The Influence of Microbiota on Health and The Role of Diet

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1.0 Introduction

According to the Center for Disease Control and Prevention, 60% of adults in the United States have a chronic disease, and 40% of the individuals from the same population have two or more.[1] Chronic diseases are conditions that last for one or more years and need medical attention or restrictions on activities of daily life, or both. Chronic diseases include cancer, stroke, diabetes, heart disease, chronic lung disease, chronic kidney disease, and Alzheimer's disease. Cancer, diabetes, and heart disease are the leading causes of death and disability, and they are the major drivers of the nation's $3.8 trillion in annual health care expenditure. Poor nutrition is among the short list of factors that cause chronic diseases. Poor nutrition includes diets that are high in saturated fat, sodium, and processed foods and low in fruits and vegetables. Chronic inflammation plays a significant role in the pathophysiology of many non-communicable diseases.

This paper discusses the role that the intestinal microbiota plays in health, chronic inflammation, and diseases. The gut microorganisms play a role through their structural parts as well as via the metabolites, the short chain fatty acids (SCFAs) that they produce. While some of these SCFAs have positive health benefits that help in reducing inflammation and chronic diseases, others have the exact opposite effects. According to scientific evidence from different disease studies, changes in the microbiota can cause a reduction in inflammation and improvement in the metabolic profile. Dietary changes and consumption of prebiotics and probiotics can result in modifications to the microbiota. Since diet plays a key role in molding the microbiome, the health benefits of the Mediterranean diet, plant-based diets, gluten-free diet, as well as prebiotics and probiotics are included.

2.0 Microbiome vs. Microbiota

According to Berg, the extended definition of the microbiome includes living organisms such as algae, archaea, bacteria, fungi, protists, phages, plasmids, prions, viruses, and viroids.[2] In addition, it includes non-living organisms such as free DNA and RNA. In short, the microbiome is a collection of microbial genomes. There are more than 10^{14} microorganisms in the gastrointestinal tract, and the majority are yet to be known.[3] The collection of these microbes is what is known as the microbiota.

3.0 Intestinal Barrier and Role of Microbiota

The intestinal barrier of the gastrointestinal tract has selective permeability.[4] It allows water and nutrient absorption and prevents antigens from moving into the bloodstream. The intestinal epithelial cells (enterocytes) are connected via different tight junctions (TJ) that help in the select permeability, and in maintaining intracellular interactions among enterocytes. Compromised functioning of the junctions leads to an increase in intestinal permeability resulting in transporting inflammatory mediators.[5] The reduced tightness in the enterocytes may lead to chronic intestinal inflammation and result in many disorders in the junctions.

Microbiota plays many roles in the body. Among them are digestion, immunity, production of metabolites, regulating lipid storage, inflammation, insulin signaling, and initiation of gastrointestinal diseases and cancer.[6] Other roles include vitamin synthesis and intestinal oxygen and pH levels.[7] The gut microbiota is an important part of the intestinal barrier. Commensal microbes compete with pathogenic ones for place and nutrients, and they help in proliferating epithelial cells.[8] The microbiota affects the condition of the intestinal barrier via the production of (SCFAs) that occurs via fermentation.[9] Most gut microbiota prefers carbohydrates for fermentation. However, if carbohydrates are not available, protein is used.

SCFAs such as acetate, butyrate, and propionate, affect energy homeostasis and metabolism.[10] They help in maintaining glucose homeostasis, insulin sensitivity, and regulate adipose tissue, skeletal muscles, and liver function. Therefore, SCFAs have the potential of preventing obesity and its related problems. SCFAs turn on G protein receptors 41 (GPR41) and 43 (GPR43), which lead to the expression of TJ proteins and modulation of endocrine cells. SCFAs interact with GPR43 in the fat tissue and result in a reduction in fat depositions.[11] This leads to a reduction in lipolysis and inflammation and an increase in adipogenesis and leptin release. Lipid accumulation is inhibited through increasing insulin activity and oxidation of fatty acids due to SCFAs activating AMP kinase in the muscles.[11,12] An increase in fatty acid uptake is affected by the metabolite propionate via the lipoprotein lipase inhibitor angiopoietin-like 4.[11] A reduction in intracellular lipolysis by acetate and propionate occurs through reduced hormone-sensitive lipase phosphorylation via interacting with the SCFA receptor GPR43. Likewise, an increase in peroxisome proliferator-activated receptor (PPAR)-y–mediated adipogenesis by acetate, propionate, and butyrate occurs through the regulation of GPR43-related mechanism. Refer to Figure 1 in Appendix A[13] for potential biological effects in humans.

4.0 Microbiota Derived Inflammation: Pathogen-Associated Structural Parts

The microbiota contributes to the development of the immune system by supporting the progress of the regulatory T cell lymphocytes that reduce pathogens.[14] Increased migration of the microbiota causes inflammation. Lipopolysaccharides (LPS) and endotoxin bind to the CD 14 membrane receptor on the surface of the immune and epithelial cells.[15] This leads to the production of proinflammatory cytokines tumor necrosis factor α (TNF-α) and interleukin 1β (IL-1β). Inflammation causes disruptions in the intestinal barrier, which results in gut permeability and increased chronic low-grade inflammation in the appendix. Refer to Figure 2 in

Appendix B.[16] An increase in the presence of LPS in the plasma is related to chronic inflammation and is known as metabolic endotoxemia, a condition that is linked to many ailments such as non-alcoholic fatty liver disease, type 2 diabetes, chronic kidney disease, and cardiovascular disease.[17]

5.0 Microbiota Derived Inflammation: Metabolites

Besides influencing the immune system through their structural parts, Microorganisms influence the immune system through their metabolites.[7] SCFAs have many positive health effects on the host's metabolism. The metabolite Butyrate gives nourishment to the epithelial cells and thickens the mucin resulting in tight junctions in the intestinal barrier. The metabolite propionate provokes L-enteroendocrine cells to free glucagon-like peptide 1 and peptide tyrosine-tyrosine. This creates a feeling of fullness and results in prohibiting the processes of cholesterol synthesis, and fatty acids in the liver that leads to a reduction in obesity and related diseases.

On the other hand, acetate has negative effects on metabolic states and leads to obesity.[18] It helps in lipid synthesis and thus leads to dyslipidemia. In addition, it increases the appetite through the increased production of gastric ghrelin. The bacterial metabolite Trimethylamine N-oxide (TMAO) is related to a higher risk of cardiovascular disease.[19] Higher levels of this metabolite prompt activation of NLR family pyrin domain-containing 3 (NLRP3). It is an intracellular protein that is responsible for inflammatory actions. It helps regulate the proinflammatory cytokines IL-1β and IL-18 via caspase-1 activation. Furthermore, it synthesizes proinflammatory proteins that have pro-atherosclerotic effects, such as cyclooxygenase 2 (COX2), E-selectin, IL-6, and intracellular adhesion molecule 1.

The synthesis of deoxycholic acid (DCA), a secondary bile acid, is caused by the microbiota deconstructing the bile acids in the intestine.[20] A high fat diet can increase DCA by ten folds. High DCA is connected to impairment in the intestinal epithelial cohesion, which leads to inflammation that is activated via NLRP3 inflammasome. Elevated secondary bile acid levels lead to the creation of reactive oxygen and nitrogen species.[21] In addition, high bile acids destroy cell membranes, mitochondria, and DNA, increasing the risk of colon cancer.

The fermentation of proteins leads to harmful bacterial metabolites such as p-cresol sulfate (pCS) indoxyl sulfate (IS) and p-cresol sulfate (pCS).[22] Patients with chronic kidney disease have high levels of IS and pCS. Furthermore, there is a positive correlation between higher IS and pCS and the development of chronic kidney and cardiovascular diseases.[9] These harmful bacterial metabolites steer toward dysbiosis and higher intestinal permeability that increases inflammation.

6.0 Modifying the Microbiota

Since dysbiosis and increased intestinal permeability result in low-grade chronic inflammation that contributes to metabolic disorders and obesity, modifying the microbiota may decrease inflammation and metabolic disorders.[17] Diet may be used to lower systemic inflammation. The following section discusses different diets, nutrients, prebiotics, and probiotics.

6.1 The Mediterranean Diet

The Mediterranean diet (MD) is a healthy one and is associated with reducing the risks of cancer, cardiovascular and metabolic diseases.[23] It encourages consuming fresh fruits and vegetables, whole grains, legumes, moderate amounts of fish, and small amounts of dairy and meat. The health benefits of this diet include anti-cancerous, antioxidant, anti-inflammatory, and lipid-

lowering effects. In addition, according to recent studies, the MD diet influences the microbiome.[24] It regulates the gut microbiota and reduces endotoxemia.[25] The Tagliamonte et al. study examined the effects of the MD diet and the Western diet on the intestinal microbiota.[26] The results after eight weeks showed an increase in R. hominis, Roseburia faecis and Akkermansia muciniphila in the MD diet in comparison to the Western diet. The MD diet lowered plasma arachidonoylethanolamide. This showed that the MD may have anti-inflammatory effects on increasing the tightness of the intestinal junctions. The effects of the MD diet on the microbiome are due to the consumption of dietary fiber, plant protein, unsaturated fatty acids, and polyphenols.[27]

6.2 Plant-Based Diet

The amount of Escherichia coli, Bifidobacteria, and Enterobacteria were less in plant-based diets compared to the omnivorous ones.[28] In addition, the ratio of Prevotella-to-Bacteroides is lower in individuals who ingested fiber and starch in comparison to those who followed the Western diet.[29] Following a plant-based diet increased the number of Bacteroidetes, and decreased Firmicutes. This is advantageous in preventing and treating obesity.[30] From Trefflich et al., vegans had an elevated number of Roseburia and Faecalibacterium.[31,32] This bacterium produces butyrate resulting in an improved intestinal barrier. The change in the microbiota is linked to decreased serum levels of LPS, C-reactive protein (CRP) and TNF- α in vegans versus omnivores.

A gluten-free diet (GFD) is medically used for individuals with celiac disease (CD) and non-celiac gluten sensitivity.[33] Individuals with CD who do not follow GFD will develop intestinal dysbiosis. Pathogenic bacteria such as Serratia, Prevotella, and Klebsiella, increased while beneficial bacteria such as Bifidocteria and Firmicutes decreased in comparison with healthy

individuals. Although individuals with CD who followed GFD had a reduced variety of bacteria and less diversity of Bifidobacterium and Lactobacillus species, the concentrations of SCFAs they had in their guts were close to the ones of the healthy individuals.[34] Despite the use of GFD, it was observed that people with CD symptoms have increased amounts of Prevotella, and lower amounts of Bacteroidetes and Firmicutes when compared with the microbiome of individuals who have no CD symptoms.[35] Healthy individuals who followed GFD ended up having lower amounts of Faecalibacterium prausnitzii, Bifidobacterium, and Lactobacillus, and higher amounts of Enterobacteriaceae, and Escherichia coli.[36,37] This could be due to lost prebiotics' properties of gluten upon removing it from the diet.[38]

6.3 Fiber

A lot of the benefits of following a plant-based diet come from the inclusion of fiber when compared with the Western diet.[39] Fiber includes waxes, dextrins, lignans, pectins, and cellulose; some of the fiber is considered prebiotics. Sources of fiber include fruits, vegetables, legumes, and whole grains. Animals do not have the capability to digest fiber in their gastrointestinal tract.[40] However, it gets fermented in the colon by intestinal bacteria. Bacteria use it as food and as a result, produce beneficial SCFAs. According to So et al. systematic review, the results from 59 studies that included 1900 participants showed a remarkable increase of Bifidobacterium spp.[41] In addition, based on the results from 28 studies that included 850 participants, a remarkable increase of Lactobacillus spp. was observed. According to a study conducted on elderly participants, the diversity of the microbiota was notably higher in those that consumed a high fiber diet in comparison to those that consumed high fat and a low-fiber diet.[42] In addition, inflammatory markers such as CRP, IL-6, and TNF-α, were notably higher among the group that consumed a low-fiber diet.

6.4 Prebiotics

Prebiotics are substrates consumed by the host's microorganisms resulting in health benefits to the host.[43] There is a certain set of criteria that needs to be met for a food item to be named prebiotics. These include being resistant to stomach pH, ability to induce growth in the gut microbiota, ability to ferment by the intestinal microbiota, and not being hydrolyzed and absorbed in the GI tract. In addition, prebiotics lower intestinal pH, and keep water in the intestine. While prebiotics are a subset of fiber, it is worth mentioning that not all fiber is prebiotics. Carbohydrates are the main macronutrient that provides prebiotics, and they include oligosaccharides and polysaccharides.[44] Prebiotics include fructooligosaccharides (FOS), galactooligosaccharides (GOS), inulin, resistant starch, polyunsaturated fatty acids (PUFAs), conjugated linoleic acid (CLA), and polyphenols. Since FOS and GOS are the most popular prebiotics, they will be detailed in the following section.

Fructooligosaccharides (FOS) are fructans that are made of 2-10 fructofuranose linked via B bonds.[45] FOS sources include asparagus, bananas, onions, honey, artichokes, and wheat. FOS supplements help in the development of the Lactobacillus sp. and Bifidobacteria sp. Bacteria.[46] Patients with Crohn's disease who used FOS supplements had a remarkable increase in fecal bifidobacterial concentrations. Gu et al. study looked at the effects of FOS use on mice microbiota. The result was a noticeable increase in Actinobacteria especially Bifidobacterium and Coprococcus, and a decrease in Bacteroidetes and Proteobacteria.[47] In another study conducted on mice, the results showed the use of FOS decreased inflammatory markers such as IL-6 and TNF-α. Mice who used FOS showed higher levels of SCFA in the serum and feces.[48]

Galactooligosaccharides (GOS) are formed from galactopyranosyl compounds and found in foods such as chickpeas, beans, and lentils.[49] GOS is made from soybeans and lactose sugar that

is found in cow's milk. The use of GOS in infants and newborns results in positive effects on their microbiome.[50] GOS and FOS have positive effects on the total number of lactic acid bacteria such as Bifidobacterium, and Lactobacillus, and that is why they are added to milk mixtures. In addition, GOS shows positive effects on these bacteria across the life span.[51] It reduces the pathogenic bacteria Clostridium. Taking GOS mixture resulted in an increase IL-10 and IL-8 concentrations and a decrease in IL-1β. In a 10-week study where elderly individuals consumed 5.5 grams per day of GOS, it was observed that the number of C. cocoides-E, Lactobacillus-Enterococcus spp., and Bifidobacterium spp. increased, while the number of Bacteroides spp., E. coli, the C. histolyticum group, and Desulfovibrio spp. decreased in comparison to the placebo group.[52] In addition, the study found that GOS intake resulted in an increase in NK cell activity and IL-10 production. However, there was a reduction in the concentration of IL-1β, IL-6, and TNF-α implying GOS's anti-inflammatory effect. Refer to Figure 3 in Appendix C for effects of nutritional interventions on specific bacteria.[16]

6.5 Probiotics

Probiotics are live microorganisms that provide health benefits to the host when consumed in adequate amounts.[53] In a 12-week study on animal models, Wang et al. successfully demonstrated the positive effects of the probiotic's strains Bifidobacterium animalis subsp. lactis I-2494 and Lactobacillus paracasei CNCM I-4270 and L. rhamnosus I-3690 on reducing the effects of a high-fat diet.[54] The benefits included an enhancement of glucose metabolism and reductions in body weight gain and fatty liver. Further, these probiotics significantly lowered the percolation of pro-inflammatory macrophages into adipose tissue thus lowering its inflammation and obesity-related issues. In humans, just as shown in animal models, probiotics inhibit the nuclear factor (NF-κB) pathway and lower cytokines resulting in reduced chronic low-grade

inflammation.[55] In smokers, lactobacillus plantarum 299v decreased IL-6 and the risk factors of cardiovascular disease thus improving the inflammatory profile.[56] Lactobacillus helveticus R389 from fermented milk lowered the production of IL-6 and increased the secretion of interleukin 10, an anti-inflammatory agent.[57] Akkermancia muciniphila bacterium was shown to lower the concentration of lipopolysaccharide in the serum, elevate the thickness of the mucus, and improve glucose tolerance and fasting glucose concentration.[58] Clinical trials demonstrated that the consumption of probiotics significantly lowered serum hs-CRP, TNF-α, IL-6, IL-12, and IL-4 and increased the anti-inflammatory cytokine IL-10.[59] Furthermore, the health benefits of consuming probiotics have been shown in many conditions such as rheumatoid arthritis, metabolic syndrome, liver diseases, coronary heart disease, and metabolic syndrome. See Table 1 in Appendix D for probiotics' health effects on various health conditions.[16]

7.0 Conclusion and Applications

The gut microbiota plays several crucial functions in the body. They do that through their structural elements and through the production of certain metabolites that are known as short-chain fatty acids (SCFAs). Certain SCFAs have positive health effects, while others have negative impacts. Among the positive side effects are energy homeostasis and metabolism, potential in preventing obesity and its related diseases, reduction in fat accumulation, and the development of the immune system. On the other side, the negative health effects include obesity, dyslipidemia, a higher risk of cardiovascular disease, colon carcinogenesis, chronic kidney disease, dysbiosis, and higher intestinal permeability and increased inflammation. Among other factors, an unhealthy diet may result in an imbalance in the intestinal microbiota. A healthy diet such as the MD or the plant-based, with the inclusion of prebiotics, and probiotics plays a

significant role in sustaining a healthy microbiota and decreases the risk of chronic inflammation and diseases.

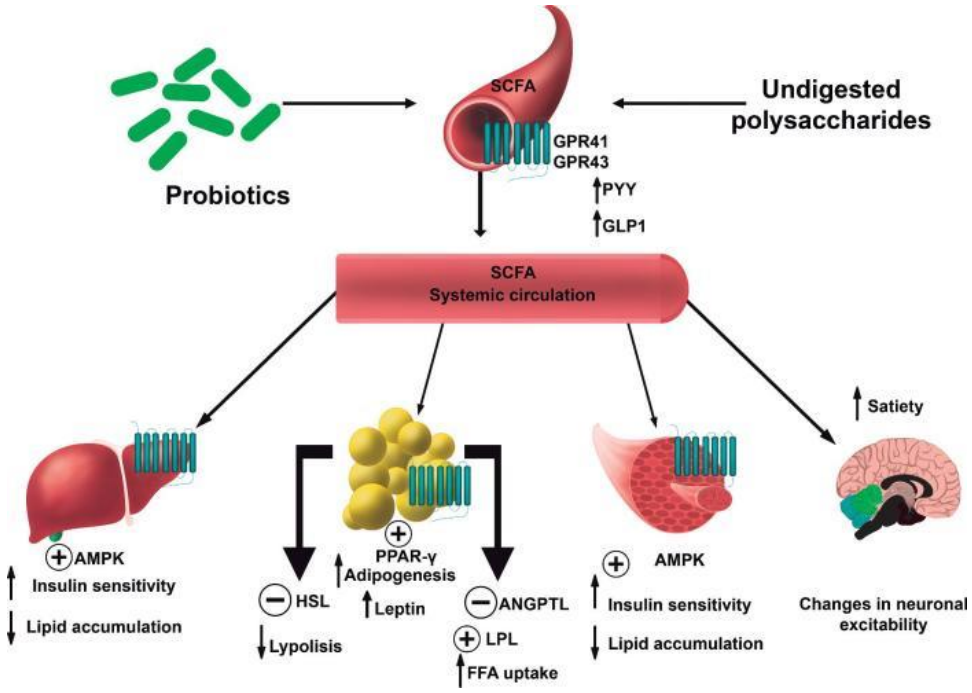
The Mediterranean diet has anti-inflammatory effects through increasing the tightness of the intestinal junctions and is associated with reducing the risk of chronic diseases such as cardiovascular and metabolic diseases and cancer. Therefore, future dietitians ought to advise their patients to check out the Food Insight Organization, which provides a short article that gives a quick overview[60] and a more detailed document explaining the MD diet.[61] In addition, the American Heart Association (AHA)[62] and the Cleveland Clinic (CC)[63] are two useful resources on the MD diet. Furthermore, the MD infographic by the Old Ways Organization[64] is a good visual that includes health, environmental, as well as economic benefits that are associated with the MD diet. Finally, the MyPlate[65] website has several recipes that follow the MD diet. This website is easy to navigate and offers many general tips on a healthy balanced diet.

Based on the results of the studies that are referenced in this paper, prebiotics and probiotics are associated with decreasing inflammatory markers, increasing anti-inflammatory markers, and demonstrating health benefits with many conditions. Therefore, to gain a better understanding of prebiotics and probiotics, the International Scientific Association for Probiotics and Prebiotics organization (ISAPP) should be consulted. This website provides valuable information through its blog,[66] infographics,[67] and videos.[68]

Research about the microbiome is in its infancy. It includes living organisms such as bacteria, archaea, fungi, protists, algae, viruses, phages, plasmids, viroids, and prions. To date, most research has focused on bacteria only, and therefore limited information on the interactions between the bacteria and other microorganisms exists. What is known today is a good start, however, the microbiome is still an area to be further studied.

Appendix A

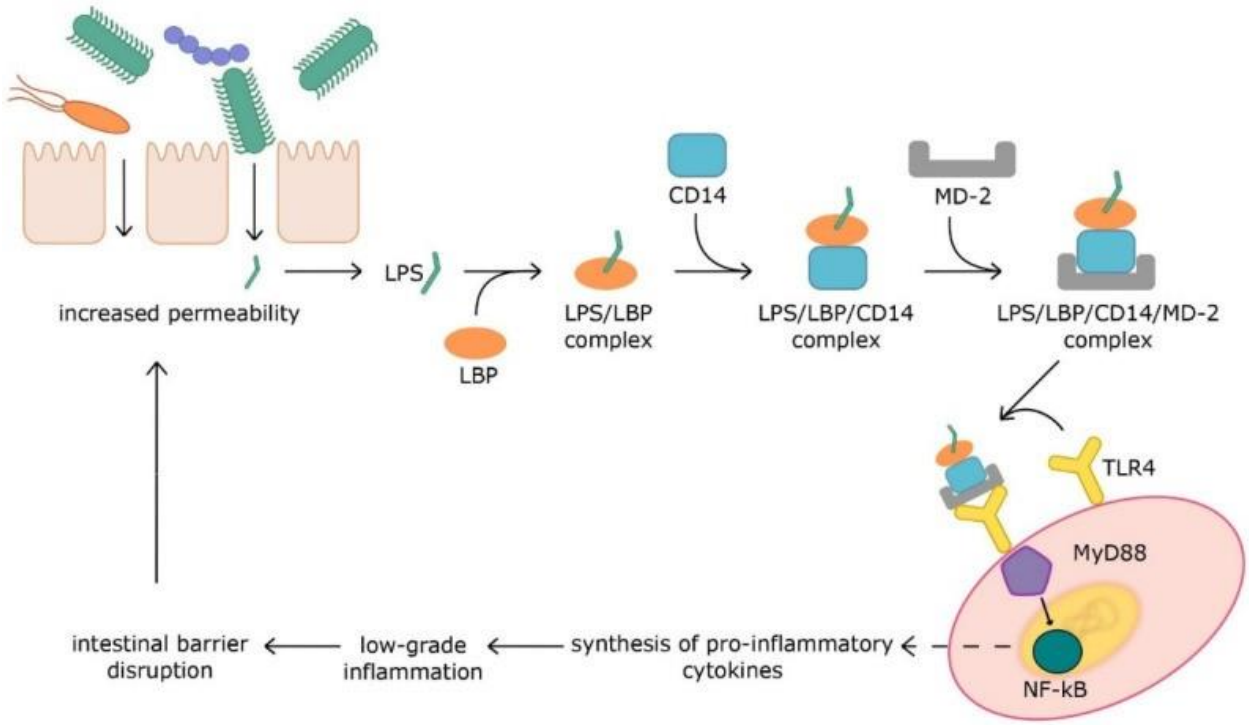
Figure 1



"Potential biological effects of SCFAs in humans. AMPK, AMP kinase; ANGPTL, angiopoietin-like; GLP1, glucagon-like peptide 1; GPR, G protein-coupled receptor; HSL, hormone-sensitive lipase; LPL, lipoprotein lipase; PPAR-γ, peroxisome proliferator-activated receptor-γ; PYY, polypeptide YY."

Appendix B

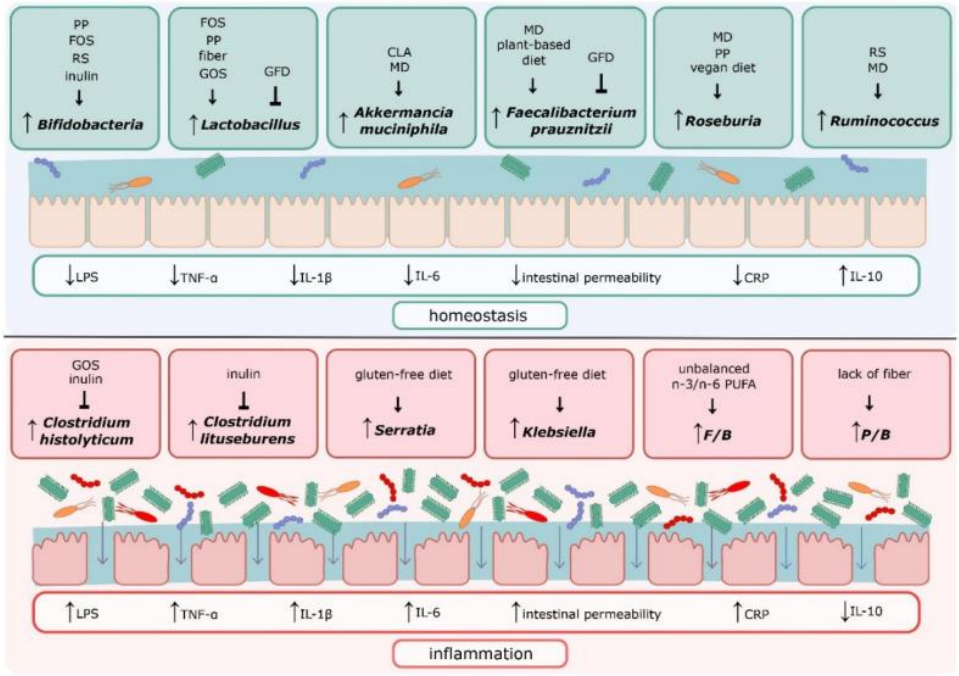
Figure 2



"Mechanism of LPS' influence on inflammation and intestinal permeability. Aberrations: LPS—lipopolysaccharide; LBP—LPS-binding protein; CD14—cluster of differentiation 14; MD-2—myeloid differential factor 2; TLR4—toll-like receptor 4; MyD88—myeloid differentiation factor 88; NF-κB—nuclear factor kappa-light-chain-enhancer of activated B cells."

Appendix C

Figure 3



"Effect of nutritional interventions on specific bacteria. Abbreviations: PP—polyphenols; FOS—fructooligosaccharides; RS—resistant starch; GOS—galactooligosaccharides; GFD—gluten-free diet; CLA—conjugated linoleic acid; MD—Mediterranean diet; LPS—lipopolysaccharide; TNF-α—tumor necrosis factor α; IL-1ß—interleukin 1ß; IL-6—interleukin 6; CRP—C-reactive protein; IL-10—interleukin 10."

Appendix D

Table 1. “Literature Review on Probiotics’ effects in various health conditions.”

Reference	Health Condition	Sample Size	Probiotics	Duration	Effect in Inflammation	Other Effects
Bernini et al. 2015 [121]	metabolic syndrome	26 probiotic group 25 control group	fermented milk with 2.72 × 10^{10} CFU Bifidobacterium lactis HN019	45 days	↓ TNF-α ↓ IL-6	↓ BMI ↓ total cholesterol ↓ LDL
Akkasheh et al. 2016 [122]	major depressive disorder	20 probiotic group 20 control group	Lactobacillus acidophilus (2 × 10^{9} CFU/g), Lactobacillus casei (2 × 10^{9} CFU/g), Bifidobacterium bifidum (2 × 10^{9} CFU/g)	8 weeks	↓ hs-CRP	↓ BDI total scores ↓ insulin ↓ HOMA-IR ↑ glutathione
Zamani et al. 2016 [123]	rheumatoid arthritis	30 probiotic group 30 control group	Lactobacillus acidophilus (2 × 10^{9} [CFU]/g), Lactobacillus casei (2 × 10^{9} CFU/g), Bifidobacterium bifidum (2 × 10^{9} CFU/g)	8 weeks	↓ hs-CRP	↑ DAS28 ↓ insulin ↓ HOMA-B ↓ total cholesterol ↓ LDL

Moludi et al. 2021 [124]	coronary artery disease	22 probiotic group + caloric restriction 22 control group + caloric restriction	Lactobacillus rhamnosus GG (1.6×10^9 CFU)	12 weeks	↓ IL-1ß	↓ LPS
Han et al. 2015 [125]	alcoholic hepatitis	60 probiotic group + alcohol abstinence 57 control group + alcohol abstinence	Lactobacillus subtilis/Streptococcus faecium (1500 mg/day)	7 days	↓ TNF-α	↓ LPS
Kobyliak et al. 2018 [126]	Non-alcoholic fatty liver disease	30 probiotic group 28 control group	Lactobacillus + Lactococcus (6×10^{10} CFU/g), Bifidobacterium (1×10^{10} CFU/g), Propionibacterium (3×10^{10} CFU/g), Acetobacter (1×10^6 CFU/g)	8 weeks	↓ TNF-α ↓ IL-6	↓ liver fat ↓ AST ↓ GGT

"Aberrations: UCF—colony-forming unit; TNF-α—tumor necrosis factor α; IL-6—interleukin 6; BMI—body mass index; LDL—low-density lipoprotein; hs-CRP—high-sensitivity C-reactive protein; BDI—Beck Depression Inventory; HOMA-IR—homeostasis model assessment of insulin resistance; DAS—Disease Activity Score of 28 joints; HOMA-B—homeostatic model assessment-B cell function; IL-1ß—interleukin 1ß; LPS—lipopolysaccharide; AST—aspartate aminotransferase; GGT—gamma-glutamyl transferase; ↑—significantly increased; ↓—significantly decreased."

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