010). SCFAs produce chemokines such as CINC-2 and MCP-1, cytokines like TNF-α, IL-10, IL-2, and IL-6 and help leucocytes to migrate to inflammation sites and destroy pathogens (Vinolo, 2011; Cox *et al.,* 2009; Luster *et al.,* 2005). SCFAs also cause apoptosis of lymphocytes, neutrophils, and macrophages (Aoyama *et al.,* 2010; Bailón *et al.,* 2010; Fei and Zhao, 2013) (Fig. 3).

Strategies

Microbiota therefore is an essential organ of the human body and its total absence impairs social behavior leading to anxiety and stress response (Desbonnet *et al.,* 2014; Foster *et al.,* 2013). Various microbiome modulation-based therapeutic strategies are to be followed for modulating gut microbiota towards a healthy one and form the body of the review (Fig.4).

Dietary Interventions

The dynamic ecosystem of gut microbiota depends upon various factors such as age, lifestyle, environment, genetic predisposition and mainly diet. Diet along with other factors impacts the gut microbiota and brain-gut axis, which in early stages help in protection against the onset and progression of disorders linked with development and mental health. Certain dietary interventions serve as alternative or adjuvant strategies for the management of neurodegenerative disorders (NDDs) emphasizing long-term consequences on health and aiming at their prevention and treatment.

Fat-rich diet

Maternal high-fat diet-induced obesity during pregnancy can be managed by modifying the gut microbiota composition of the offspring thereby determining the socio-emotional behavior and cognitive abilities of the child (Rivera *et al.,* 2015). Supplementation with *Bifidobacterium breve* strain from birth promotes the growth of the resident *Bifidobacteria* to mitigate negative consequences associated with C-section progeny such as social behavior and anxieties. Infants with longer duration of breastfeeding have increased levels of *Bacteroides fragilis* and *Lactobacillus* to restore health-promoting microbiome in Caeserian-born progeny (Coker *et al.,* 2021). Dietary supplementation of omega-3-polyunsaturated fatty acids (PUFAs) in the early life period provides protection against neurological impair-ments (Lei *et al.,* 2013; Gow *et al.,* 2013).

A high-fat diet is known to alter the gut microbial composition and is associated with cognitive decline and ADHD (attention deficit hyperactivity disorder), yet pieces of evidence for ADHD management based upon gut microbiota-directed interventions need further confirmation (Fernandez-Real *et al.,* 2015). However, prenatal and early infancy supplementation with *Lactobacillus rhamnosus* GG (LGG) shows a decreased risk of developing ADHD (Rianda *et al.,* 2019). A high saturated fat dietalso leads to an increase in Proteobacteria and Firmicutes and a decrease in Bacteriodetes, increasing gut permeability, insulin resistance, and adipose tissue inflammation (Malesza *et al.,* 2021).

Milk fat intake causes gut inflammation due to the thriving of sulfate-reducing bacteria (Devkota *et al.,* 2012). Monounsaturated fatty acids (MUFAs) enhance the richness of *Prevotella,* Enterobacteriaceae family members, Parabacteroides, and *Turicibacter* genera showing positive health effects and increasing diversity of gut microbiota (Wolters *et al.,* 2019). A diet rich in coconut oil increases *Lactobacillus, Allobaculum, Clostridium, Staphylococcus,* and Firmicutes hence adipose tissue inflammation (de Moura e Dias *et al.,* 2018). Polyunsaturated fatty acids (PUFAs) have the potential to produce butyrate and enhance *Lachnospiraceae* taxa (Noriega *et al.,* 2016). Prolonged high saturated fat intake causes high production of bacterial amyloids which is associated with misfoldings of proteins and enhanced neuroinflammation. High-fat diet intake leads to an abundance of *Enterococcaceae, Roseburia, Staphylococcus, Dorea,* and *Coprobacillus* with reduced cognition abilities and slow brain metabolism (Sanguinetti *et al.,* 2018).

Gluten-free, casein-free, and food additives-rich diet

Foods rich in salicylates and artificial additives contribute to ADHD development. Gluten-free and casein-free diets (GFCF) are found to be effective for autism spectrum disorder (ASD) treatment (Paniwowarczyk *et al.,* 2018). GFCF diets do not produce opioid peptides BCM7 (β-caso morphin7) when subjected to partial digestion of gluten and casein peptides which otherwise correlates with negative effects on mental health. These food-derived opioid peptides tend to cross the blood-brain barrier to reach and bind with their respective receptors in the brain and act as neuromodulators to affect neurotransmission and unfold the pathogenesis of ASD (Jarmołowska *et al.,* 2019). Gluten tolerance can be assumed by a gluten-free diet when taken with prebiotics and probiotics with concomitant increase in Clostridiaceae, Victivallaceae and Coriobacteriaceae families and reduced *Roseburia* feces and *Ruminicoccus bromii* causing a possibility to cure celiac disease (Bonder, 2016). Certain food additives such as aspartame, saccharin, and sucralose increase *Bacteroides spp* and decrease *Bifidobacterium* and *Clostridium spp* leading to glucose intolerance (Suez *et al.,* 2014).

Ketogenic Diet

Ketogenic diet has been found to have a high therapeutic potential for pediatric epilepsy and many other mental disorders (Castro *et al.,* 2015). The Keto diet (KD) leads to reduced levels of tumor necrosis factor (TNF-α) in plasma and Interleukin-1β (IL-1β) in the brain with favorable effects in Schizophrenia (SZ) patients (Dupuis *et al.,* 2015). KD intake is known to trigger loss of microbial diversity with decreased *Bifidobacteria* and increased *E.coli, Shigella, Akkermansia muciniphila,*and *Parabacteroides merdae* resulting in protection against epileptic seizures (Olson *et al.,* 2018). Oral intake of L-carnitine and phosphatidylcholine is reported to elevate levels of trimethylamine (TMA) and its proatherogenic metabolite trimethyl amine-N-oxide (TMAO) with increased risk of atherosclerosis and associated cardiovascular diseases (CVDs) (Koeth *et al.,* 2013). TMAO contributes to atherosclerotic plaques, increased coronary plaques, plaque-rupture possibilities, and

enhanced risk of the coronary syndrome and myocardial infarction (Zhu *et al.,* 2016; Tang *et al.,* 2013; Tang *et al.,* 2015) (Fig. 5).

The onset of depression induced by an inflammatory cytokine interferon-α (IFN-α) can be avoided by pretreating with eicosapentaenoic acid (EPA) (Su *et al.,* 2014). Intake of the ketogenic diet leads to an increase in *Desulfovibrio spp.* and *E. coli* with a corresponding rise in gut inflammations and a decrease in *Bifidobacterium* and *Dialister* (Lindefeldt *et al.,* 2019).

Early introduction of the ketogenic diet modulates the gut microbiome to enhance brain vascular functions and improve cognition and memory via the production of SCFAs which reduces leakiness of the gut and limits the diffusion of lipopolysaccharides (LPS), thereby reducing the risks for Alzheimer's disease (AD) and improving the overall health of the brain.

Release of gamma amino butyric acid (GABA) for the overall health of the brain is attributed to increased levels of *Akermansia muciniphila, Bacteroides fragilis, Dialister invisus,* and *Bifidobacterium adolescentis* upon intake of Mediterranian keto diet. Western diet on the other hand leads to an abundance of *Helicobacter pylori, Prevotella, Campylobacter,* and *Porphyromonas* with subsequent release of LPS, the later enters the bloodstream to activate TLR-4 dependent CD14 and causes damage to the intestinal barrier to enhance permeability of gut and release of pro-inflammatory cytokines (Kim *et al.,* 2021; Qin *et al.,* 2007). With the keto diet, the neurotransmitter epinephrine, GABA release is enhanced with decreased production of reactive oxygen species (ROS), biogenesis of mitochondria, hyperpolarization of neurons, and energy metabolism gene upregulation (Bough and Rho, 2007).

These begin a cascade of synaptic disruption and neuro-inflammation that is the root cause of neurodegenerative diseases.

High and Low-Calorie Diets

A very low-calorie diet fed to obese patients for 6 weeks is known to alter gut microbiota (Simões *et al.,* 2014). Obesity and non-alcoholic fatty liver disease (NAFLD) can be prevented by making alterations in gut microbe composition based on diet (Henao-Mejia *et al.,* 2012). Reduction in dysbiosis occurs with dietary intervention to alter the composition of microbiota to a favorable and stable state such as a decrease of *Acinetobacter spp* and increase of *Corynebacterium.* Decreased *Actinobacter* is correlated with enhanced cytokine response in patients with chronic mucocutaneous candidiasis (CMC) and hyper immunoglobulin E syndrome (HIES) with fungal pathogens *Candida albicans* and *Staphylococcus aureus* for fighting against these two immunodeficiencies (Smeekens *et al.,* 2014).

The prevalence of *Akkermansia* in the gut largely determines the basal metabolic rate in humans (Xu *et al.,* 2022). For ulcerative colitis (UC) remission, an anti-inflammatory diet is highly recommended (Kedia *et al.,* 2022). High sugar intake induces colon inflammations by increasing the levels of *Akkermansia muciniphala,* enhancing gut permeability, and reducing the production of SCFAs. This is mediated by the production of an enzyme that degrades the mucus layer (Khan *et al.,* 2020; Laffin *et al.,* 2019). Probiotic intervention declines recovery of endotoxin from the gut of obese, diabetic, and hypertensive subjects from 35% to non-detectable traces with resolved issues of hypertension, hyperinsulinemia, and hyperglycemia (Fei and Zhao, 2013).

Animal and Plant-Based Proteins

Dietary intake of animal protein-based and dairy products leads to an abundance of *Bacteroides, Bilophila,* and *Alistipes* which further increase TMAO, nitrosamines, and ammonia. TMAO with pro-atherogenic potential leads to an increased risk of CVDs (David *et al.,* 2014; Barrea *et al.,* 2019; Zhang *et al.,* 2022).

The animal protein-based diet also exacerbates the growth of *Desulfovibrio spp* that produces H_2S and increases gut inflammation. On the contrary, plant-based proteins increase the abundance of beneficial bacteria such as *Eubacterium faecalibacterium, Clostridium, Roseburia, Bifidobacterium,* and *Lactobacillus* while decreasing *Bacteroides* and *Clostridium* (Swiątecka *et al.,* 2011; Graf *et al.,* 2019).

Polyols and Polysorbate-rich diet

Polyols induce laxative effects and also an increased *Bifidobacterium* in humans. Polysorbate 80 and carboxymethyl cellulose can promote gut inflammation with an increase of *Akkermansia muciniphila* and proteobacteria (Ruiz-Ojeda *et al.,* 2019; Chassaing *et al.,* 2015; Chassaing *et al.,* 2017).

Vegetarian and Vegan diets

Vegetarian and vegan diets lead to an abundance of *Bacteroides, Clostridium, Faecalibacterium,* and *Klebsiella* and lower levels of *Bilophila* (Matijaˇsi´c *et al.,* 2014; Ruengsomwong *et al.,* 2016).

Dietary interventions have a significant impact on gut microbiota but short-term and long-term interventions need a detailed study to see if the short-term intake has a long-standing impact on gut microbiome diversity. Beta diversity can be dealt with short-term interventions but it is hard to deal with alpha diversity. Detailed studies are required to investigate the changes in microbial composition in response to habitual dietary strategies.

If the host acquires microbial resilience, the diversity returns to its original state after interventions otherwise it tends to establish a new microbiome profile (Smits *et al.,* 2017). Therefore, diet and gut microbiota act synergistically to provide resilience against diseases.

Effects of fasting or starvation on human gut microbiota

Fasting in humans leads to an abundance of *Christensenellaceae* species. A decreased abundance of firmicutes such as *Lachnospiraceae* and *Ruminococcaceae* and an increase of *E. coli* and *Bilophila wadsworthia* with a calorie-restricted diet is reported (Mesnage *et al.,* 2019). While Ramadan fasting led to elevated levels of *Faecalibacterium prausnitzii, Roseburia, Eubacterium, Akkermansia, Butyricicoccus pullicaecorum* (Ozkul *et al.,* 2020) and *Bacteroides fragilis* (Ozkul *et al.,* 2019).

Within one week of calorie-restricted diet intake, an initial increase in abundance of *Lactobacilli* and *Enterobacteria* is seen with a subsequent decline by the end of the intervention. Genera *Clostridium-XIV, Coprococcus,* and *Lachnospiracea* decrease due to fasting while *Faecalibacterium* is known to increase (Ozkul *et al.,* 2020). The abundance of *Lachnospiraceae, Blautia* and *Faecalibacterium* is observed after intermittent fasting.These bacterial genera produce butyrate in the gut and counterbalance dysbiosis in the gut of patients suffering from multiple sclerosis (MS). Therefore, dietary programs and fasting regimens can serve as important non-pharmacological interventions for the treatment of various diseases.

Nutritional Supplements

Protective effects of specific nutrients like zinc, iron, iodide, and omega-3-PUFA and adverse effects of food coloring agents, sugar, and preservatives are found to be associated with increased risk of ADHD and obesity (Pelsser *et al.,* 2020; Bowling *et al.,* 2017). A deficiency of vitamins such as A, C, B_6, B_{12}, D, and folate has been found to trigger an onset of ASD (Fraguas *et al.,* 2019). Deficit of nervonic acid (NA), a monounsaturated omega-9-fatty acid is known to develop psychosis in patients with high clinical risk (Amminger *et al.,* 2012), while omega-3-fatty acid supplementation tends to reduce psychotic conversion rates (Moon, 2010; Cadenhead *et al.,* 2017). Elevated Hcy serum levels (homocysteine) are related to the development of cardiovascular diseases, SZ, and Alzheimer's disease (Tinelli *et al.,* 2019). A low level of serum Vitamin D is observed in SZ patients while Vitamin D is found to have a negative correlation with psychosis severity (Gracious *et al.,* 2012). Low dietary intake of vitamin C is associated with an increased risk of SZ. So, clinical management of SZ, in patients is diet dependent and also associated with celiac disease (Cha and Yang, 2020). Alterations in the diet by introducing protein supplementation can havea significant imbalance in gut microbiota. In studies conducted, a diet complemented with protein intake was found to be correlated with an increase in the population of *Bacteriodetes* and a decrease in health-related taxa including *Bifidobacterium longum, Blautia* and *Roseburia.* Also*, Lactobacilli* and other butyrate-producing bacteria are reduced in abundance (Ma *et al.,* 2017) along with a decrease in SCFAs-producing phylum such as *Coprococcus.* Protein supplements with probiotics could form a part of future strategies to mitigate the imbalance of microbiota in place of only protein supplementation and can result inrecovering the dysbiosis. However, further research is required to determine sources and doses of protein in support of health benefits for the sports community. Therefore, long-term protein supplementation with proteins hurts gut microbiota. Protein overfeeding also leads to lower levels of malondialdehyde which is a marker for oxidative stress and it can lead to changes in populations of microbiota and their metabolites (Moraes *et al.,* 2017). Vitamin A supplementation increases *Bacteroidetes* and decreases in *Actinobacteria, Bifidobacterium, Clostridium, Enterobacter, Escherichia,* and *Proteobacteria* populations. β -carotene intake results in decreased *Bacteroides,* and an increased

Firmicutes and *Clostridium* (Liu *et al.,* 2017; Li *et al.,* 2017). Increased *Proteobacteria* and *Actinobacteria* result due to retinol intake (Mandal *et al.,* 2016). The duration of *E.coli* infections after supplementation with vitamin A is due to a decrease in IL-8 and monocyte chemoattractant protein-1 concentrations (Long *et al.,* 2011).

Vitamin B_2 provides an anti-oxidative environment in the gut which favors the growth of *Faecalibacterium prausnitzii* and reduces *E. coli* colonization, thereby decreasing pro-inflammatory processes and hence finding applications in IBD treatment. B_2 supplementation is associated with reduced inflammatory effects due to low oxidative stress, C-reactive proteins, low IL-2, and decreased erythrocyte sedimentation rate (ESR) (von Martels *et al.,* 2019). An increased intake of Vitamin B_2, B_5, B_6, and B_{12} leads to a corresponding increase inthe abundance of *Prevotella* and a decrease in *Bacteroides* populations (Carrothers *et al.,* 2015). Also, deficiency of cobalamine (Vit B_{12}), vitamin B_9 (folic acid), and piroxidine (Vit B_6) is found to be associated with schizophrenia (SZ) development. In other words, vitamin B supplementation results in increased microbial interactions, metabolism, and signaling besides ensuring enhanced microbial diversity, specifically beneficial microbes that are enriched by Vitamin A, D, and E.

Vitamin C, E, and B_2 reduce redox potential. Vitamin C ensures increased SCFA production and exhibits antibacterial, antiviral, and antimicrobial properties (Mousavi *et al.,* 2019). Vitamins A and D lead to increased immune function and also enhance barrier functions. Diseases of the gastrointestinal tract such as inflammatory bowel disease are correlated with a deficiency of vitamin D (Cross *et al.,* 2005) which alters microbiome diversity with an increased *Coriobacteriaceae, Streptococcus, Bifidobacterium, Dorea* and *Coprococcus* while decreased *Odoribacter* and *Desulfovibrionaceae* (Pham *et al.,* 2021; Chatterjee *et al.,* 2020).

Vitamin D supplementation also reduces the abundance of gamma proteobacteria like *Pseudomonas, E.coli,* and *Shigella. Haemophilus, Blautia,* and *Veillonella* while increased *Prevotella* and *Lachnospira*. Higher intake of vitamin E results in decreased *Proteobacteria.* Vitamin E and iron supplementation lead to the enrichment of butyrate-producing bacteria (Tang *et al.,* 2016) and decreased vitamin E can enhance pathogenic *Citrobacter* in mice models (Smith *et al.,* 2011). Vitamin K supports bacterial diversity in the gut microbiome (Fenn *et al.,* 2017).

Antibiotics

Antibiotics play a significant role in eradicating some diseases. Abundance of overgrown *colitis* bacteria in patients can be reduced with certain antibiotics. Similarly, antibiotics such as Minocycline and Sulfazalazine reduce symptoms of rheumatoid arthritis patients which target the causative microbes that are bacteria (Stone *et al.,* 2003). Administration of antibiotics during pregnancy, infancy, childhood, or even during adolescence influences colonization and diversity of gut microbiome to determine various neurocognitive disorders later in life (Younge *et al.,* 2019; Burger *et al.,* 2020)

At the same time, the use of broad-spectrum antibiotics results in short-term and long–term perturbation of diversity in the resident microbiome community of the host that has detrimental impacts leading to the killing and reduction of beneficial microbes such as *Faecalibacterium prausnitzii*to cause deleterious effects on host health too. For instance, low levels of *F. prausnitzii* are found to be prevalent in IBD patients (Sokol *et al*., 2009; Dubourg *et al.,* 2014).Antibiotic-associated diarrhea (AAD) can be another outcome of the elimination of beneficial gut microbiota, in the absence of which *Clostridium difficile* gets a chance to thrive well and can further lead to diarrhea and colitis (Buffie *et al.,* 2012; Mc Donald 2017).

Decreases in accompanied serotonin levels, secondary bile acids, and tryptophan hydrolase influence gut motility (Ge *et al.,* 2017). Also, there is a decrease in SCFA production with corresponding low levels of butyrate and propionate. (Mu *et al.,* 2017) The absence of useful microbes under antibiotic influence results in immunological and physiological changes to the gut environment. Mucus thickness and gastric motility are reduced with improper functioning of intestinal cells and immune cells (Cehenzli *et al.,* 2013) and chances of invasion by pathogens and subsequent inflammations become high (Wlodarska *et al.,* 2011). Barrier functions of intestinal cells are also impaired which can lead to the development of ulcerative colitis, *Salmonella,* and *Helicobacter* infections (Machills *et al.,* 2013; Gillis *et al.,* 2018).

Altered microbial composition due to antibiotics results

in deficiencies of certain vitamins and metabolites that are produced by beneficial bacteria. Antibiotic intervention alters the gut microbiota and is known to reduce the severity of multiple sclerosis (MS) in human murine models. This is attributed to reduced secretion of pro-inflammatory cytokines such as IL-17.

Antibiotics therefore create persistent off-target microbiome disturbance called dysbiosis that can further lead to disorders and diseases related to host immunity and result in increased abundance of antibiotic-specific resistance genes. Antibiotics result in reduced colonization resistance with a concomitant increase in susceptibility to specific opportunistic pathogens such as Azithromycin-resistant *Clostridium difficile, Salmonella,* and *Vancomycin-resistant Enterococci* (Brandl *et al.,* 2008; Sequeira *et al.,* 2020; Wu *et al.,* 2020).

More research is needed to understand how different antibiotics alter gut microbiomes to better regulate the indiscriminate usage of antibiotics and avoid risks of antimicrobial-resistant infections. Consistent use of antibiotics during childhood results in the development and abundance of bacterial antimicrobial resistant (AMR) genes called resistome which posesa risk of obesity, diabetes, asthma, allergy, and later adiposity in life (Block *et al.,*2018; Marra *et al.,* 2009; Chen *et al.,* 2021; Stokholm *et al.,* 2014). Class of antibiotics, duration of administration, usage, and follow-up time impact the diversity and composition of the microbiota. The use of other therapies such as probiotics, synbiotics, and FMT (Fecal Microbiota Transplantation) must be emphasized post-antibiotic treatment to restore the gut microbiota community.

Several therapies such as bacteriophage therapy, bacteriocins use, FMT, probiotics, synbiotics, and use of monoclonal antibodies are important alternatives to the use of antibiotics that pose target-specific results with minimal damage to the microbiota thus emphasizing the need to develop therapies in addition to methods of conserving and restoring the perturbed microbial-communities post-antibiotic treatments.

Probiotics

The live microorganisms which when consumed in adequate amounts bring about health benefits to the host or active bodies with essential functions for promoting health aspects (Gasbarrini *et al.,* 2016).

Lower levels of *Bifidobacteria* and *Blautia* gut bacteria in mice are linked with the production of less tryptophan which acts as the serotonin precursor (Golubeva *et al.,* 2017). *Bacteroides fragilis* or *Lactobacillus reuteri*, when administered, bring about gastrointestinal and behavioral changes in ASD (Pama, 2019). ASD-suffering children report GI pain and increased levels of *Clostridiales,* decreased levels of *Veillonellaceae, Coprococcus,* and *Prevotella* (Luna *et al.,* 2017), butyrate-producing taxa *Ruminococcaceae, Eubacterium, Lachnospiraceae,* and *Erysipelotrichaceae* together with low production of SCFAs in adults (Liu *et al.,* 2019). Selected strains *of Bifidobacterium longum infantis* and *B. bifidum* can abolish food-derived opioid peptides to contribute to host health (Olivares *et al.,* 2018). Different probioticstrains such as *Lactobacillus rhamnosus, L. reuteri,* and *Bifidobacterium infantis,* when administered in combination, reduce incidences of seizures and epileptic activity due to increased GABA levels in the brain and accompanied by reduced oxidative stress in the brain (Bagheri *et al.,* 2019). A reduction in *Bacteroides, Prevotella, Bacteroides fragilis, Bifidobacterium* and *Eubacterium, Clostridium, and Coccoides* groups is seen in rheumatoid arthritis patients (Scher *et al.,* 2013). When inoculated in a probiotic combination, thisprovides chances for rheumatoid arthritis management. Also, members of families Lactobacillaceae of Firmicutes, Rikenelleceae, and Porphyromonadaceae suggest an immune-regulative role in diabetes.

Probiotics strains including *Bacillus spp* (*Bacillus breve, B. bifidum, B. subtilis, B. longum, B infantis), Lactobacillus casei, L. acidophilus, L. delbrueckii, L. helveticus, L. plantarum, L. salivarius, L. rhamnosus, Lactococcus lactis lactis,* and *Streptococcus thermophiles* when administered in MS patients, reduce IL-6 and BDNF levels (Rahimlou *et al.,* 2020) with a decreased release of IFN-γ, IL-1β and increased expression of anti-inflammatory IL-4, IL-5, and IL-8 (Dargahi *et al.,* 2020). Gastrointestinal bacteria activate stress circuits via vagus pathways (Lyte *et al.,* 2006).

A probiotic mixture of *Bacillus mesentericus, Clostridium butyricum, and Streptococcus faecalis* is known to reduce the symptoms of Schizophrenia (SZ) (Nagamine *et al.,* 2012). While a mixture of ten strains of *Lactobacillus* and four strains of *Saccharomyces* up-regulates G-protein-coupled receptor 43/41 (GPR 43/41) and triggers GLP-1 secretion with subsequent release of insulin (Wei *et al.,* 2015) and holding the potential for management of diabetes. Certain probiotics show beneficial effects in relieving stress-related behaviors and

anxiety thus modulating depressive states in rats. Parallel studies are required in humans too (Dinan *et al.,* 2013). Administration of *Lactobacillus plantarum* is correlated with a reduction in infarct size and improved functioning of the left ventricle after myocardial infarction. *L rhamnosus* is known to reduce left ventricle hypertrophy. A high abundance of *Odoribacter* is associated with low blood pressure in obese people due to more production of butyrate and other SCFAs **(**Gomez-Arango *et al.,* 2016**).** Therefore probiotics used in adjunctive medications give more reliable and effective outcomes in various cardiovascular disorders (Lam *et al.,* 2012; Gan *et al.,* 2014**).**

The use of probiotics and synbiotics can prove as a good option to restore the microbiota community post-antibiotic treatment. Probiotics produce antimicrobial peptides and bacteriocins and together these suppress the growth of non-commensals, enhance the barrier function of the gut, and modulate immunity (Cazorla *et al.,* 2018). FMT supplementation followed with three strains of *Lactobacillus* can restore IL-22 production and reduce inflammations which opens avenues of probiotics as therapeutic agents. However, FMT is considered more beneficial as probiotics use cannot regain the entire microbial balance in the gut (Suez *et al.,* 2018).

Prebiotics

Resistant to gastric acidity and digestive enzymes of the host, non-absorbable, fermentable by gut bacteria, and having the potential to activate gut microbiota selectively, these probiotics are exploited towards the human interests of maintaining good health. Galacto-oligosaccharides (GOS) and resistant starches (RS) can stimulate *Bifidobacteria, Lactobacilli* largely and *Bacteroidetes, Enterobacteria,*and *Fermicutes* to some extent (Louis et. al. 2016, Ze, *et al.,* 2012).

These bacteria degrade prebiotics to produce SCFA which are small enough to diffuse from enterocytes and impact extra-intestinal organs such as the central nervous system (CNS), cardiovascular system, immune system, etc. Prebiotic supplementation resultsin an elevated *Bifidobacteria* population to improve Crohn's disease, IBS, IBD, and even UC (Lindsay *et al.,* 2006). Dysbiosis of microbiota in Crohn's disease is well elucidated with low levels of immunoregulatory *Faecalibacterium prausnitzii* (Sokol *et al.,* 2009). Prebiotics show anti-adherence properties and prevent the binding of bacterial pathogens to attachment sites by disrupting adhesion-oligosaccharides, thus reducing the chances of gastrointestinal infections (Sharon, 2006). Similarly, pectic oligosaccharides, chitin oligosaccharides, and mannose oligosaccharides also act as adherence agents.

Synbiotic therapy comprising of *Bifidobacterium lactis, Lactobacillus, Rhamnosus,* and inulin reduce the chances and rate of colorectal cancer by improving the intestinal barrier strength (Candela *et al.,* 2011; Pool-Zobel, 2005). The population of harmful pathogens can be kept under check by prebiotics through direct binding or cytokine production. Prebiotic metabolites tend to improve the fetal immune system by crossing through the placenta. Prebiotic intake also reduces the use of antibiotics and reduces the duration of the disease. B(2⟶1) fructans lead to an abundance of interleukin-4 (IL-4) in serum, toll-like receptor-2 (TLR-2) mediated immune response, CD_{282+}/ TLR_{2+} myeloid dendritic cells (Clarke *et al.,* 2016). Blood levels of IL-8, IL-1β, IL-10, and C-reactive protein (CRP) become high due to GOS (galactooligosaccharides) intake and also better working of NK cells consuming GOS (Vulevic *et al.,* 2008; Vulevic *et al.,* 2015). This leads to reduced expression of IL-6 and phagocytosis in monocytes and granulocytes (Guigoz *et al.,* 2002). FOS (Fructooligosaccharides) and GOS show regulatory effects on neurotransmitters N-methyl-D-aspartate (NMDA) and synaptic disorders by altered gut microbiota diversity (Smith *et al.,* 2015; Waworuntu *et al.,* 2014). Higher gastrointestinal disorders are correlated with autism (Adams *et al.,* 2011). FOS supplementation is known to restore *Bifidobacterium, Bacteroides, Clostridium, Roseburia,* and *Phascolartobacterium faecium* with a positive impact on anorexia nervosa (Liu *et al.,* 2021).

Lactulose has preventive potential for hepatic encephalopathy (Mudd *et al.,* 2016; Müller *et al.,* 1966) by lowering the pH of the lumen and reducing the production of ammonia due to inhibited glutaminase activity. The side effects of lactulose like nausea and flatulence are overcome by another prebiotic lactitol which is better than lactulose and equally effective for curing hepatic encephalopathy (Blanc *et al.,* 1992). Prebiotics play a significant role in improving allergic skin problems like atopic dermatitis (Grüber *et al.,* 2010), lowering the risk of CVD, reducing the level of total cholesterol, low-density lipoprotein (LDL) (Tiwari *et al.,* 2011) and inflammatory elements. Non-alcoholic fatty liver disease (NAFLD) can be managed with prebiotics more efficiently along with medication (Tarantino and Finelli, 2015) and also enhances calcium absorption and

acts as a promising agent to improve the overall health of humans. A link has been found to exist between gut microbiota and NAFLD (Abu-Shanab and Quigley, 2010), non-alcoholic steatohepatitis (NASH), and obesity (Chierico *et al.,* 2017). Risk of sepsis, bacteremia, and severe malnutrition endocarditis in immune-compromised patients are attributed to prebiotics due to an incompetent intestinal epithelial barrier (Tsai *et al.,* 2019). Intake of low dietary prebiotics reduces saccharolytic bacteria specifically *Bifidobacteria.* SCFAs produced from the action of colonic bacteria on prebiotic fibers modulate cytokine production and expansion of T-cells to favor the homeostasis of colonocytes and decrease the possibilities of inflammations (Lee and Hase, 2014).

In diabetes T2DM, butyrate-producing bacteria are scarce while *Clostridiales sp*., *Eubacterium rectale, Faecalibacterium prausnitzii, Roseburia inulinivorans* and *Roseburia intestinalis* are enriched. Pathogens like *Bacteroides caecae, Akkermansia muciniphila, Desulfovibrio, E.coli,* and *Clostridium* are also enriched (Qin *et al.,* 2012).

For the reduction of resident gut microbiota-based disorders and keeping in mind the needs of each society and specific population, designing specific prebiotics is a challenging task and a topic of future research.

Synbiotics

Probiotics and prebiotics when consumed as a mixture constitute synbiotics. This is based upon formulating probiotics such as *Bifidobacterium* and *Lactobacillus* clubbed with prebiotics such as inulin, cellobiose, psyllium, GOS, lactitol, FOS, and β-glucan for different time durations. Synbiotics have the potential to modulate microbiota and benefit diseases such as IBS, obesity, diabetes, infections, and chronic kidney disease with significant enrichment of *Bifidobacterium* (McFarlane *et al.,* 2019). A combination of *B. longum* and inulin and another combination of *Lactobacillus* and GOS enhances the *Bifidobacterium* to different extents. Synbiotics comprising *Lactobacillus plantarum,* lactulose, and arabinose effectively adjust the blood glucose, lipid profile, and body weight of T2DM patients to ideal levels. Lactulose produces low molecular weight organic acids to reduce the pH of the intestine (Aït-Aissa and Aïder, 2014), and L-arabinose checks sucrose breakdown to reduce weight and manage diabetes (Panesar and Kumari, 2011). The presence of *L. plantarum* is favorable for the thriving of *Bifidobacterium* which in turn reduces plasma endotoxins and ammonia in the blood. Therefore, synbiotics on the whole serve to play a role in detoxification, hypolipidemia, and hypoglycemia in T2DM patients as compared to a single probiotic or prebiotic. Synbiotics, therefore maintain homeostasis of intestinal flora and provide a new solution for managing T2DM. *Lactobacillus rhamnosus,* in a combined interventional approach for immunotherapy, provides promising results for the prevention of food allergies as compared to probiotics alone, thereby corroborating synbiotics as a more integrated, refined, and successful approach for the management of diseases through gut-microbiome modulation. The release of bacterial toxins and production of pro-inflammatory cytokines also contribute to dysbiosis that needs to be addressed to with synbiotics intervention. Total *Bifidobacterium spp., Actinobacteria, Actinobacteriota, Lactobacillus, Parabacteroides, Ruminococcaceae, Firmicutes, Methanobrevibacter, Prevotella* enrich upon synbiotics supplementation whereas *Enterobacteriaceae, Bacteriodetes, Proteobacteria, Desulfovibrio, Oscillospira, Verrucomicrobiota, Bacteroidota, Akkermansia muciniphila, Roseburia* and *Zonulin*decline in population (Ouwehand *et al.,* 2009; Costabile *et al.,* 2017; Kanazawa, 2021; Krumbeck *et al.,* 2018).

The effect of synbiotics on gut microbiome results in enhanced SCFA-producing microbes and corresponding improvised gut health. Increased production of butyrate and propionate with pronounced anti-inflammatory effects and a more preserved intestinal barrier with more expression of inflammatory cytokines have a direct impact on immune and neuronal modulation (Gill *et al.,* 2018). Microbes such as *Alloprevotella, Ruminococcaceae, Prevotellaceae,* and *Catenibacterium* are more abundant with the intake of a synbiotic fiber-rich diet (Neyrinck *et al.,* 2021) and mediate their action by improving the intestinal barrier (Chen *et al.,* 2019), reducing inflammations, increasing more SCFAs producing bacteria such as *Eubacterium ruminantrim*, modulating action of enzymes to manage obesity and showing the synergistic effect on T2DM. On the contrary, the intake of synbiotics results in decreased abundance of pathogenic *Erysipelato,* and *Clostridium* and with corresponding low chances of diet-induced obesity (Jo *et al.,* 2021; Mukherjee *et al.,* 2024; Oh *et al.,* 2021). Synbiotics lead to an abundance of *Alistipes* and *Parasutterella* to maintain bile acid levels and regulate the metabolism of cholesterol (Mukherjee *et al.,* 2020) with the later while *Alistipes* offers protection against

colitis, fibrosis, cancer, and CVD (Parker *et al.,* 2020). Decreased *Ruminococcus gnavus* is detected due to synbiotics intake with the corresponding effect of the same against Crohn's disease. *Dialister* and *Prevotella* increase upon intake of *Bifidobacterium bifidum, B. longum, Lactobacillus acidophilus,* and *L. rhamnosus* as synbiotics. Prevotellaceae UCG-003 acts as a modulator of inflammations in the intestine. *Streptococcus salivarius* increases due to synbiotic intake with corresponding reduced inflammations (Kaci *et al.,* 2014) while *Colidextribacter* levels are lowered with corresponding reduced inflammatory metabolites (Gu *et al.,* 2022).

The potential of *Ruminococcus albus* and *R. flavefacines* lies in producing butyrate to provide energy to the intestinal cells while acting as anti-cancerous entities (Sergeev *et al.,* 2020).

Further research is required to work out the best possible combinations of probiotics and prebiotics, their proportions, dosage, duration, and mode of delivery for the most effective regimens to meet the need for microbiota-modulating therapies.

Postbiotics

Various inanimate microorganisms or bioactive compounds including inactivated cell preparations or microbial cells metabolites, non-toxic and non-viable compounds, or food constituents derived from microorganisms that offer health benefits come under the category of postbiotics. These include SCFA, bacteriocins, EPS (exopolysaccharides), vitamins, enzymes, and peptides in inactivated cell preparations and mediate their health effects by strengthening the gut barrier, reducing gut inflammations, and promoting antimicrobial actions against gut pathogens. SCFAs activate their receptors on intestinal epithelial cells to mediate signals for the maintenance of the epithelial barrier and also for the regulation of the immune system (Sun *et al.,* 2016). All the five SCFAs viz. acetic acid, propionic acid, butyric acid, pentanoic acid, and hexanoic acid increase after intake of postbiotics along with the increase of other metabolites such as p-methoxy cinnamic acid and α-linolenic acid while piperine, capsaicin, theophylline, phenylalanine, tryptophan, 5-hydroxy tryptophan, aromatic amino acids, kynurenine and other related metabolites decrease. A primary bile acid Chenodeoxycholic acid also decreases which is linked with diarrhea (Yu *et al.,* 2018; Panpetch *et al.,* 2021; Hill *et al.,* 1991; Chaiyasit and Wiwanitkit, 2016; Zheng *et al.,* 2020).

Intestinal motility is regulated by propionic acid, valeric acid, citric acid, malic acid, lactic acid, and butyric acid through different mechanisms such as affecting colonic smooth muscles functioning, vagus nerve and stimulating mucosal receptors (Rondeau *et al.,* 2003) by altering intestinal pH and eliminating harmful bacterial metabolites (Sun *et al.,* 2017; Bosi *et al.,* 2007). Production of anti-inflammatory interleukin IL-10 is enhanced by 3-indole acrylic acid to suppress cytokine IL-6 and IL-1β, posing a good anti-inflammatory effect. 5 HT (5 hydroxy tryptamine) mediates its effect by enhancing the gut mucosal barrier to elicit anti-diarrheal properties (Iancu *et al.,* 2023). Heat-treated *Lactobacillus* (LB) has the potential to mitigate diarrhea which is accompanied by post-antibiotic treatments.

Anxiety and sleep disturbance associated with diarrhea are taken care of by postbiotic interventions effectively (Nishida *et al.,* 2019). Quality of life in IBS patients is improved by *Lactobacillus* (LB) by relieving bloating, and abdominal pain, reducing weekly stools and frequency of diarrhea (Nocerino *et al.,* 2017).

Butyrate is anti-inflammatory and anti-carcinogenic (Barcenilla *et al.,* 2000). UC, Crohn's disease, and colorectal cancer patients become devoid of butyrate-producing bacteria. Propionate also has anti-carcinogenic effects and has the potential to check hypertensive cardiovascular damage. While acetate shows anti-inflammatory effects. Therefore, butyrate and propionate-rich postbiotic preparations produced from bacterialcultures are administered to handle diseased conditions. Butyrate-producing bacteria being food-unsafe are replaced by food-safe lactate-producing bacteria which produce lactate and subsequently later can be converted into butyrate or propionate via different pathways (Flint *et al.,* 2014; Gänzle, 2015; Louis *et al.,* 2022) to rule the option of foodborne infections from *Salmonella typhimurium* (Barbara, 2006).

Similarly, EPS from *Lactiplantibacillus plantarum* improves the strength of the intestinal barrier by enhancing the tight junction proteins expression and preventing pro-inflammatory cytokine expression (Zhou *et al.,* 2018; Neurath, 2014; Chen and Sundrud, 2016; Luettig *et al.,* 2015).

EPS from other bacteria such as lactic acid bacteria has anti-proliferative and anti-oxidative potential and can be

delivered to the gut from postbiotic preparations (Kodali and Sen, 2008; Sharma *et al.,* 2014). Antimicrobial peptides called bacteriocins inhibit specific microbes without affecting the beneficial ones dwelling in the gut (Gálvez *et al.,* 2007).

Postbiotics facilitate the flourishing of cellulose-producing bacteria and reduce the population of methanogens. The proliferation of beneficial genera such as *Bifidobacterium, and Lactobacillus* is promoted while that of pathogenic ones like *E.coli* and *Enterococci* is inhibited with postbiotics intake (Liu *et al.,* 2021). Increased beneficial gut bacteria include *Faecalibacterium, Prausnitzii, Microviridae, Fournierella, Lawsonibacter, Ruminococcu, Bifidobacterium aerophilum, Dialister hominis, Angelakisella, Dysosmobacter, Pseudoruminococcus* while decreased population include *Amedibacterium intestinale, Succinivibrio, Fusobacterium, Duodenibacillus, Alistipes, Megamonas funiformis, Bifidobacterium adolescentis, Blautia, Holdemania filiformis, Metalysinibacillus, Ruminococcus,*and pathogens like *Megamonas* after postbiotic intervention **(**Scott *et al.,* 2022; Thu *et al.,* 2011; Izuddin *et al.,* 2019). Cell wall components and cytoplasmic extracts obtained from these beneficial bacteria act as the most common probiotic producers for effective postbiotics which in turn can manage several health conditions by acting as anti-inflammatory, anti-oxidative, antiproliferative, immunomodulatory, anti-obesogenic and antibacterial therapeutic agents with plasma sugar reducing, cholesterol reducing potential (Sokol *et al.,* 2008; Jensen *et al.,* 2010; Jensen *et al.,* 2007).

Lactococcus stimulates immune cells to produce cytokines for better overall. *Pediococcus acidilactici* and *P. pentosaceus* produce bacteriocins and other antimicrobial metabolites showing anti-adipogenic effects). Similarly, β-glucan obtained from *Saccharomyces cerevisiae* cell wall has the effective role of scavenging hydroxyl radicals and serves as an antioxidant (Pourahmad *et al.,* 2011), and acts as postbiotic to regulate the immune system via TLR-2-MyD88-nuclearfactor (NF)-κB signaling pathway (Diaz *et al.,* 2018; Jin *et al.,* 2019). Lipoteichoic acid (LTA), exopolysaccharides, and cell surface proteins from Lactic acid bacteria also act as antioxidants. Mannan from yeast cell walls stimulates immunocytes to produce immunoglobulins and cytokines. Postbiotics have been explored for human health effects beyond the gut including skin, oral cavity, and vagina besides being implicated in commercial products for human health. Being non-proliferative, these have to be supplied regularly and in appropriate dosage to induce positive effects on the host for successful therapeutics**.** Postbiotics thus serve as promising tools for the management of metabolic disorders, GI tract diseases, mental disorders, respiratory problems, cancer, etc. These tend to safeguard against bone loss with reduced insulinemia, total plasma cholesterol, reduced hyperuricemia, reduced obesity, and T2DM (Tang and Li, 2021). Also, postbiotic intake as *L. acidophilus* and *L. paracasei* result in lower chances of childhood diarrhea, gastroenteritis, otitis media, and pharyngitis in children (Humphrey and Williamson, 2001; Haukioja *et al.,* 2006; Corsello *et al.,* 2017).

Psychobiotics

Psychobiotics refer to microbiota-targeted interventions which have the potential to treat psychiatric disorders. Probiotics and prebiotics together support optimal mental health by influencing microbial profiles to bring about overall homeostasis and improve cognitive abilities and are considered psychobiotics. A high abundance of beneficial bacteria like *Bifidobacterium bifidum* is associated with the intake of vegetables, dietary fibers, and milk products with concomitant decreased depression scores (Uemura *et al.,* 2019). Dietary fibers and fermented foods show anti-inflammatory effects (Swann *et al.,* 2020; Dürholz *et al.,* 2020; Wouw *et al.,* 2020; Marco *et al.,* 2017). An altered gut microbiome is considered for the pathogenesis of neuropsychiatric diseases. Psychobiotics include probiotics that mediate their effect on the human brain through the gut-brain axis. Therapeutic potential of psychobiotics in various mental health outcomes such as stress, anxiety, autism spectrum disorder (ASD), depression, insomnia, anorexia nervosa, Parkinson's disease, diabetic neuropathy, and multiple sclerosis (MS), ADHD, SZ and neurodegenerative disorders like dementia must be promoted and explored further to alleviate the burden of mental ailments (Sudo, 2019).

Psychobiotics mediate their action by regulating neurotransmitters such as gamma amino butyric acid (GABA), serotonin, brain-derived neurotrophic factor (BDNF), SCFAs, and enteroendocrine hormones by lowering pro-inflammatory cytokines and elevating the number of anti-inflammatory cytokines such as IL-10 (O'Mahony *et al.,* 2015; Cheng *et al.,* 2019; O'Riordan *et al.,* 2022; Dinan *et al.,* 2013). The possible underlying mechanism includes the controlled release of corticosterone and adrenocorticotrophic hormone after the recolonization of bacteria with synbiotics.

Table.1 Effects of antibiotics on colonization of human gut microbiota.

Antibiotic Class	Examples	Increasing colonization rates	Decreasing colonization rates	Reference
Penicillin	Pen V Amoxicillin Ampicillin Oxacillin Amox + clavulanate	*Enterobacteria* *Bacteroidaceae*	*Bifidobacteria* *Lactobacilli* *Eubacteria* *Lachnospiraceae*	Les Dethlefsen *et al.,* 2008
Cephalosporins	Cefalor Cefotaxime Ceftizidine Cefuroxime Cefepime	*Clostridia* *Bacteroides sp.*	*E. coli* *Bifidobacteria* *Enterobacteriaceae*	Les Dethlefsen *et al.,* 2008
Macrolides	Azithromycin Clarithromycin Erythromycin Spiramycin	*Bacteroidetes* *Proteobacteria* Resistant *Enterobacteria* *Streptococci* *Enterococci*	*Actinobacteria* *Lachnospiraceae* *Veillonella* *Clostriales*	Les Dethlefsen *et al.,* 2008
Quinolone Fluoroquinolone	Ciprofloxacin Norfloxacin	Resistant *E.coli*	*Lachnospiraceae* *Coprococcus* *Enterobacteriaceae*	Les Dethlefsen *et al.,* 2008
Carbapenems	Carbapenems Meropenems Ertapenem	Enterococci	Eubacteria Lactobacillus Bacteroides Bifidobacteria Streptococci Clostridia Enterobacteria	Jernberg *et al.,* 2007
Lincomycin	Clindamycin	Enterobacteriaceae	Blautia, Bacteroides	Jernberg *et al.,* 2007

Table.2 Bacteriocins source and target bacteria.

Name of the Bacteriocin	Source	Target	References (from Emma Scott)
Curvacin A and Sakacin 1	*Latilactobacillus sakei subsp. sakei*	*Listeria monocytogenes*	Camargo *et al.,* 2018
Plantaricin L-1	*Lactiplantibacillus plantarum subsp. plantarum*	*Listeria monocytogenes*	Zhou, 2007
Plantaricin MG	*Lactiplantibacillus plantarum subsp. plantarum*	*Listeria monocytogenes,Salmonella typhimurium*	Gong, 2010
BM1157	*Companilactobacillus crustorum*	*Listeria monocytogenes*	Camargo *et al.,* 2018
Gassericin A Gassericin T	*Lactobacillus gasseri*	*Listeria monocytogenes, Bacillus cereus,Staphylococcus aureus*	Pandey, 2013
Antilisterial ABP-118	*Ligilactobacillus salivarius*	*Listeria monocytogenes, Enterococcus,Bacillus, Listeria, Staphylococcus,Salmonella species*	Gálvez, 2007; Patel, 2015

Table.3 Correlation between common metabolic diseases (CMDs) and human phagosomes**.**

Diseases (CMDs)	Effect of phages	Reference
Metabolic Syndrome	↓ Phagosome diversity & richness ↓ Clostridiaceae phages ↓ Bifidobacteriaceae phages ↓ Ruminococcaceae phages ↑ CrAssphages ↑ Bacteriophage phages	Ma *et al.,* 2018; Borin *et al.,* 2023; Rasmussen *et al.,* 2020
Type 2 Diabetes	↑ Gram-negative phages ↑ Enterobacteriaceae phages ↑ Klebsiella phages ↑ Shigella phages	Han *et al.,* 2018; Sandoval-Vargas *et al.,* 2021; Chen *et al.,* 2020; Ma *et al.,* 2018; Han *et al.,* 2018;
Atherosclerotic Cardiovascular Disease	↑ Enterobacteriaceae phages ↑ Streptococcus phages	Valles-Colomer *et al.,* 2023; Jie *et al.,* 2017
Pre-Hypertension	No change in diversity ↑ Enterobacterial phage (mEp390) ↑ Pseudomonas phage (phi2) ↑ Cronobacter phages ↑ *Salmonella* phages ↑ Serratia phage (phiMAM1)	Yan *et al.,* 2017
Hypertension	No change in diversity ↑ phage 86 ↑ Cyanophage (S-T1M5) ↑ *Klebsiella* phage (KP32) ↑ *Salmonella* phage (FSL-SP-004)	Han *et al.,* 2018
Non-alcoholic fatty liver disease	↑ *Streptococcus* phages ↑ *Leuconostoc* phages ↑*Escherichia* and *Enterobacteria* phages ↑ Blood glucose levels ↓ *Lactococcus* phages ↓ BMI, HbA1C levels	Lang *et al.,* 2020; Mao *et al.,* 2023; Caussy *et al.,* 2019

Table.4 Gut dysbiosis and altered gut metabolite levels in GI Symptoms (Krishnamurthy *et al.,* 2023).

GI Symptom	Gut Microbiota	Gut Metabolite	Altered levels
Flatulence Bacteria	*Klebsiella, Pneumonia, Proteus, E.coli, Clostridium, Actinobacteria, Phascolactobacterium, Bacteroides, Coprococcus, Blautia, Bifidobacteriales, Oscillospira, Ruminococcaceae, bacteriodales, Clostridales*	↑H_2, CO_2, H_2S, CH_4	↑
Hydrogen & Carbon Dioxide-Producing Bacteria	*Bacteroidetes, Firmicutes*	↑H_2, CO_2, H_2S, CH_4	↑
Sulfate-Reducing Bacteria	*Desulfovibrio Sp*	↑H_2, CO_2, H_2S, CH_4	↑
Methane –Producing Archaea	*M. Smithii, M stadtmanae*	↑H_2, CO_2, H_2S, CH_4	↑
Constipation Bacteria	*Coprococcus, Ruminococcus, Blautia, Anaerotruncus, Bifidobacterium, Lactobacillus Bacteroides, Prevotella, Roseburia*	Butyrate, Acetate, Propionate, Methane ↑	↑
Diarrhea Bacteria	*Streptococcus spp, Blautia, Faecalibacterium Lachnospiraceae, Ruminococcaceae Bacteroides, Lactobacillus, Bifidobacteriaceae*	Butyrate Acetate Propionate ↓	↑ ↓
Diarrhea Fungi	*C. albicans, C. tropicalis C. Krusei, Torulopsis glabrata, Trichosporon spp, Geotrichum spp*	Butyrate Acetate Propionate ↓	↑
Diarrhea Virus	Rotavirus, Adenovirus, Norovirus, Anellovirus Calcivirus, Astrovirus, Picobirnavirus, Enterovirus, Dependovirus, Sapovirus, Bufavirus, Bocavirus	Butyrate Acetate Propionate ↓	↑
Abdominal Pain	Methane–Producing Archaea: *M. smithii* Fungi, Aspergillus spp.	Methane ↑	↑ ↑
Bloating Bacteria	*Proteobacteria, Faecalibacterium Actinobacteria, Bacteroides Uniformis Bifidobacterium adolescentis* Methane Producing Archaea: *M. smithii*	Methane ↑	↑ ↓ ↑

Figure.1 Chronic diseases implicated from gut microbiome.

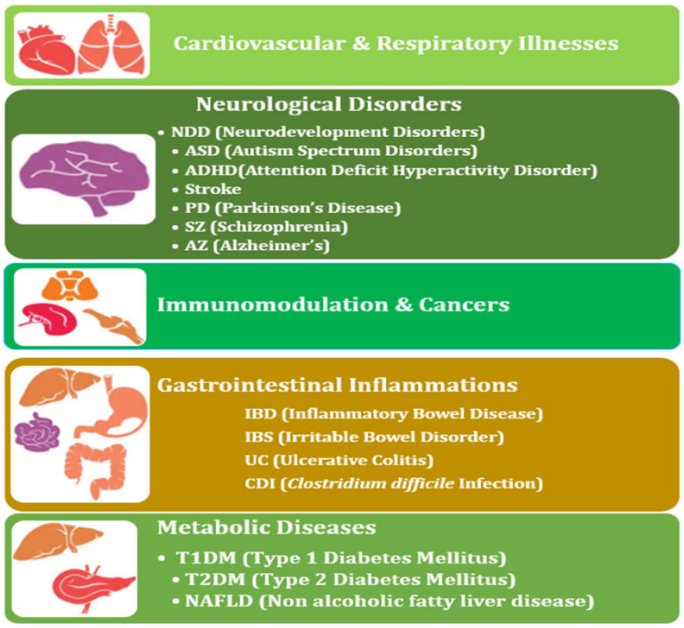


Figure.2 Challenges of Microbiome modulation based therapies.

Figure.3 Mechanism of action of gut microbiome.

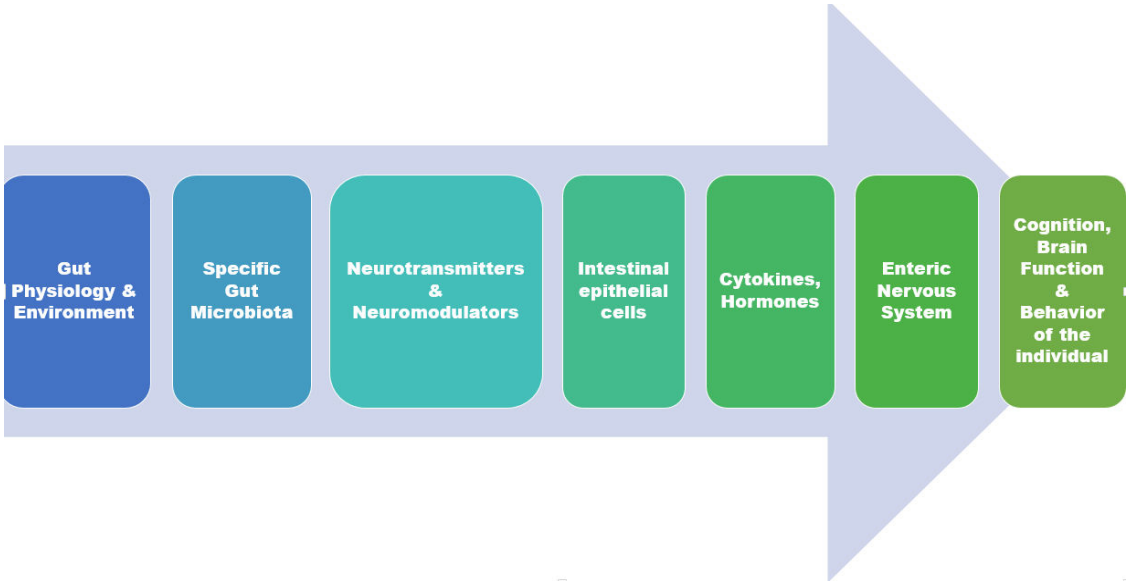


Figure.4 Microbiome modulation-based therapeutic interventions.

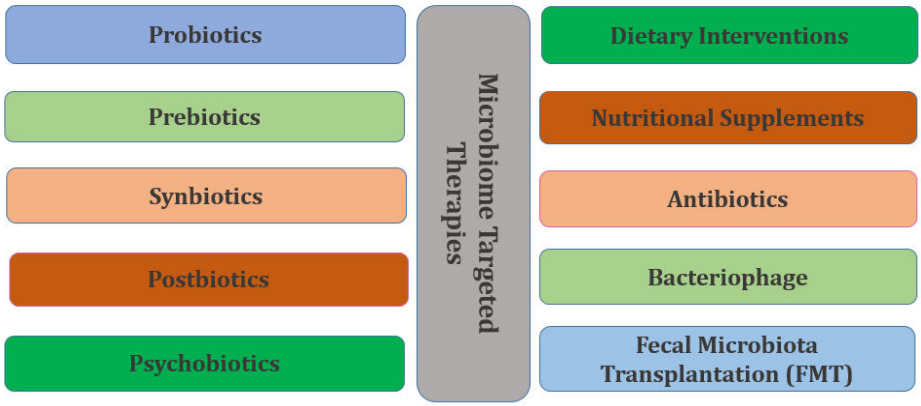


Figure.5 Mechanism of action of gut microbiota associated with CVDs.

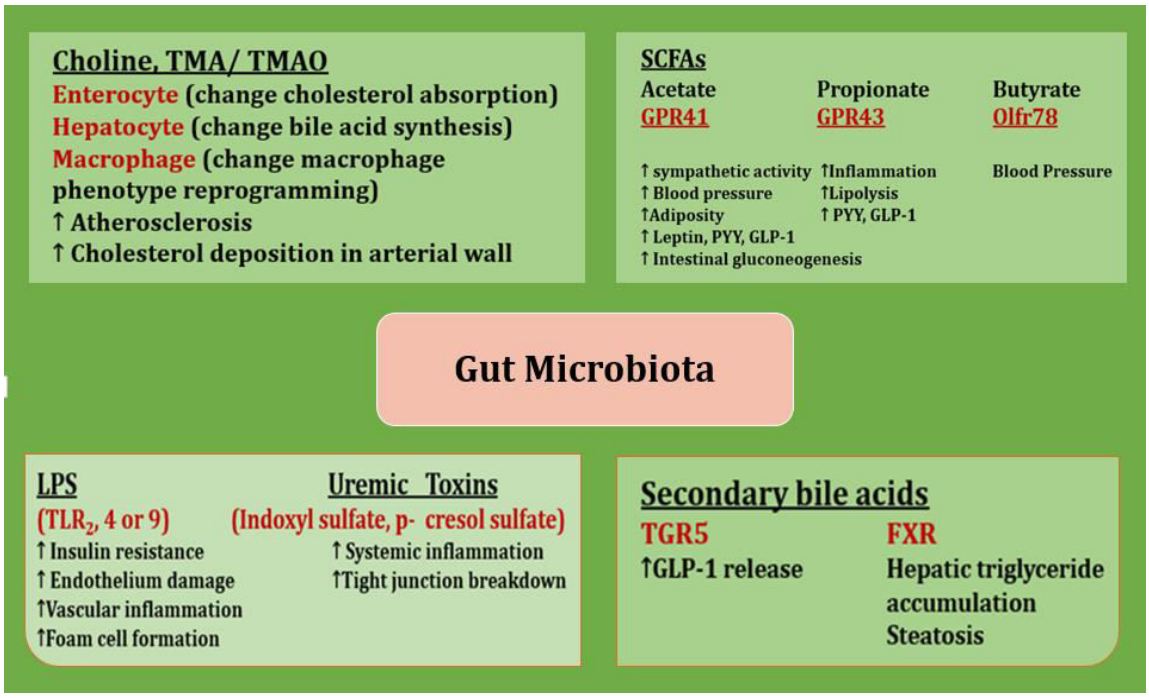
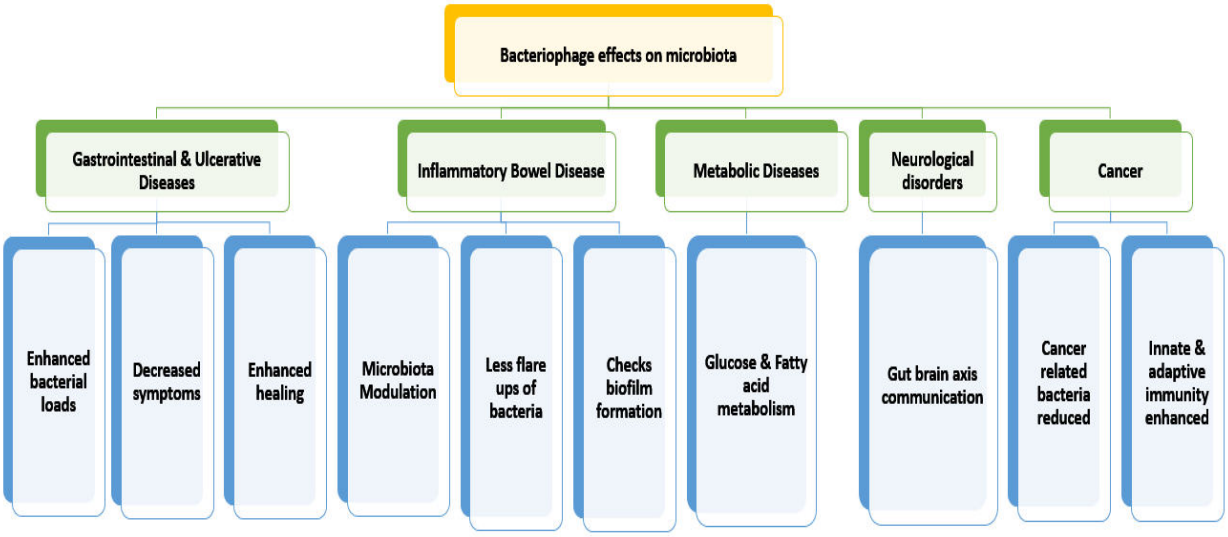


Figure.6 Role of bacteriophage in specific gut microbiota-related diseases.



Increased pro-inflammatory cytokines increase blood-brain barrier permeability by activating the hypothalamus-pituitary axis thereby leading to decreased serotonin levels and causing depression which can be managed by affecting the hypothalamus pituitary adrenal axis and hence reducing the production of inflammatory cytokines and enhancing the production of SCFAs, proteins, and neurotransmitters (Sudo *et al.,* 2004; Dowlati *et al.,* 2010; Barbosa *et al.,* 2020). SCFAs help proliferate regulatory T-cells and production of cytokines, maturation, and functioning of microglia (Cowan and Petri, 2018). GABA and glutamate-

producing gut bacteria result in neuronal excitability and enhance synaptic plasticity for improvising cognition. GABA also plays a significant role in preventing neurological diseases, type-1 diabetes, cancer, and immune disorders (Diez-Gutierrez *et al.,* 2020). SCFAs lead to the synthesis of serotonin and the expression of tryptophan hydroxylase-1, a precursor for the synthesis of serotonin. Gut microbiota also influences the expression of BDNF, the lower levels of which are correlated with anxiety and depression (Bistoletti *et al.,* 2019). Psychobiotics also delay the reuptake of neurotransmitters from the synaptic cleft, thereby increasing their duration and release in the synaptic cleft. These also reduce hs-CRP, increase GSH, reduce triglycerides, and insulin levels, and increase antioxidant capacity (Tamtaji *et al.,* 2019). Increased levels of peripheral tumor necrosis factor α (TNF-α) have been correlated with enhanced decline in cognition and infections in Alzheimer's disease. Neuro-inflammations are also linked with high levels of TNF-α, transforming growth factor beta (TGF-β) in cerebrospinal fluid (CSF), and increased activation of microglia in dementia (Heneka and Kummer, 2014; Marogianni *et al.,* 2020).

Administration of *Lactobacillus plantarum* has been found to prevent gliosis andsubsequently improve cognitive behavior in animal models of AD with reduced neuro-inflammations (Huang *et al.,* 2021). Probiotics containing *Bifidobacterium bifidum, Lactobacillus acidophilus, L. fermentum, and L. reuteri* are found to be associated with decreased TNF-α, IL-1, IL-8, and increased levels of TGF-β, PPAR-γ gene expression which shows anti-inflammatory properties (Borzabadi *et al.,* 2018).

Psychobiotics can be obtained from functional foods containing those probiotic species that can produce GABA and induce the production of neuro-hormones and neurotransmitters. *Bacillus spp.* and *Enterobacter xiangfangensis* are known as GABA-producing bacteria (Luang *et al.,* 2020). *Acetobacter aceti, Acetobacter sp, L. fructivorans, L. fermentum, Leuconostoc spp., Enterococcus faecium, L. kefiranofaciens, Candida krusei,* and *Candida format* found in Kefir grains have potential to improve memory and language functions in AZ patients (Ton *et al.,* 2020). Similarly, fermented milk contains *L. helveticus* to improve cognition in aged adults (Chung *et al.,* 2014).

GABA-producing *L. brevis* is known to have antidepressant action without side effects (Ko *et al.,* 2013). Foods prepared after the fermentation of *Laminiaria japonica* and adding *L. brevis* provide protection against dementia (Reid *et al.,* 2018). Similarly, anti-stress and anti-fatigue effects of rice bran fermented with *Saccharomyces cerevisiae* are seen (Kim *et al.,* 2002). Probiotic yogurt containing *B. lactis* and *L. acidophilus* helps to reduce depression, anxiety, and stress (Mohammadi *et al.,* 2016). *Bacillus subtilis, Lactobacillus spp., L. rhamnosus* can produce nitric oxide (NO), a neurotransmitter involved in regulating gut functions (Gusarov *et al.,* 2013). The peptide hormone GLP-1 produced by gut microbiota acts in neuroprotection causing proliferation and apoptosis ofneural cells, lowering Aβ plaques, improving memory, stimulating nerve regeneration, and reserving dopaminergic neurons (Kim *et al.,* 2017). Probiotics also improve the metabolism of glucose, reduce neuro-inflammation, and check the progression of AD.

Psychobiotics are therefore safe with a low risk of causing an illness. Individuals may show mild symptoms of abdominal discomfort with psychobiotic supplementation till the prevailing microbiota adjusts. Sometimes rashes, itching, and other allergies such as endocarditis, bacteremia, and fungenia may occur as a response to a few strains of bacteria especially in immunocompromised persons but these allergies will go away once psychobiotic intake is discontinued (Sotoudegan *et al.,* 2019). Psychobiotics have been used in dairy, fermented products, and soybean products to be included in the diet for significant mental health (Barbosa, 2020).

Therefore, psychobiotics show their probiotic potential by reducing levels of pro-inflammatory and enhancing anti-inflammatory effects shifting the gut microbiome composition towards more regulated inflammatory pathways involving modulation of the immune system through the production of neuroactive compounds and influencing gut barrier functions (Mohammadi *et al.,* 2019). Research on psychobiotics must be carried out further to see their effectiveness, dosage, safety, long-term effects, and possible side effects while ensuring high standards for the quality and purity of their products so that these form a valuable tool for the treatment of neurological problems.

Bacteriophage

These are the viruses that infect bacteria and serve as key drivers of the composition and functioning of the

bacterial community thus playing a vital role in gastrointestinal and cardio-metabolic diseases (CMDs) such as IBD, IBS, diabetes type 1 (T1DM), diabetes type 2 (T2DM) and *Clostridium difficile* infection (CDI) by preventing the formation of biofilms (Liu *et al.,* 2022; Norman *et al.,* 2015; de Jonge *et al.,* 2022; Yang *et al.,* 2021; Zhao *et al.,* 2017). (Fig.6.) Phages are therefore considered the most potent therapeutic intervention, these biological agents being active for a longer duration than antibiotics after administration and having a narrow target host range with minimum side effects on humans as they replicate within the target bacterium without mutilating mammalian cells. These possess a higher degree of specificity as selectively target the pathogens making their action more effective by producing better, specific, and safe bacteriolytic agents as compared to antibiotics (Kim *et al.,* 2019).

The role of phages is mediated through phage therapy and fecal virome transplantation (FVT). Bacteriophage attaches to mucin, checks the attachment of bacteria and its colonization to the mucin layer, and prevents the death of epithelial cells. The *E. coli* bacteriophage is known to contribute to amyloid secretion which further induces islet amyloid polypeptide (IAPP) to cause breakdown of beta cells and production of beta antigens that play a significant role in type 1 diabetes (T1DM). IAPP also acts as an autoantigen to develop either autoimmunity or T1DM (Tetz *et al.,* 2019). Besides this, prophages produce various neurotoxins and endotoxins for causing botulism, cholera, diphtheria, shigellosis, and scarlet fever (Waldor and Mekalanos, 1996, Jun *et al.,* 2013; Parajuli *et al.,* 2017; Muthuirulandi *et al.,* 2019; Sakaguchi, 2005). Phage administration leads to an increased abundance of *Eubacterium spp* and a decrease in *Clostridium perfringens* (Shkoporov and Hill, 2019). Phage administration leads to reduced levels of *Ruminococcus gnavus* and *C. sporogenes* with decreased synthesis of tryptamine. Likewise, phage VD13 results in a decreased number of *E. faecalis* and hence decreased tyramine and cytolysin production (Dorrestein *et al.,* 2014; Wahida *et al.,* 2021). Phages alter the bacterial function of metabolism and absorption of bile salts from the human gut (Hsu *et al.,* 2019). Phages activate B and T cells to produce antibodies and cytokines by the gut bacteria (Gogokhia *et al.,* 2019).

Phage therapy is successful in urinary tract infection (UTI), gastrointestinal diseases and antibiotic-resistant infections (Duan *et al.,* 2021). While FVT emerges as a therapy for managing obesity and T2DM (Rasmussen *et al.,* 2020; Manrique *et al.,* 2021; Borin *et al.,* 2023). FVT involves the transfer of viral components from the stools of a healthy person to the recipient who has dysbiosis to restore its microbiome (Biazzo *et al.,* 2022).

Making the transfer free from unwanted viruses and bacteria poses the biggest challenge in phage therapy. The potential role of the bacterium *Faecalibacterium prausnitzii* has been indicated in the pathophysiology of IBD (Ma *et al.,* 2018). Schizophrenia (SZ) patients include *Lactobacillus* phage phi-adh more predominantly (Yolken *et al.,* 2015). A high abundance of *Acanthocystis turfaea chlorella* virus-1 (ATCV-1) is correlated with decreased cognitive functioning due to altered gene expression (Yolken *et al.,* 2014). Phage therapy is in use against *E. coli, Streptococcus,* and *Klebsiella pneumoniae* infections, and combinations of phages are implicated in targeting *E. coli* for gastrointestinal infections (Febvre *et al.,* 2019). Engineered phages are delivered to the gut to modify the composition of disease-associated bacteria by promoting the growth of SCFAs producing bacteria to restore and establish the lost dysbiosis. Therefore, phages can be exploited for diagnosis and prognosis of CMDs while leaving the beneficial bacteria unaltered and also are capable of acting synergistically with antibiotics making them more effective. Possibilities of FVT-based therapeutic studies find extended and promising use in endometriosis (Kitaya and Yasuo, 2023), rheumatoid arthritis (Koziel and Potempa, 2022), and periodontitis where the vagina and oral microbiome are also involved. Therefore, the concept of manipulation of the gut microbiome holds the potential for management of diseases.

Fecal Microbiota Transplantation (FMT)

Among various interventions to restore the diversity and composition of the microbiota, fecal microbiota transplantation (FMT) aims at the transfer of fecal microbial content from a healthy individual to the intestine of a diseased person. FMT has been successfully effective in recurrent *Clostridium difficile* infections (CDI). Treatment success of CDI is found to rely upon bacteriophage transfer during FMT (Zuo *et al.,* 2018). This technique is suggested to treat diarrhea in HIV patients due to *Clostridium difficile* infection. (Elopre and Rodriguez, 2013). FMT in humans forms the basis of treatment of several diseased conditions elucidating that gut microbiota could be the cause of disease rather than a consequence of it (Smits *et al.,* 2013; Aroniadis and Brandt, 2013). Safety concerns are

important, especially in advanced gastrointestinal tract complications that may occur post-FMT (Wortelboer *et al.,* 2019; Ooijevaar *et al.,* 2019; DeFilipp and Bloom, 2019). FMT can be exploited for the management of IBD, IBS, and hepatic encephalopathy.

In IBS patients, the SCFA-producing species such as *Bifidobacterium* and *Ruminococcus sp* are enriched after FMT while *Akkermansia muciniphila* reduces at 12 months period after FMT (Parada *et al.,* 2019; Cruz *et al.,* 2019). FMT infusions from lean donors result in an increased population of *Eubacterium hallii* and *Roseburia intestinalis* with enhanced insulin sensitivity (Duncan *et al.,* 2007) as an association is observed between *Roseburia* and glucose homeostasis in addition to the cardiometabolic role of FMT.

Antimicrobial drugs fail to provide a long-term solution for the management of diseases and chronic conditions. The treatment efficiency is increased only through the engraftment of beneficial species through FMT (Keshteli *et al.,* 2017). It plays a role as a new treatment strategy for malignant tumors, metabolic syndromes, nervous system diseases, and autoimmune disorders.

A non-invasive method of implementing FMT includes the use of FMT-freeze-drying capsules or frozen capsules which are replacing the invasive methods where fresh fecal matter is administered through the distal part of the gut under strictly anaerobic conditions to acquire eubiosis of the gut (Nimgampalle and Kuna, 2017; Tamtaji *et al.,* 2019). Overall success and therapeutic effect of FMT rely upon the match between the donor and the recipient. A large number of small molecules produced by microorganisms, significant SCFAs such as butyrate, production of anti-inflammatory substances lead to strengthening the gut barrier functions leading to the effective success of FMT microbiota inoculated (Zheng *et al.,* 2022).

Therefore gut microbiota is resilient and can be reshaped and reconstructed. Microbiome-targeted therapies aim to rehabilitate disturbed microbiomes to ensure restoring dysbiosis, preventing and curing diseases, and attempting to develop precise therapeutics and treatments. Under normal physiological conditions, gut microbiota helps in the digestion of food, checks the entry of invading pathogens, produces a variety of metabolites good for human health, and strengthens the immune system. Gut microbiota can serve as a key component, the composition of which is influenced by dietary interventions, starvation or fasting, nutritional supplementation, antibiotics, probiotics, prebiotics, postbiotics, synbiotics, psychobiotics, bacteriophages, and FMT. The introduction of beneficial microbiota forms the platform to develop alternate strategies to preview and cure several chronic ailments, especially autoimmune disorders.

Diseased conditions have been successfully managed and cured in different animal models by manipulating gut microbiota, still, data from such human interventions is less conclusive as the ability of introduced microbes for successful colonization in the gut depends upon the already prevailing microbiota. So, animal model-based clinical trials need to be clinically brought into practice to explain the discrepancies between success and failure in human trials. Thus, a comprehensive analysis of human gut microbiomesbased on their genetics and metabolic predispositions needs further exploration of how various microbiome modulation-based interventions can result in effective prognosis, prevention, and treatment to monitor their progress in combating the comorbidities and to anticipate future complications.

Future Prospectives

The mechanism of the factors that lead to neurodegenerative diseases, immunomodulation and certain types of cancers, gastrointestinal inflammations, metabolic disorders, cardiovascular, and respiratory diseases, and how these are associated with gut microbiome profiles needs to be unveiled. Exhaustive research is required to create individual microbiota profiles and bring them into practice to know the status of gut health, and their correlation with diseases and to decipher the possibilities of the development of diseases and attempting to treat these diseases by manipulating gut microbiota towards the homeostasis. Eventually, this knowledge must form the platform for improving human health by bringing it into clinical practice. Important therapeutic strategies for gut modulation included in this review are dietary interventions, FMT, phage therapy, use of prebiotics, probiotics, postbiotics, synbiotics, and psychobiotics. FMT needs to be made more effective by working out the effective dosage, its transplantation method, and adopting different pre-treatments of frozen preparations. Phage therapy though has elucidated work on metabolic disorders, further research is required to standardize the technique to bring it to medical practice. The potential of psychobiotics to interact with gut microbiota modulation towards a healthy one needs to be

accurately and more precisely uncovered opening the avenues of psychobiotics in adjunct therapies for improving the quality of life for the entire mankind.

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Neena K. Dhiman: Investigation, formal analysis, writing—original draft.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

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Consent to Participate Not applicable.

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Conflict of Interest The authors declare no competing interests.

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