Current Insights on the Modulation of Gut Microbiome and Its Effect on Human Health

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Abstract

The gut of human beings is inhabited by a diverse group of microorganisms, around trillions, which makes it a new essential endocrine organ and shows a symbiotic connection with a host, and they metabolize the food ingested and produce diverse bioactive and dietary compounds. This may include organic acids, bacteriocins, and short-chain fatty acids, which provide potential to impact on physiological and pathological conditions of the host and maintain homeostasis. In recent times, due to rapid advancement in technology, our understanding about microbiome has also expanded. The modulation of the microbiome leads to disturbance in homeostasis, which causes imbalance and leads to dysbiosis, and the gut barrier integrity gets disturbed and immunological reaction leads to inflammation. This chapter reviews the current insights on various diseases and gastroenterological disorders associated with the modulation of the gut microbiome and how probiotics help in maintaining the healthy gut with intact gut barrier by regulating the expression of tight junction proteins, perhaps leading to good human health.

Keywords

Colon cancer · Dysbiosis · Gut microbiome · Irritable bowel disease/syndrome · Obesity · Probiotics

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2.1   Introduction

Mammalian gut is inhabited by a wide range of microbial communities, which are described as the gut microbiome. Due to advancement in technology and with omics study, our understanding toward the organisms colonizing the gut, their functionality, and their roles in healthy humans and gut-related diseases has significantly advanced (Schmidt et al. 2018). Like conventional culture-dependent techniques, culture-independent approaches like the use of next-generation sequencing technology and 16S rRNA sequencing revealed the abundance of the microbial community residing in the gut (Eckburg et al. 2005). In the gut, the microbial cell concentration exceeds 10^{11} cells/g contents, which makes up 1–2 kg of our body mass. It accounts for more than five million different genes, and 1000 to 1500 different species like Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, Fusobacteria, Cyanobacteria, and Verrucomicrobia are well represented (D'Argenio and Salvatore 2015). So the complex interplay between the gut microbiome and the host physiology has become a hot topic of research (Ghaisas et al. 2016).

Genetic inheritance and environmental factors affect the gut microbiome, and each individual has a substantially diverse microbiome, which mainly helps in maintaining the homeostasis of the host, as there is a symbiotic relationship; the host is benefitted by colonic fermentation; The barrier effect can be observed against opportunistic pathogen colonization, as well as the growth of the gut immune system and also they synthesize beneficial metabolites and nutrients for the host. In turn, the host provides shelter and nutrients for the microbial complex in the gut environment.

Due to the diverse range of environmental, host, and immunological factors, there would be an imbalance or maladaptation in gut microbiota; such imbalance could be termed dysbiosis. In developed countries, improved hygiene, the decrease in the count of vaginal deliveries, the low rate of breastfeeding, and the pervasive use of antibiotics affect the indigenous gut microbiota. As these children grow, there will be a shift in healthy symbiotic microorganisms to enteric pathogens leading to immune and inflammatory disorders (Jain and Walker 2015). Further, we shall discuss various diseases/disorders caused because of gut dysbiosis and current research issues to overcome these clinical conditions with probiotics intervention.

2.2   Probiotics in the Treatment of Gut Diseases

The phrase "probiotic" is derived from the Greek language; it means "for life" since ancient times mankind knew about the use of fermented food for maintaining good health; even in the Old Testament there is a description of consumption of sour milk by Abraham for longevity. The first reference or idea of the probiotic concept was given by Nobel Laureate Elie Metchnikoff and proposed that to displace putrefactive and pathogenic intestinal organism, one must consume fermented milk containing lactobacilli, which maintain good health and increase longevity. In the year 1954, Ferdinand Vergin published an article on "Anti-und Probiotika" in which he used the term "probiotic" where a list of several useful microorganisms and effects of the

antibacterial agents and antibiotics on intestinal microbiota was published. Later, after few years, according to Lilly and Stillwell (1965), microorganisms that are beneficial as well as those that produce growth-promoting factors for the organisms were described as probiotics, and the term has been customized over a period of time. Now the widely accepted definition is the following: "probiotics are live strains of microorganisms which when administered in adequate amounts confer a health benefit on the host" by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO), followed by the International Scientific Association for Probiotics and Prebiotics (ISAPP). Many probiotic strains that are extensively studied for human use and many probiotic products in the market developed using different species of bacteria are listed in Table 2.1 (Azad et al. 2018).

The mechanism of action of probiotics has been postulated in many ways; however, the exact mechanism of action was sparsely deciphered; some postulates are as follows: when taken in the adequate amount, probiotics fight for epithelial cell receptors and form colonizing barriers, and the other pathogenic strains cannot adhere to gut cells and compete for survival with one other. Besides, these probiotic organisms produce a class of antimicrobial compounds called bacteriocins, along with certain other metabolic products like lactic acid, diacetyl, short-chain fatty acids, and hydrogen peroxide, which kills pathogenic bacteria. These organisms have a symbiotic relationship with the gut and, in turn, stimulate immune response and show some immunomodulatory effects by increasing the secretion of immuno-globulin A and enhance the activity of natural killer cells, macrophages, and other immune cells (Khalighi et al. 2016). Due to these properties, many researchers propose probiotics as one of the alternative treatment aids for gastrointestinal disorders. Beneficial aspects of probiotics are depicted in Fig. 2.1.

2.2.1 Obesity

Obesity is a rising epidemic worldwide and the fifth leading cause for death. An estimate says that at least 2.8 million adults die due to obesity (Ahmed et al. 2014). It is defined as atypical or unbalanced fat buildup that may impair health. Obesity is the result of an energy imbalance between calories consumed and utilized. Consumption of high-fat/high-sucrose diets is one of the primary causes of obesity, and it is measured in terms of body mass index (BMI). If an individual is having a BMI less than 25 kg/m^2, the person is considered as normal; if the BMI is above 25 kg/m^2, then the individual is considered as overweight, and if the BMI crossed 30 kg/m^2, then the individual is considered as obese. Further, obesity patients are divided into three categories based on the BMI: first-degree obesity, if a person has a BMI between 30 and 35 kg/m^2; second-degree obesity, if a person has a BMI between 35 and 40 kg/m^2; and third-degree obesity, if BMI is between 40 and 45 kg/m^2. Even waist circumference is used for classifying obesity wherein visceral/central or subcutaneous obesity has been taken into account. If women have a waist circum-ference of over 88 cm and if men have a waist circumference of over 102 cm, then they are said to be having visceral/central or subcutaneous obesity. Waist-to-hip

Table 2.1 List of commonly used organisms as probiotics

Lactobacillus spp.	Bifidobacterium spp.	Bacillus spp.	Streptococcus spp.	Enterococcus spp.	Saccharomyces spp.
L. acidophilus	B. breve	B. coagulans	S. thermophilus	E. faecium	S. cerevisiae
L. plantarum	B. infantis				
L. rhamnosus	B. longum				
L. paracasei	B. bifidum				
L. fermentum	B. thermophilum				
L. reuteri	B. adolescentis				
L. johnsonii	B. animalis				
L. brevis	B. lactis				
L. casei					
L. lactis					
L. delbrueckii					
L. gasseri					

Modulation
IgA and IgG immune cells
B cells and T killers Cells
Inflammatory response

Evidence-based effects
Obesity
Infectious and Antibiotic Associated
Diarrhea
Type-2 Diabetes
Lactose Intolerance
Inflammatory Bowel Disease
Irritable Bowel Syndrome
Colon Cancer
Non-Alcoholic Fatty Liver Disease
Osteoarthritis
Celiac Disease

Species-Level
Pathogen antagonism
Gut barrier reinforcement
Bile salt metabolism
Production of enzymatic activities
Neutralization of carcinogens

Production
SCFA butyrate
Vitamin K2
Enzymes
B-vitamins

PROBIOTICS

Absorption
Vitamins like B12
Minerals iron and magnesium
Glucose
Fatty acids

Strain-Level
Neurological
Immunomodulatory
Endocrinological
Specific bioactive molecules

Widespread
Colonization
Competitive Exclusion Of Pathogens
Production Of SCFAs
Regulation Of Intestinal Transit
Normalization Of Perturbed
Microbiota
Increase Turnover Of Colonocytes

Function
Intestinal Motility(Healthy bowel
movements)
Bile Creation and Gastric Secretion
Gatekeeper of what's allowed in
blood stream

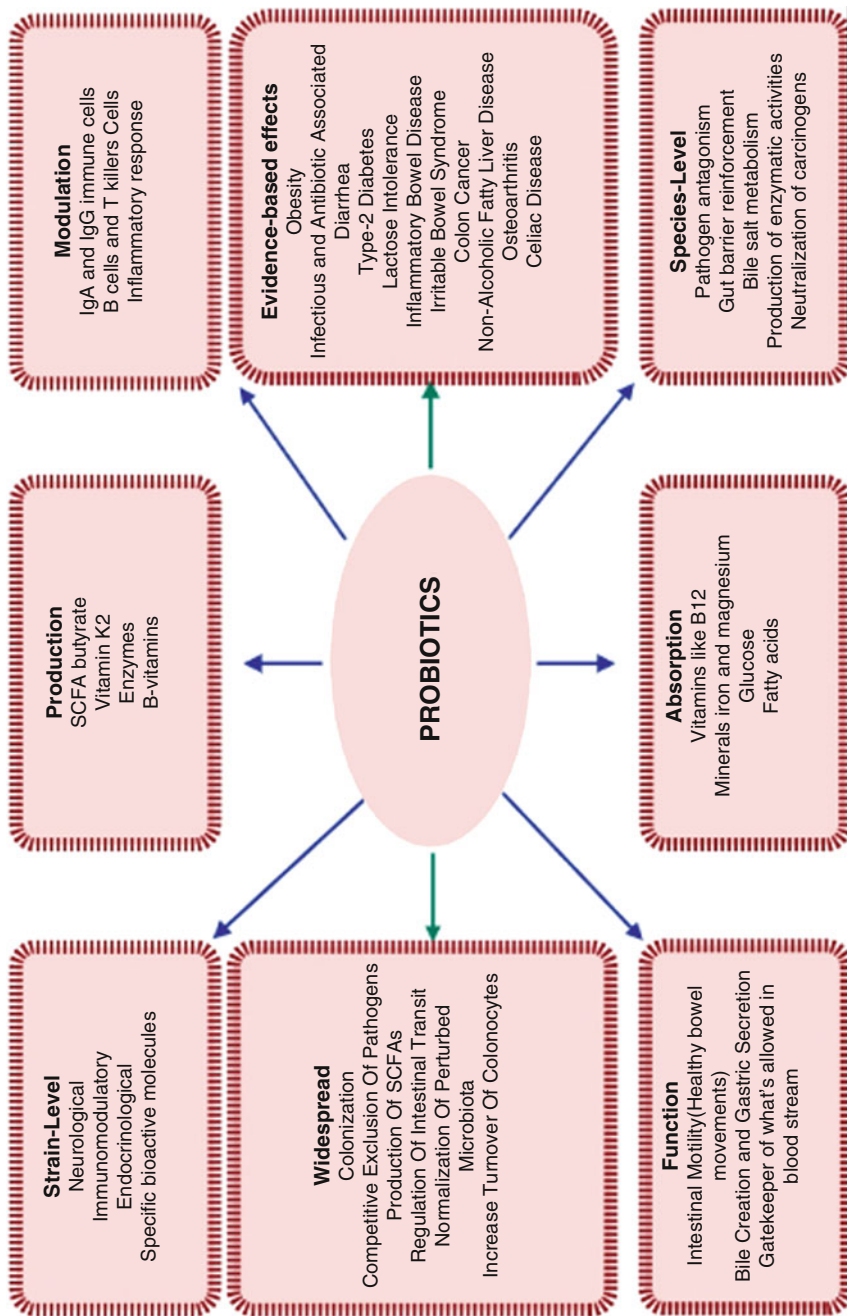**Fig. 2.1** Different beneficial aspects of probiotics, created with BioRender.com

ratio, body adiposity index, waist-to-height ratio, Rohrer's ponderal index, neck circumference, Benn's index, skinfold thickness, and fat mass index (Rouxinol-Dias et al. 2016; Simmonds et al. 2016; Bellenger et al. 2019) are also other indices.

Obesity can cause low-grade systemic inflammation, which is a crucial factor in the development of metabolic-related disorders like type 2 diabetes mellitus, osteoarthritis, cardiovascular disease, and colon cancer (DiBaise et al. 2008). A number of research groups have given evidence of lean and obese persons with different gut microbiota and plays a crucial role in obesity. In one of the studies, when germ-free mice were colonized with lean and obese microbiota separately, the mice that were colonized with obese microbiota had an increase in body fat compared with the mice colonized with lean microbiota. It is evident from the results that gut microbiota could cause fat deposition (Turnbaugh et al. 2006).

Another study revealed that an imbalance in the *Bacteroides*/Firmicutes ratio leads to dysbiosis and increase in the Gram-negative bacteria count and its component. In this, mainly lipopolysaccharides found on the outer membrane are the triggering factor of metabolic endotoxemia, which leads to obesity and clinical diabetes. High-energy and high-fat diet with rising concentration along with nuclear factor kappa B (NF-κB) and Toll-like receptor (TLR4) expressions is linked to endotoxemia (Creely et al. 2007; Cani et al. 2008). As we consume a high-fat diet, there is a change in the gut microbial diversity, and the permeability of the gut increases and LPS triggers an inflammatory cytokine expression. This occurs as a result of downregulation of genes that code for occluding and tight junctions, which is a root cause of Insulin resistance. Thus, it has been proved that dysbiosis will lead to obesity and other metabolic disorders (Bellenger et al. 2019).

A study conducted by Kim et al. (2018) observed that probiotic strain *Lactobacillus gasseri* BNR17 isolated from human breast milk showed significant results in inhibiting increased adipose tissue weight and body weight. A test was done on the age group of 25 to 75 years, and their BMI was between 25 and 35 kg/m^2 such 90 volunteers were randomized, double-blind, placebo-controlled trial for 12 weeks. The patients were given high-dose BNR-H 10^{10} CFU/day and low-dose BNR-L 10^9 CFU/day; both groups showed decreased visceral adipose tissue (VAT), and also there was a significant decrease in waist circumference when compared with the placebo group. The finding claims that visceral fat mass in obese adults was reduced due to BNR17 intake. In another randomized, double-blind trial study that was conducted only on women who were obese and had excess body weight, they were administered with a bacterial count of 2×10^{10} CFU/day of a probiotic mix that consisted of *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactococcus lactis*, *Bifidobacterium bifidum*, and *Bifidobacterium lactis* for 8 weeks, and then waist circumference (-3.40% to -5.48%) and waist-height ratio (-3.27% to -5.00%) were reduced significantly in the group who received probiotic mix when compared with the placebo group, which proved that probiotic mix intake reduces abdominal adiposity (Corado et al. 2017).

2.2.2 Infectious Diarrhea

Infectious diarrhea is also known as gastroenteritis and stomach flu. It is the inflammation of the stomach and small intestine due to infection along with symptoms like diarrhea, nausea, vomiting, abdominal pain, fever, and dehydration, and if this diarrhea due to infection lasts for 14 or less than 14 days, it can be called acute diarrhea. If it continues for more than 4 weeks, then it is said to be chronic diarrhea. Around 2.5 million deaths worldwide occur due to diarrhea, and there were around 1.3 million deaths and more than two billion cases of gastroenteritis in the year 2015. Children, especially those under the age of 5, were among the most affected groups, mainly due to unhygienic conditions. Diarrhea is generally caused by rotavirus, while in adults, it is caused by norovirus. However, bacteria, fungi, and parasites can also cause gastroenteritis. (Barr and Smith 2014; Fernández-Bañares et al. 2016).

Normal intestinal physiology is disturbed during infectious diarrhea by fluid and electrolyte secretion; for example, *Vibrio cholerae*, a Gram-negative comma-shaped bacillus produces cholera toxin (CT), an oligomeric protein made up of two subunits, A and B. Subunit B helps subunit A to enter into gut epithelial cells, and then subunit A regulates adenylate cyclase by ADP ribosylation and increases cAMP production. This in turn activates PKA, which phosphorylates CFTR channel and increases Cl^- secretion. The activity of two sodium transporters, NHE2 and NHE3, is decreased by increased cAMP production and affects Na^+ absorption; therefore, NaCl levels increase in the lumen of the intestine (Cheng et al. 1991).

In addition, *Clostridium difficile* is a causal agent of diarrhea, acute colitis, and inflammation and produces exotoxins, namely, toxin A and toxin B (TcdA and TcdB) along with binary toxin (CDT). TcdA adheres to the host cell via glycoprotein (gp) 96, whereas TcdB gains entry via dissolved tight junctions between two cells and binds to an unknown receptor. These are cytotoxic enzymes that disrupt cytoskeletal integrity by glycosylating *Rho* protein and also affect ion transport and cause accumulation of sodium, chloride, and potassium ions. Apart from this, these toxins initiate an inflammatory response by activating IL-6, IL-1, and TNF-α in the infective tissue (Hodges and Gill 2010). The presence of microorganisms, especially pathogens, may lead to disruption in gut homeostasis and inflammation and continues as a chronic condition leading to inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and other metabolic disorders. If diarrhea persists for a longer time and is not treated properly, especially in children, it may lead to dehydration and finally death.

Probiotic strains such as *Lactobacillus reuteri*, *Bifidobacterium lactis* Bb12, *L. casei* Shirota, and *Lactobacillus rhamnosus* GG can be used in acute rotavirus diarrhea. These strains shorten the duration of diarrhea (Isolauri 2003). Basu et al. (2007) reported that *Lactobacillus rhamnosus*(LGG) can decrease the frequency as well as the duration of diarrhea-related symptoms and reduce the stay time in the hospital for the patients suffering from persistent diarrhea (PD). They took 235 patients from North Bengal, India, and divided them into two groups. The test group was given oral rehydration solution and LGG, whereas the control group was

given oral rehydration solution only. It was found that the mean duration of diarrhea was reduced in the test group compared to the control group.

2.2.3   Type 2 Diabetes

In the twenty-first century, type 2 diabetes mellitus (T2DM) is among the very common disorders and has become the third-largest disease after cancer. The frequency of T2DM has increased worldwide in recent years. According to the International Diabetes Federation, it has been estimated that by the year 2040, approximately 642 million people would suffer from T2DM. T2DM is depicted by hyperinsulinemia in target organs and insulin deficiency caused by the destruction of β-cells in the pancreas. It has been observed that this destruction is partly contributed due to obesity. Overweight induces low-grade inflammation in obese individuals that leads to insulin resistance, and the increased level of inflammatory cytokine causes oxidative stress and destroys the β-cells in the pancreas. Genetics, lifestyle, stress, and environmental factors play a key role in the epidemiology of T2DM (Guariguata et al. 2014; Chatterjee et al. 2017).

A study carried out by Larsen et al. (2010) revealed gut dysbiosis in T2DM patient group compared to the healthy glucose tolerance group. In their experiment, a total of 36 male adult subjects were taken and they were divided into two groups among them, 18 were healthy controls, and another 18 were T2DM patients, and they were of different age group and BMI. It was found that the gut microbiota of the normal healthy person was different from the T2DM patient's microbiota. Another recent study made use of 16S rRNA-based high-throughput sequencing of three different groups of human subjects with T2DM diabetes, prediabetes, and healthy glucose tolerance. The results clearly stated that there is a structural modulation of the gut microbiome in the T2DM patient group which may lead to dysbiosis compared with the tolerance group (Egshatyan et al. 2016).

T2DM and obesity are inflammatory diseases. The patients show elevated circulating levels of haptoglobin, serum amyloid A, C-reactive protein (CRP), sialic acid, cytokines, chemokines, and interleukins like interleukin-6 (IL-6), IL-1β, IL-1, and TNF, and its receptor antagonist IL-1RA concentration was elevated in the patients with prediabetes, T2DM, and obesity. CRP is the biomarker for T2DM-associated cardiovascular disease. The mechanism involved is induced expression of pro-angiogenic and inflammatory genes in macrophages due to hypoxia. The main metabolic pathway involved in the process is *NF-κB and JNK pathway*. The expression of NF-κβ target genes such as cytokines including TNFα, IL-6, and IL-1β promotes insulin resistance that has been initially produced in the adipose tissue and liver and then migrates through circulation to other parts of the body like the kidneys and circulating leukocytes, and vessel walls, skeletal and cardiac muscle induce insulin resistance in T2DM patients (Donath and Shoelson 2011).

Another most crucial pathway plays a significant role in cellular processes, and cellular physiology such as cell survival, proliferation, protein synthesis, lipid metabolism, and maintaining glucose homeostasis is done by phosphoinositide

3-kinase/protein kinase B (PI3K/AKT) pathway. In the host, almost 90% of glucose utilization has been observed in skeletal muscles, which are insulin stimulated. Knockdown experiments of AKT protein showed decrease in insulin-induced glucose uptake, whereas overexpression led to increased uptake of glucose. AKT functions by phosphorylating AS160 and by activating GagAKT. The glucose transporter GLUT4 is activated by AS160, which transports glucose from stored vesicles into skeletal cells, whereas GagAKT promotes glycogen synthesis. Likewise in the pancreas, activation of this pathway increases the synthesis of insulin from β-cells in obese and T2DM patients. PI3K/AKT pathway is blocked or dysfunctional, which affects β-cells, and insulin production is reduced. This further affects other tissues by insulin resistance (Huang et al. 2018).

Further, in a study, 50 volunteers were selected for a double-blind, randomized, placebo-controlled trial for 6 weeks, in which the test group was given 120 g/d of fermented milk containing probiotic strains *L. acidophilus* LA-5 and *B. animalis* subsp. *lactis* BB-12. After 6 weeks, test patients showed improved glycemic control, the levels of fructosamine and hemoglobin A_1c lowered significantly, and also inflammatory cytokines were decreased (Tonucci et al. 2017).

Another study conducted by Firouzi et al. (2017) reported a decrease in fasting insulin level in patients who were enrolled in a randomized, double-blind, parallel-group, controlled clinical trial, where 136 patients aged between 30 and 70 years suffering from T2DM were selected, and among them, the test group received a probiotic strain mixture of *Lactobacillus and Bifidobacterium* for 12 weeks. A significant reduction in glycated hemoglobin and fasting insulin was observed in the test group compared to the placebo group.

Shah and Swami (2017) carried out a meta-analysis and found that fasting blood glucose, HbA1c, and HOMA-IR showed a significant reduction in T2DM patients; on the other hand, there was no reduction in serum insulin concentration. These results were obtained by 12 randomized controlled trials involving 770 T2DM patients, and they were treated with probiotics; perhaps probiotics are an alternative way for controlling T2DM.

2.2.4 Lactose Intolerance

A large section of the world population is intolerant to many food items, in that 70% of adults suffer from lactose intolerance with clinical symptoms like abdominal pain and distention, flatus, and diarrhea after consumption of lactose-containing food. Lactose intolerance is an inability to digest lactose (LI) due to deficiency of lactase or β-galactosidase enzyme in the small intestine (Harrington et al. 2008). In lactose intolerance, undigested lactose in the colon could be fermented by some gut bacteria, producing acid and gas, leading to the development of lactose intolerance symptoms (Horner et al. 2011; Savaiano et al. 2011). Probiotic bacteria provide health benefits to the host gut, like protection from pathogen colonization, restoration of the gut microbiome composition, and prevention of gastrointestinal disorders (Matthews et al. 2005; Heyman 2006; Gayathri and Vasudha 2018). Many probiotic bacteria

have been used in the treatment of lactose intolerance, mainly genera *Bifidobacterium* and *Lactobacillus*.

A number of research teams have been working on probiotics for the lactose intolerance treatment. In a study, Almeida et al. (2012) examined LI patients supplemented with yogurt containing *L. casei* Shirota and *B. breve* for 4 weeks, and it showed proof of reduced symptom scores. In another study, Li et al. (2012) conducted an experiment on post-weaning Balb/c mice with LI symptoms, which were orally administered with 1×10^8 CFU of *L. lactis* for 4 weeks and compared with control mice for diarrhea test and showed suppressed intestinal motility after lactose challenge.

Additionally, a comparative study was conducted by Ojetti et al. (2009). They treated LI patients with *L. reuteri*, and they showed a reduction in gastrointestinal symptoms after consumption of lactose. He et al. (2008) examined LI patients treated with *B. longum* supplementation and showed the β-galactosidase enzyme activity during and after supplementation. Later, Luyer et al. (2010) studied the effect of *B. animalis and B. longum* supplementation for the modification of gut microbial composition and β-galactosidase activity. Overall studies revealed that the consumption of probiotic bacteria improves the lactose digestion and alleviates the lactose intolerance symptoms and other gastrointestinal disorders.

2.2.5 Inflammatory Bowel Disease (IBD)

In genetically susceptible host, the immunological response of commensal microflora mediated a complex disease known as ulcerative colitis (UC) and Crohn's disease (CD). Together these disorders are called inflammatory bowel disease (IBD). The incidence of IBD is high, affecting 1.5 million Americans and 2.2 million Europeans and several hundred thousand people in Asia and other developed countries. IBD is a consequence of a complex interaction between microbial, genetic, immunologic, and environmental factors, which arises due to fast-track lifestyle, fast food, behavior, smoking, lack of physical exercise, sleep, stress, and genetic susceptibility, and gut dysbiosis caused by excessive use of antibiotics also plays a significant role in disease pathogenesis. Patients experience diarrhea, rectal bleeding, abdominal pain, inflammation, and weight loss in both CD and UC (Ananthakrishnan 2015).

Gut dysbiosis is one of the significant causes of IBD as studies found that patients with IBD have decreased Firmicutes proportions and increased *Bacteroides* and Enterobacteriaceae. CD patients have abundant *Enterococcus* spp., *Clostridium difficile*, *Escherichia coli*, *Shigella flexneri*, and *Listeria* spp. compared to the healthy individual. These alterations in the homeostasis of the gut lead to an inflammatory environment in the gut. Therefore, innate and adaptive immune cells produce pro-inflammatory cytokines such as IFN-γ, IL-1β, TNF-α, and IL-17, which enhance the inflammation leading to gut epithelial damage (Venegas et al. 2019).

There is a continuous interaction among the gut microbiota and the immune cells. Some of these interactions are beneficial. The interaction with capsulated

Bacteroides fragilis, coated with polysaccharide A, when they evade host defense and come in contact with immune cells like regulatory T cells and dendritic cells, produces anti-inflammatory cytokines like IL-10 and TGF-β, which help in maintaining tissue homeostasis in IBD patients. Further, the anti-inflammatory response genes like *ATG16L1* and *NOD2* are dysregulated, which impairs the sensitivity of receiving protective signals. Enterobacteriaceae induces TH17-dependent inflammation by producing IL-17 cytokine in CD and UC (Shamoon et al. 2019), and the study shows the association of gut microbiota and their role in IBD.

Sood et al. (2009) reported that a commercial probiotic mixture named VSL#3 contains eight different species, namely, *Lactobacillus casei*, *Lactobacillus delbrueckii*, *Bifidobacterium infantis*, *Bifidobacterium longum*, *Streptococcus salivarius*, *Lactobacillus plantarum*, *Lactobacillus acidophilus*, and *Bifidobacterium breve*; when used as a treatment strategy on patients with mild-to-moderate UC, VSL#3 showed an effective response in achieving clinical response and remissions in the patients, and they found that there was 50% decrease in Ulcerative Colitis Disease Activity Index (UCDAI) within 6 weeks.

Another study conducted by Steed et al. (2010) used a synbiotic approach, wherein 35 patients who were suffering from Crohn's disease were subjected to a double-blind, placebo-controlled trial and the test group was treated with a synbiotic mixture of *Bifidobacterium longum* and Synergy 1. A significant decrease in TNF-α and the clinical symptoms of Crohn's disease was observed.

2.2.6 Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is one of the most general chronic functional gastrointestinal disorders; it is defined as a functional chronic disorder distinguished by abdominal pain or tribulation coupled with altered bowel habits. The prevalence of IBS is around 14%. Generally, women are more affected than men; in the UK alone, the prevalence rate of IBS is 10 to 20%, and roughly one in five people suffers from IBS. If a person recovered from acute bacterial gastroenteritis, the chance of that patient getting IBS was found to be 30%. The criteria that are used in the diagnosis of IBS are according to Rome IV, and it has divided IBS into four subtypes: IBS-C, IBS with predominant constipation; IBS-D, IBS with predominant diarrhea; IBS-M, IBS with mixed bowel habits; and IBS-U, unclassified IBS. Symptoms of IBS persist for more than 6 months, and the patient may not have any structural gut abnormalities. Symptoms may include pain in the abdomen or discomfort, bloating, and distorted bowel habit. The pain in the abdomen is reduced when stool and mucus change or pass from the rectum, or when the patient defecates completely, but the pain is intensified when the patient takes food. Also the rate of anxiety, stress, and depression is higher in the patient suffering from IBS (Sutcliffe 2019).

IBS is a complex disease, and the fundamental cause is not understood completely. It is suggested in the literature that in addition nonspecific pathogenic

factors like food intolerance, genetic influence, gut microbiota, and intestinal dysbiosis perhaps induce IBS (Chong et al. 2019). Food tolerance is one of the major causes of IBS in 89% of patients. Certain food like lactose-containing food, vegetables, fat-rich foods, and artificial sweeteners triggers the symptoms of IBS; food containing FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) worsens IBS symptoms due to the fermentation as well as osmotic effects. In allergic patients, gluten/lactose-containing diet can also worsen the patient condition. Several studies have shown that a patient suffering from IBS has SCN5A, a sodium channel gene that got mutated, which has been associated with abdominal pain and prolonged QT interval. However, many genes are linked to IBS pathogenesis, genes coding for immune regulation, epithelial barrier function, serotonin signalling, and bile acid synthesis; cannabinoid receptors, glutamate receptor, ionotropic, delta 2 interacting protein (GRID2IP), and KDEL endoplasmic reticulum protein retention receptor 2 (KDELR2) are associated with the risk of IBS development. One of the studies involving 110 IBS patients revealed that patients suffering from IBS have a decreased level of beneficial bacteria such as bifidobacteria, *Bacteroides*, Methanobacteriales, and *Prevotella* species and increased pathogenic strains like *Streptococcus* spp., *Enterococcus faecalis*, *Clostridium difficile*, and *Giardia duodenalis* and other gas-producing organisms which lead to the activation of immune cells, infiltration of immune cells, and the release of inflammatory cytokines such as IL-6, TNF-a, and IL-1 are all caused by abdominal distension and gut permeability. Stress, which affects the gut-brain axis and increases the release of pro-inflammatory cytokines like IL-8 and IL-6, is another major component that leads to dysbiosis and causes IBD and IBS. Secretion of these pro-inflammatory cytokines activates hypothalamic-pituitary-adrenal (HPA) and hypothalamic-autonomic nervous system axes and triggers the release of corticotropin-releasing factor (CRF), adrenocorticotropic hormone, and cortisol (Strege et al. 2018; Lazaridis and Germanidis 2018; Chong et al. 2019; Hadjivasilis et al. 2019).

Agrawal et al. (2009) prepared fermented milk using the strain *Bifidobacterium lactis*, and 64 female patients suffering from IBS-C were selected for study. They divided them into two groups: the test group and control group. The test group was administered with fermented milk for 4 weeks, and the results were compared to those of the control group (without *Bifidobacterium lactis*); the test group showed improvement in individual symptoms of IBS like abdominal pain, bloating, urgency, incomplete evacuation, straining, and gas. O'Mahony et al. (2005) reported that *Bifidobacterium infantis* 35,624 was a better candidate than *Lactobacillus salivarius* UCC4331 for treating IBS and the test group showed improvement in the symptoms of IBS.

2.2.7   Colon Cancer

Colon cancer, also known as colorectal cancer (CRC), is cancer that develops in the colon, a section of the large intestine. It encompasses colon and rectal cancer of the

digestive tract's lower end and is the third biggest cause of cancer-related fatalities. Due to CRC, there were 147,950 new cases, and 53,200 estimated deaths were reported in the United States (Pothuraju et al. 2020). The cases of CRC are increasing to pandemic scale by subsequent morbidity and mortality; the annual rate of CRC in India is about 35,000 out of 3.5 million cancer cases (Velayutham and Velayutham 2019). Risk factors for colon cancer include personal history of CRC or IBD, family history, lifestyle (especially in dietary habits), lack of physical activity, alcohol consumption, smoking, etc. (Cassiem and de Kock 2019).

CRC can be catalogued into familial, inherited, and sporadic based on the origin of the mutation. Worldwide familial CRC accounts for 35% of cases; Inheritance, genetic factors, and environmental factors all play a role in CRC in these patients. There are about 5% CRC cases of inherited cancer, and they are classified into two groups: non-polyposis and polyposis cancer. Non-polyposis cancer is called hereditary non-polyposis colorectal cancer (HNPCC); it occurs due to mutation in the DNA repair mechanisms. Lynch syndrome is the chief cause of HNPCC; if there is a mutation in an allele of protein-coding genes for DNA repair like MLH1, MSH2, PMS1, PMS2, and MSH2, it can lead to Lynch syndrome in HNPCC group of patients. Inherited CRC is caused by the growth of numerous malignant polyps in the colon, a condition known as familial adenomatous polyposis (FAP). Sporadic malignancies, which account for 70% of CRC cases, are caused by point mutations. It starts with polyps or non-malignant adenomas due to mutation in a tumor suppressor gene, adenomatous polyposis coli (APC), followed by a mutation in TP53, KRAS, and DCC. These mutations transform the polyps into a carcinoma state (Armelao and de Pretis 2014; Mármol et al. 2017).

There is no clear evidence on how dysbiosis induces CRC, but patients suffering from IBD and chronic inflammation are at increased risk of getting CRC, and even the secondary metabolites produced from altered gut microbiota can damage the DNA and would induce malignancy. In a study conducted on European patients, three CRC human subjects were compared with healthy patients, and it was found that *F. nucleatum* count was high in CRC patients and they had more adenomas than the healthy patients. Similar results were also reported in CRC patients in the USA and China (Kostic et al. 2013; Li et al. 2016).

Two groups of *B. fragilis* colonize the gut; one has a symbiotic relationship with the host, and the other can produce a toxin called BFT, which induces inflammation by stimulating the production of IL-18 cytokine, and it even disturbs epithelial homeostasis resulting in CRC (Sears et al. 2014). Some strains of *E.coli* produce the bacteriocin colibactin, which has pro-tumor properties and causes DNA double-stranded breaks and chromosome instability, and it is found at a high level in CRC patients (Allen-Vercoe and Jobin 2014).

Asha and Gayathri (2012) conducted in vivo study on mice wherein the combination of probiotic strains *L. fermentum* and *L. plantarum* along with vincristine was used in the feed given to mice, and results showed that there was a marked decrease in ammonia concentration and β-glucuronidase enzyme activity and also a significant reduction in aberrant crypt foci (ACF) when compared to the control.

Liu et al. (2011) conducted a study on 100 patients with a control group of 50 members and a test group of 50 members, and the probiotic group was given encapsulated bacteria containing *Lactobacillus plantarum*, *Lactobacillus acidophilus*, and *Bifidobacterium longum* orally for 6 days before the operation and continued to receive the encapsulated bacteria for 10 days after the operation. They found improvement in postoperative complications such as infection-related complications, the incidence of diarrhea, decrease in enteropathogenic bacteria, and enhancement in the expression of proteins of the mucosal tight junction.

A study was conducted on selected patients (52) who were diagnosed with colorectal cancer and underwent surgery 4 weeks before the trial. Twenty-five patients received placebo, and 27 patients received a mixture of six viable strains: *Bifidobacterium bifidum* BCMC® 02290, *Lactobacillus lactis* BCMC® 12,451, *Lactobacillus casei* subsp. BCMC® 12,313, *Bifidobacterium longum* BCMC® 02120, *Lactobacillus acidophilus* BCMC® 12,130, and *Bifidobacterium infantis* BCMC® 02129 two times daily for about 6 months. Results showed inhibition of surgical infections along with a significant reduction in pro-inflammatory cytokines in treated groups (Zaharuddin et al. 2019).

2.2.8   Non-Alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is a disruption of systematic functioning in which extra fat is stored in the liver; it is one of the growing concerns worldwide, leading to chronic liver diseases from fibrosis, cirrhosis, steatosis to non-alcoholic steatohepatitis (NASH) and ultimately hepatocellular carcinoma. The pervasiveness of NAFLD is high in the Middle East with 32%, followed by South America with 31%, and Asia with 27% (Safari and Gérard 2019).

There is no clear knowledge of the pathophysiology of NAFLD, although elements that are thought to play a role in NAFLD pathogenesis include nutrition, interaction with the environment, lifestyle, lipid and glucose metabolism, and biochemical and immunological abnormalities, as well as the significant role of gut bacteria. Since there is a link between the liver and gut through the portal vein that supplies blood, nutrient metabolites produced from gut microbiota and even bacteria move to the liver. In dysbiosis condition, lipopolysaccharides (LPS), also termed endotoxins, are also passed to the liver as there is a dysfunction in the tight junction of the gut cells; when these metabolites enter into the liver, they generate a response from Kupffer cells. Toll-like receptor interacts with the foreign particles of bacteria and bacteria themselves which leads to inflammation response and NAFLD in the liver (Quesada-Vázquez et al. 2020).

Some of the bacteria are directly related to the progression of NAFLD. Recent studies on *Bilophila wadsworthia*, a Gram-negative proteobacterium, revealed that it raises key cytokines like serum amyloid A and IL-6 by producing endotoxin such as LPS, which elicits inflammation in the liver. It also disrupts the gut barrier tight junction proteins and their expression, which in turn affects bile production and causes dysbiosis (Everard et al. 2013; Feng et al. 2017). When the gut has increased

the number of *Klebsiella pneumonia*, a Gram-negative proteobacterium, the production of alcohol exceeds the detoxification capacity of the liver which produces reactive oxygen species leading to inflammation and steatohepatitis; several genes overexpress and fat storage increases, and synthesis of unsaturated fatty acid and other metabolites leads to NAFLD similar to alcoholic fatty liver disease (Yuan et al. 2019). *Helicobacter pylori* infection elicits several inflammatory cytokines like TNF-α, IL-8, IL-6, and IL-1β that elicit inflammation, and insulin resistance is caused by the release of leptin from infectious tissues, which causes fat deposition and leads to NAFLD (Ning et al. 2019).

A study carried out by Ahn et al. (2019) involved 68 obese and nonalcoholic fatty liver disease (NAFLD) patients. They were divided into control and test groups; a probiotic mixture of six bacterial strains (*Pediococcus pentosaceus*, *Lactobacillus rhamnosus*, *Lactobacillus paracasei*, *Bifidobacterium lactis*, *Lactobacillus acidophilus*, and *Bifidobacterium breve*) was given to the test group for 12 weeks, and change in intrahepatic fat (IHF) and visceral fat area (VFA) fraction was measured. After 12 weeks, there was a mean difference of -2.61%, indicating IHF, and bodyweight of the test group was considerably lower in NAFLD patients as compared to a control group.

A batch of 64 obese children with NAFLD was chosen for a 12-week randomized triple-blind trial, and they were given a probiotic supplement. The test group received a capsule containing four different probiotic strains, namely, *Lactobacillus rhamnosus* DSMZ 21690, *Bifidobacterium lactis* DSMZ 32269, *Bifidobacterium bifidum* ATCC SD6576, and *Lactobacillus acidophilus* ATCC B3208. On the other hand, the control group received a similar capsule without probiotics. After a period of 12 weeks, a decrease in enzymes aspartate aminotransferase and alanine aminotransferase and a significant decrease in low-density lipoprotein-C, cholesterol, and triglycerides were observed in the test group. It was also observed that although there was a decrease in the waist circumference, there was no change in body mass index z-score. Sonography of the liver after the trial was reported in 17 (53.1%) and 5 (16.5%) of patients in the intervention and placebo groups, respectively (Famouri et al. 2017).

2.2.9 Osteoarthritis

Osteoarthritis (OA) is a degenerative disorder portrayed by the dynamic weakening of the articular ligament, bringing about agony and all-out joint incapacity at propelled stages. In the USA, 31 million people suffer from OA; global estimate prevalence exceeds 250 million. Illness movement can be subject to hereditary and epigenetic factors, sex, ethnicity, and age. The major factor is obesity, and a strong relationship can be seen between body mass index and knee (Szychlinska et al. 2019). A few dietary components, alongside quality and amount of supplement consumption, have been found to be engaged with the pathogenesis of OA. Among these, nutrients, unsaturated fats, and magnesium appear to assume a key job. It has been demonstrated that low admission of vitamin D and vitamin C is a

potential hazard factor for knee OA, while certain nourishing food, for example, milk and dairy items, meat, and poultry, are beneficial for knee OA (Musumeci et al. 2015). Also, wrong propensities (smoking, stationary life, liquor misuse) and unfortunate dietary propensities (quick and greasy nourishment) may incline individuals to stoutness and accordingly to numerous different inconveniences which may prompt the advancement of extreme metabolic dysfunctions. It is additionally notable that inactive conduct is related to an expanded danger of building up a few incessant infections. It is an independent hazard factor for both dreariness and mortality that has been proven (Warren et al. 2010).

One of the breakthrough facts revealed by the research study is that some of the gut microbiomes were found in the cartilage of the knee and hip samples from patients, and 16 s RNA gene deep sequencing analysis stated that OA patients had Betaproteobacteria compared to normal control who had Actinobacteria and Clostridia; increasing Betaproteobacteria is the marker for patients suffering from the metabolic disorder due to dysbiosis condition (Schott et al. 2018). Besides adipose tissue surrounding the joint cells produce adipokines such as leptin which indirectly increases inflammation. Patients with OA have a higher level of leptins in there synovial fluid compared to normal patients; this leads to elevated levels of IL-6 through various signalling pathways like PI3K/AKT, p38 MAPK, and JAK2/STAT3 pathways and the release of certain other cytokines and other factors like MMP9, MMP13, TNFα, and IL-1 which induce inflammation and damage to the cartilage in the joints (Zeddou 2019).

Lei et al. (2017) conducted a double-blind, placebo-controlled trial on 537 osteoarthritis patients; the test group was given skimmed milk containing *Lactobacillus casei* Shirota (LcS) for 26 weeks, and the control group was given placebo. The result showed that probiotics promote bone metabolism which reduced inflammatory response and pain, and there was a change in serum levels of high sensitivity C-reactive protein. Similarly, Lyu et al. (2020) carried out an experiment using a probiotic strain TCI633 (*Streptococcus thermophilus*) on 80 patients with osteoarthritis for 12 weeks, and improvement in serum collagen type II C-telopeptide (sCTX-II) and serum C-reactive protein (sCRP) was observed when compared with the placebo group. Therefore, the selection of ideal probiotic isolate may provide an alternate approach for osteoarthritis even though more thorough investigations need to be conducted for concrete conclusions.

2.2.10 Celiac Disease

Celiac disease (CD) is a type of persistent enteropathy with a multifactorial disorder that mainly causes small intestinal injuries and malabsorption of minerals and nutrition. The wheat protein gluten and related cereal proteins that escape human digestive enzyme activity are the primary cause of the disease. Further, the complete exclusion of gluten from the diet is the only remedy available for CD patients (Gayathri and Rashmi 2014). Several studies suggested the use of microorganisms for the preparation of gluten-free/reduced foods (De Angelis et al. 2006a, b; Gass

et al. 2005). Currently, CD is a common condition that may be diagnosed at any age, but formerly CD was considered as a rare malabsorption syndrome of infancy. According to World Gastroenterology Organisation (WGO) data, out of 100, one person is diagnosed with CD in the Western population, whereas out of 300, one will suffer from CD in other parts of the world, and it is predominant in females than males with a ratio of 2:1. CD has become a focal and universally distributed, according to studies, and serological diagnosis in India, Africa, and the Middle East revealed the same prevalence rate as in Western countries. The presence of human leukocyte antigens HLA-DQ2 or HLA DQ-8 molecules gets triggered from gluten protein of wheat and other cereals, and that generates circulating autoantibodies to tissue transglutaminase (tTG) which leads to the disease (Visser et al. 2009; Lorand and Graham 2003). Not all people develop CD; only 1 to 4% of people develop CD if they have aberrated HLA-DQ2 or HLA-DQ8 genes (Sollid 2000). Although the strong association between CD and HLA DQ2/DQ8 has been well documented, CD may not be present at the time of birth or before the introduction of gluten in the diet (Green and Cellier 2007; Dube et al. 2005) and usually does not manifest before the age of 2 years even in the individuals expressing HLA DQ2/DQ8 (Hill 2006; Ludvigsson et al. 2001). The analysis was based on the morphological assessment of the small intestinal mucosa obtained at three distinct conditions:

(a) Initial flat mucosa when the patient has ingested gluten.
(b) Upon withdrawal of gluten from the diet, there must be an improvement in the small intestinal mucosa.
(c) Deterioration of the mucosa is seen due to gluten.

Further, antibodies such as endomysial antibodies (EMA), tissue transglutaminase antibodies (tTGA), and antibodies against gliadin (AGA) of the IgA class are also significant diagnostic tools for CD. Among them, EMA and tTGA are widely used. The role of HLA DQ2/DQ8 in the development of CD has opened genetic tests involving HLA typing. However, in a majority of the cases, HLA DQ2/DQ8 carriers do not develop CD, and therefore, genetic tests for CD diagnosis have limited application (Liu et al. 2005).

Treatment of CD can be done using several non-dietary strategies like the use of larazotide acetate, which is a tight junction regulator, and it decreases the intestinal tight junction permeability; furthermore, the use of corticosteroids like budesonide for inhibition of tTG activity and sequestering polymers help in changing the structure of gliadin, which in turn reduces the tissue damage and symptoms of CD (Ciacci et al. 2009; Liang et al. 2009; Paterson et al. 2007). Strategies for the long-term treatment of CD raise a concern regarding issues like safety and efficacy as the response to these strategies is not the same for each individual CD patient and is found to be unsatisfactory(Gayathri and Rashmi 2014). As there is a concern over the non-dietary alternative strategies, by creating genetically modified crops of wheat, rye, and barley or by breeding the less immunogenic crop varieties, the gluten content in the diet can be reduced. Otherwise, the patient must adopt altered

gluten polypeptides or exclude gluten from their diet for the rest of their lives, or they can use probiotics for fermentation, where gluten is digested, as an alternative. (De Angelis et al. 2006a, b; Gass et al. 2005).

De Angelis et al. (2006a, b) further reported the effectiveness of VSL#3, a combination of eight strains: *Bifidobacterium breve*, *B. longum*, *B. infantis*, *Lactobacillus plantarum*, *L. acidophilus*, *L. casei*, *L. delbrueckii* subsp. *bulgaricus*, and *Streptococcus thermophilus.* The enzymes produced by VSL#3 during the fermentation process of the dough digest gliadin polypeptides, epitopes of gliadin, and digest proline-rich peptides.

Lindfors et al. (2008) conducted an in vitro study on Caco-2 cells derived from the human colon, where the effect of the probiotic strain *Lactobacillus fermentum* or *Bifidobacterium lactis*, separately; they found that *B. lactis* inhibited increased epithelial gliadin-induced permeability and also increased the expression of Zonula occludens-1 protein. In another in vitro study (Laparra and Sanz 2010), there was reduced expression of pro-inflammatory biomarkers which proved that the gliadin was altered by *Bifidobacterium* spp.

2.3   Conclusion

Gut microbiome modulation and its effect on human health and diseases are interrelated. Further research is certainly required to disentangle these complexities, and advancement in pre- and probiotic research and management of the gut microbiome along with this correlation and careful analysis would certainly impact the gut microbiome and improve human health.

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