A Review on Benefits of Probiotics on Human Health

A review paper, submitted to the Department of Pharmacy, Daffodil International University to complete the course of B.Pharm.

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APPROVAL

This project titled "**A Review on Benefits of Probiotics on Human Health**" submitted by Israt Jahan Tamanna, ID: 191-29-1508, Department of Pharmacy, Daffodil International University has been accepted as satisfactory for the partial fulfilment of the requirements for the degree of B. Pharm and approved as to its style and contents.

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DECLARATION

I hereby declare that, this project report "**A Review on Benefits of Probiotics on Human Health**" is done by me Israt Jahan Tamanna, ID: 191-29-1508, Department of Pharmacy, Daffodil International University, under the supervision of Ms. Nazneen Ahmeda Sultana, Department of Pharmacy, Daffodil International University, to fulfil the partial requirement for the degree of Bachelor of Pharmacy. I am declaring that this project is my original work.

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DEDICATION

THIS WORK IS DEDICATED TO MY LOVING PARENTS, SUPPORTIVE SUPERVISOR, AND WONDERFUL FRIENDS. THEIR UNWAVERING SUPPORT, LOVE, AND ENCOURAGEMENT HAVE BEEN INSTRUMENTAL IN MY SUCCESS AND THE COMPLETION OF THIS PROJECT. I AM GRATEFUL FOR THEIR PRESENCE IN MY LIFE AND FOR THEIR CONSTANT MOTIVATION.

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Abstract

Probiotics are live microorganisms that offer several health benefits when consumed in adequate amounts. They are found in several fermented foods and dietary supplements. The objective of this literature review is to evaluate and synthesize the existing research on probiotics, focusing on their mechanisms of action, efficacy, safety, and potential clinical applications. The present study is a literature review that evaluated the current research and reviews on the health, safety, and benefits of probiotics for human and animal health. It can be concluded that, probiotics are being recognized as a promising dietary supplement that can positively impact human health by regulating the gut microbiome. Probiotics have shown promise in reducing the risk and severity of several diseases, including diarrhea, respiratory infections, inflammatory bowel disease, and liver disease. Additionally, probiotics may have a positive effect on mental health and cognitive function. However, there are limitations to the current research, including methodological and interpretational issues. Further research is needed to fully understand the mechanisms of action of probiotics and to investigate their potential benefits in different populations and for specific health outcomes. Overall, probiotics have significant nutritional and health potential and may be a useful addition to a healthy diet and lifestyle. The reviewed literature indicates that probiotics can potentially modulate several axes, including the gut-brain axis, gut-liver axis, and metabolism, thereby affecting mental health, liver function, and insulin sensitivity. However, there are still some limitations in the studies conducted to date, and further research is needed to fully understand the impact of probiotics on specific health outcomes in different populations and age groups. Despite these limitations, incorporating probiotics into a healthy diet may provide a useful strategy for maintaining overall health and well-being.

Keywords: Probiotics, gut microbiome, health, immune system, metabolism, brain function, liver function, prebiotics, fermentation, microbial diversity.

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CHAPTER-1

INTRODUCTION

1.1 Introduction:

The International Scientific Association for Probiotics and Prebiotics defines “probiotics” as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host” [1]. These microorganisms, which consist mainly of bacteria but also include yeasts, are naturally present in fermented foods, may be added to other food products, and are available as dietary supplements. However, not all foods and dietary supplements labeled as “probiotics” on the market have proven health benefits [2].

Probiotics as they are live microorganisms that, when consumed in adequate amounts, can confer health benefits to the host. The most common types of probiotics are bacteria, such as Lactobacillus and Bifidobacterium, but other types of microorganisms, such as yeast, can also be used [3].

The human gut is home to trillions of microorganisms, including beneficial bacteria that help digest food, produce vitamins, and support immune function [4]. However, various factors such as poor diet, stress, antibiotics, and environmental toxins can disrupt the balance of gut bacteria, leading to dysbiosis (an imbalance of microorganisms in the gut) and potential health problems [5].

Probiotics work by restoring the balance of gut bacteria and promoting the growth of beneficial microorganisms [6]. They can also stimulate the production of short-chain fatty acids (SCFAs) in the gut, which have been shown to have numerous health benefits, including reducing inflammation and improving gut barrier function [7].

Research has shown that probiotics may offer a range of health benefits, including: Probiotics may help alleviate various digestive problems, such as diarrhea, constipation, and irritable bowel syndrome (IBS), they exert enhance the immune system by stimulating the production of antibodies and improving gut barrier function [8]. Some evidence suggests that probiotics may reduce the risk of developing allergies by modulating the immune system and reducing inflammation. Preliminary research has suggested that probiotics may improve symptoms of anxiety, depression, and stress by influencing the gut-brain axis [9].

1.2. Examples of Beneficial Probiotics:

Probiotics are living microorganisms that provide numerous health benefits to the human body. They are found naturally in fermented foods, such as yogurt, kefir, kimchi, sauerkraut, and miso. Here are some examples of beneficial probiotics:

1.2.1. *Lactobacillus acidophilus:*

This probiotic is commonly found in yogurt and helps maintain the balance of good bacteria in the gut. It also aids in digestion and the absorption of nutrients [10].

1.2.2. *Bifidobacterium bifidum:*

This probiotic is found in the large intestine and helps break down complex carbohydrates, such as fiber. It also promotes a healthy immune system.

1.2.3. *Lactobacillus rhamnosus:*

This probiotic is found in the gut and vagina and helps to prevent and treat diarrhea and other gastrointestinal issues [11].

1.2.4. *Streptococcus thermophilus:*

This probiotic is commonly found in yogurt and helps to break down lactose, making it easier for people who are lactose intolerant to digest dairy products [12].

1.2.5. *Saccharomyces boulardii:*

This probiotic is a type of yeast that can help prevent and treat diarrhea caused by antibiotics or infections [13].

1.2.6. *Bifidobacterium lactis:*

This probiotic is found in the gut and helps to support a healthy immune system and improve digestion [14].

1.2.7. *Lactobacillus plantarum:*

This probiotic is commonly found in fermented foods and can help to reduce inflammation in the gut and improve digestive health [15].

1.2.8. *Bacillus coagulans:*

This probiotic is known for its ability to survive in harsh environments, such as the acidic environment of the stomach. It can help to improve gut health and support a healthy immune system [16].

1.3. Classification of Probiotics:

Classification of probiotics is complex with distinct rationales. Probiotics products can be sorted to single strain probiotics and multi strain probiotics. Under single strain probiotics, groups are classified based on genus that probiotics belong to. Scientific name of probiotics is composed of two parts: genus (italicized) and species (italicized). Sometimes the strain name is included after species. Genus classification of probiotics is shown on below [17].

Table 1: Classification of Probiotics [17].

Bifidobacterium	• Breve • Infantis • Longum • Bifidum • Thermophilum • Adolescentis • Animalis • Lactis
Lactobacillus	• Acidophilus • Plantarum • Rhamnosus • Paracasei • Fermentum • Johnsonii • Brevis • Casei • Lactis • Gasseri
Lactococcus	• Lactis
Streptococcus	• Thermophilus • Cremoris
Bacillus	• Coagulans
Saccharomyces	• Cerevisiae • Pastorianus
Leuconostoc	• Mesenteries

1.4. How effective are probiotics:

The effectiveness of probiotic supplements in treating various conditions is still uncertain, despite ongoing research. Although several studies have reported positive outcomes, additional research is necessary.

Moreover, it is crucial to note that unlike medications, the Food and Drug Administration (FDA) does not require dietary supplements to undergo approval. Consequently, manufacturers can make claims about their supplements' safety and effectiveness without verification.

Therefore, it is always advisable to consult your healthcare provider or pediatrician before consuming supplements or giving them to your child, as they could interact with our medication [18].

1.5. Current Status of Probiotics Prescribing in Bangladesh: Statistics and Information:

According to current study oral rehydration therapy was found as a cornerstone for treating pediatric diarrhea. In addition, it was observed that average 3.2 drugs prescribed per encounter and more than 26.4% prescriptions contained probiotic products. Approximately 35% probiotics were prescribed by pediatricians. Bacillus and Lactobacillus were found to be the most frequently prescribed probiotic species for treating childhood diarrhea in Bangladesh. Both antibiotics and probiotics were prescribed to one-third of pediatric patients suffering from diarrhea. Only oral solid (63.7%) and oral liquid (36.3%) were prescribed as probiotic products for pediatric patients [19].

CHAPTER-2

OBJECTIVE OF THE STUDY

2. Objective:

The purpose of this literature review is to critically evaluate and synthesize the existing research on the use of probiotics in promoting health and preventing disease, with a focus on their mechanisms of action, efficacy, safety, and potential applications in clinical practice. Through a comprehensive analysis of the available evidence, this review aims to provide a deeper understanding of the role of probiotics in human health and to identify gaps in knowledge and areas for future research. Ultimately, the objective is to provide healthcare professionals, policymakers, and consumers with evidence-based information to guide decision-making and improve health outcomes.

CHAPTER-3

LITERATURE REVIEW

3. Literature Review:

3.1. Health benefits of probiotics: [20]

A study published in online by Cambridge University Press: 11 January 2019 found that The ability of probiotics to enhance the nutritional content and bioavailability of nutrients and the scientific evidence for the usefulness of probiotics in alleviating the symptoms of lactose intolerance and in enhancing growth development .

3.2. Probiotic yogurt improves antioxidant status in type 2 diabetic patients: [21]

One study published in the Journal of Nutrition found that Probiotic yogurt was found to improve blood glucose control and antioxidant status in a study. It decreased fasting blood glucose and hemoglobin A1c levels and increased antioxidant enzyme activities and total antioxidant status. However, there were no significant changes in insulin concentration or erythrocyte catalase activity.

3.3. Yogurt and other fermented foods as sources of health-promoting bacteria: [22]

Another study published in the Journal of Nutrition reviews showed that the increased consumption of fermented foods such as yogurt and kefir is associated with reduced risks of type 2 diabetes, metabolic syndrome, and heart disease, as well as improved weight management. Fermentation-associated microorganisms present in these foods, including probiotic strains, may contribute to these health benefits by influencing the gut microbiome. Studies have shown that consuming yogurt and other fermented foods may improve intestinal and extraintestinal health, and could potentially be used to treat lactose malabsorption, infectious diarrhoea, respiratory infections, and enhance immune and anti-inflammatory responses .

3.4. Probiotics in Irritable Bowel Syndrome: A Review of Their Therapeutic Role: [23]

A relevant study published in 2022, where the researchers found that adding probiotics to the routine of patients with Irritable Bowel Syndrome (IBS) led to symptomatic relief. They observed that a variety of strains in the probiotic mixtures were beneficial for IBS patients. Based on their findings, they concluded that probiotics have a beneficial role in treating chronic disorders like IBS .

3.5. Benefits of Probiotic Supplementation on Immune Response in Soldiers: A Randomized, Double-Blinded, Placebo-Controlled Trial: [24]

A study published in the Annals of Military and Health Sciences Research journal found that taking a daily probiotic supplement can improve immune function. Participants who took the supplement had higher levels of immune cells and a lower risk of respiratory infections compared to those who didn't take the supplement. These findings suggest that probiotics have potential health benefits, such as enhancing nutrient absorption, promoting gut health, reducing symptoms of IBS, and boosting the immune system. However, further research is required to identify the optimal strains and dosages of probiotics for various health issues.

CHAPTER-4

METHOD & MATERIALS

4. Method & Materials

- **Study Design:** The present study is a literature review that aimed to evaluate the current research and reviews on the health, safety, and benefits of probiotics for human and animal health.

- **Data Sources:** Multiple databases, including Google Scholar, Pubmed, Springer, Elsevier Science Direct, and Web of Science, were searched for studies published between 2010 and 2023. The search focused on the research and reviews of the last 10 years, with a major emphasis on 2016–2022. The Mendeley software was used for this review purpose.

- **Inclusion and Exclusion Criteria:** The articles chosen exclusively contained English texts and searches were carried out for the following keywords and headings: Probiotics; Health, Safety, Benefits, Farm and Abstract, Introduction, Methodology, Probiotics and Their Benefits, Association of Probiotics in Prevention of Diseases, Probiotics for Animal Health, Safety of Probiotics, Conclusions and future perspective. The duplicate articles were excluded, screened the data, factored out the unrelated works, and finally screened the full-text documents. Numerous elements that involved original articles or review papers were part of the inclusion criteria. Articles lacking access to full text and those with insufficient or irrelevant information were among the exclusion criteria.

- **Data Collection and Analysis:** Around 30 papers were reviewed for this study. All the data analysis was done in Microsoft Excel to make the working process easy. To ensure that no data was missing or conflicting, every information was reviewed for accuracy and internal consistency.

- **Timeline:** The study was initiated in December 2022 and completed at the end of March 2023.To ensure that no data was missing or conflicting, every information was reviewed for accuracy and internal consistency.

CHAPTER-5

RESULT & DISCUSSION

5. Result and Discussion:

5.1. Benefits of Probiotics on Human Health:

5.1.1. Result:

Probiotics are living microorganisms when consumed in adequate amounts, confer health benefits on the host. The health potential of probiotics has been extensively studied, and numerous studies have reported their positive benefits on various aspects of health. Here are some of the ways probiotics can benefit human health: **(Table-2).**

Table- 2: Beneficial effects of probiotics on Human Health

Aspect	Summary	Reference
Heart health	Probiotics have the potential to maintain heart health by decreasing levels of LDL ("bad") cholesterol and blood pressure.	[37] [38]
On Certain Allergies and Eczema	Previous studies indicate that specific strains of probiotics may help lessen the severity of eczema in infants and children.	[25]
Gut Health	Probiotics help maintain a healthy balance of bacteria in the gut, which is crucial for digestive health. They can also alleviate symptoms of conditions like IBS, IBD, Crohn's disease and diarrhea.	[25] [25] [26]
Immune Function	Probiotics can stimulate the production of immune system components, which can help fight off infections and diseases. They also have anti-inflammatory properties and can help modulate the immune response.	[41] [42][27]
Weight loss and Belly Fat	Probiotics have the potential to aid in weight loss through various mechanisms.	[25] [28] [29]
Nutrient Bioavailability	Certain probiotic strains can enhance the bioavailability of vitamins and minerals, such as B vitamins, vitamin D, zinc, and iron, by increasing their solubility and absorption in the gut. They are also a good source of protein, vitamins and minerals.	[45] [46] [47] [30] [31]
Infections	Probiotics can help prevent and treat various infections, including those caused by harmful bacteria like C. difficile and H. pylori.	[32] [33]
Mental Health	Probiotics can improve mood and reduce symptoms of anxiety and depression by influencing the gut-brain axis.	[33]

Inflammation	Probiotics can help reduce inflammation in the body, which is linked to numerous chronic health conditions like heart disease, diabetes, and cancer.	[34]
Skin Health	Probiotics can improve the health of the skin by reducing inflammation and promoting the growth of beneficial bacteria.	[35]
Insulin sensitivity	Probiotics have a modest but significant effect on improving insulin sensitivity, although the evidence is not entirely consistent	[36] [37] [38]
Energy metabolism	Probiotics can increase energy expenditure, decrease energy intake, and reduce fat storage	[39] [40]

5.1.2. Discussion:

Specific types of lactic acid-producing bacteria can aid in reducing cholesterol by breaking down bile in the gut [41]. Bile is primarily composed of cholesterol and is a natural digestive fluid. By breaking down bile, probiotics prevent it from being reabsorbed in the gut and potentially entering the bloodstream as cholesterol [42]. Current evidence suggests that probiotic strains available today may not significantly improve eczema compared to not using any probiotics. The correlation between probiotics and reduced eczema severity is not yet strong enough, and further research is necessary [25]. Inflammatory bowel disease (IBD) affects more than one million people in the US, and includes conditions like ulcerative colitis and Crohn's disease. Studies have shown that certain strains of probiotics, such as those from the Bifidobacterium and Lactobacillus families, may improve symptoms in people with mild ulcerative colitis [25]. However, probiotics may have limited effect on symptoms associated with Crohn's disease. Nonetheless, there is promising early research indicating that probiotics could be beneficial for other bowel disorders, including irritable bowel syndrome (IBS) [43]. Past studies suggest that the consumption of probiotics may decrease the occurrence and duration of respiratory infections. Nonetheless, the quality of the evidence supporting this claim was low [44]. Furthermore, the probiotic strain Lactobacillus crispatus has been demonstrated to reduce the probability of urinary tract infections (UTIs) in women by 50% [45]. Certain types of probiotics can hinder the absorption of dietary fat in the intestines, resulting in excretion of fat through feces instead of storing it in the body [25]. An investigation showed that synbiotic supplementation increased the number of beneficial bacteria species in the gut, particularly Bifidobacterium and Lactobacillus, and enhanced the diversity of gut microbiota [28]. However, additional research is required to fully comprehend the relationship between probiotics and weight loss [29]. Some strains of probiotics have also been found to be a good source of protein, vitamins, and minerals [46]. Protein is an essential nutrient for the human body, as it is necessary for the growth and maintenance of muscle mass and other tissues. Some strains of probiotics, particularly those from the genera Lactobacillus and Bifidobacterium, have been found to contain high amounts of protein [47]. In addition to protein, certain strains of probiotics also contain vitamins and minerals. For example, some strains of Lactobacillus and Bifidobacterium, can de novo synthesize and supply vitamins to human body. In humans, members of the gut microbiota are able to synthesize vitamin K, as well as most of the water-soluble B vitamins, such as cobalamin, folates, pyridoxine, riboflavin, and thiamine [48]. A meta-analysis of randomized controlled trials showed that probiotic supplementation improved fasting blood glucose levels and insulin sensitivity in patients with type 2 diabetes [36]. One study showed that the consumption of a probiotic yogurt containing Lactobacillus acidophilus and *Bifidobacterium lactis* for 6 weeks improved insulin sensitivity in overweight and obese individuals [38].

5.2. Mechanism of Benefits of Probiotics on Human Health:

5.2.1. Benefits of Probiotics in Mental Health:

5.2.1.1. Result:

The connection between gut health and mood or mental health is becoming more evident in numerous studies [49]. Several studies have suggested that probiotics may have potential benefits in improving anxiety, stress, and cognitive function [50].

Table 3: Selected studies investigating the impact of probiotics on mental health

Study	Probiotic Strains	Participants	Results
[51]	Lactobacillus helveticus and Bifidobacterium longum	55 healthy volunteers	Significant reduction in psychological stress and improvement in overall mood
[52]	Lactobacillus acidophilus, Lactobacillus casei, and Bifidobacterium bifidum	40 patients with major depressive disorder	Significant reduction in depression scores
[53]	Lactobacillus rhamnosus HN001	423 pregnant women	Reduced symptoms of anxiety and depression during pregnancy and postpartum period
[54]	Lactobacillus plantarum PS128	40 patients with major depressive disorder	Significant improvement in anxiety and depression scores

Probiotic supplements have shown potential in improving certain mental health conditions in both animal and human research. A recent analysis of 13 human studies revealed that taking probiotic supplements containing Bifidobacterium and Lactobacillus strains for 1-2 months can enhance memory, anxiety, depression, autism, and obsessive-compulsive disorder (OCD) [55].

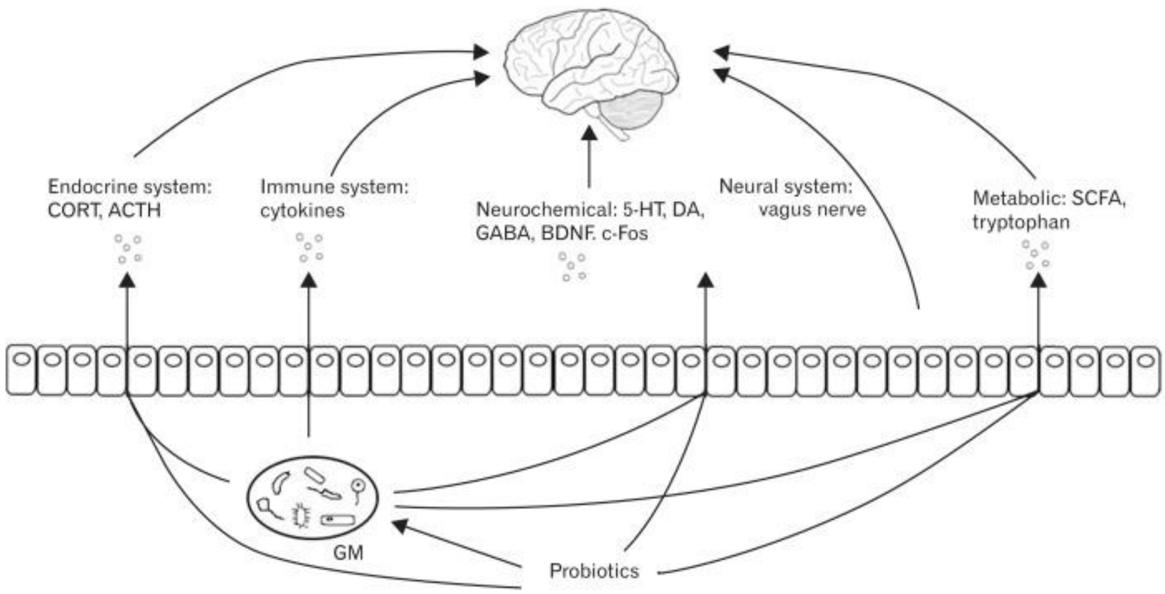

Figure-1: Beneficial effects of Probiotics on Mental Health

5.2.1.2. Discussion:

Probiotics can affect the functioning of the central nervous system through direct and indirect mechanisms. By altering the level of corticosteroid (CORT) and adrenocorticotropic hormone (ACTH), probiotics can influence the hypothalamic-pituitary-adrenal (HPA) axis. Probiotics also affect the immune system by reducing the production of pro-inflammatory cytokines and inflammation, which indirectly affects the central nervous system. Additionally, probiotics can have a direct effect on the biochemistry of the central nervous system by changing the levels of brain-derived neurotrophic factor (BDNF), c-Fos, and dopamine (DA), thus impacting brain function and behavior. Furthermore, probiotics can modify the gut microbiota (GM) by increasing the diversity and composition of beneficial bacteria [56].

A study involving 70 chemical workers, conducted for 6 weeks, revealed that daily intake of 100 grams of probiotic yogurt or a probiotic capsule resulted in an improvement in overall health, along with reduced levels of anxiety, stress, and depression [57]. Additionally, another study of 40 individuals diagnosed with depression indicated that taking probiotic supplements for eight weeks resulted in a reduction of depression levels, as well as decreased levels of inflammation markers such as C-reactive protein and hormones like insulin, compared to those who did not consume probiotics [58].

5.2.2. Benefits of probiotics the bioavailability of nutrients:

5.2.2.1. Result:

The amount and type of calcium available at the site of absorption determine the absorption pathway [59]. **(Figure -2)**

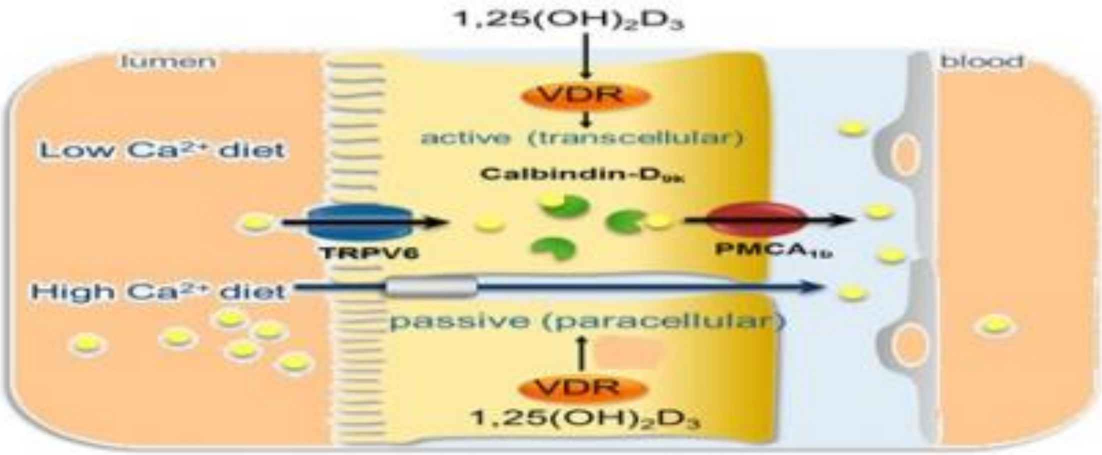

Figure 2: Intestinal Calcium Absorption [59]

Another study found that the bioavailability of iron was improved in rats fed a probiotic strain of Lactobacillus plantarum. In rats on high-fat iron-deficient diet, the supplementation of L. curvatus and L. plantarum increased serum ferroportin concentration, and L. curvatus enhanced liver expression of the Tfrc gene [60]. **(Figure 3)**

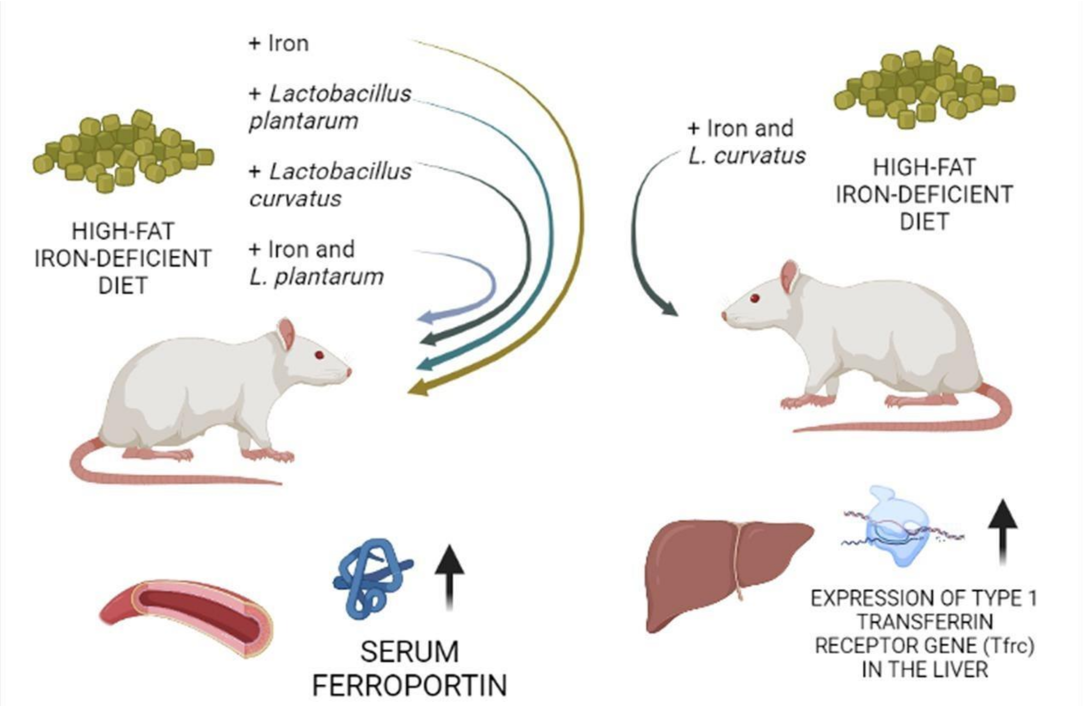

Figure 3: The impact of supplementing the probiotic bacteria Lactobacillus plantarum and Lactobacillus curvatus on specific liver iron metabolism parameters in rats fed a high-fat, iron-deficient diet [60].

5.2.2.2. Discussion:

Several studies have demonstrated the bioavailability of nutrients from probiotics. For example, Calcium bioavailability that is influenced by various factors such as the source of calcium, age, transit time, amount of calcium ingested, intestinal content, and diet. Calcium is absorbed in an ionized and soluble form and through two pathways: transcellular and paracellular. The transcellular pathway is vitamin D dependent and occurs through cytosolic calcium binding protein, while the paracellular pathway is concentration-dependent and occurs through tight junctions between mucosal cells. Most calcium absorption occurs in the small intestine, but probiotics can enhance calcium uptake in the colon through colonic fermentation. Calbindin D9K in mucosal cells regulates hormone-mediated plasma calcium levels.[48]

5.2.3. Benefits probiotics in digestion:

5.2.3.1. Result:

Probiotics (e.g. Lactobacillus, Bifidobacterium)

↓

Positive influence on gut microbiota [61]

↓

Aid in digestion of carbs, proteins, and fats [62]

↓

Breakdown of dietary fiber [62]

↓

Production of short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate [62] [63]

↓

Energy for colonocytes [63]

↓

Lower risk of colon cancer, obesity, and other diseases [63]

↓

Production of lactic acid [63]

↓

Maintenance of gut pH [63]

↓

Hostile environment for harmful bacteria [63]

↓

Prevent and alleviate digestive disorders (e.g. IBS, IBD, diarrhea) [64]

↓

Modulate immune system and reduce inflammation in the gut [65]

5.2.3.2. Discussion

Probiotics have been shown to play a significant role in maintaining overall digestive health by positively influencing the gut microbiota and impacting digestion [61]. The gut microbiota consists of various microorganisms, such as bacteria, fungi, and viruses, that play a crucial role in digestion and the absorption of nutrients [66]. Probiotics produce enzymes that aid in the digestion of carbohydrates, proteins, and fats, and help break down dietary fiber into short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate [62]. These SCFAs provide energy for the colonocytes and have been linked to a lower risk of colon cancer, obesity, and other diseases [63]. Additionally, probiotics produce lactic acid, which helps to maintain the pH of the gut and creates an environment that is hostile to harmful bacteria [63]. Studies have also shown that probiotics can help prevent and alleviate various digestive disorders, such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and diarrhea [64]. Probiotics may also reduce symptoms of IBS and IBD by modulating the immune system and reducing inflammation in the gut [65].

5.2.4. Benefits of probiotics in nutrient absorption:

5.2.4.1. Result:

Probiotics

↓

Enhancement of digestive enzyme activity [67]

↓

Improved breakdown and absorption of carbohydrates, proteins, and fats [65]

↓

Production of proteases, lipases, and lactases [65]

↓

Breakdown of proteins, fats, and lactose into absorbable molecules [65]

↓

Improved absorption of micronutrients such as iron, calcium, and zinc [65]

↓

Fermentation of indigestible carbohydrates [68]

↓

Production of short-chain fatty acids [68]

↓

Utilization of SCFAs as a source of energy by gut epithelial cells [60]

↓

Maintenance of healthy gut environment, Improvement of gut motility and Reduction of inflammation in the gut [60]

↓

Enhanced absorption of iron in the liver [60]

5.2.4.2. Discussion

Probiotics have been shown to play a crucial role in nutrient absorption, especially in the digestion and absorption of carbohydrates, proteins, and fats. The presence of probiotics in the gut has been shown to improve the breakdown and absorption of these nutrients by enhancing the activity of digestive enzymes and increasing the surface area of the intestinal wall for nutrient uptake [67].

Probiotics produce a range of enzymes, including proteases, lipases, and lactases, which aid in the digestion of proteins, fats, and lactose, respectively. These enzymes help break down these macronutrients into smaller, more easily absorbable molecules, allowing for more efficient nutrient uptake by the body. In addition, probiotics have been shown to improve the absorption of micronutrients such as iron, calcium, and zinc [65].

Probiotics can also ferment certain indigestible carbohydrates, such as dietary fiber, producing short-chain fatty acids (SCFAs), which can be utilized as a source of energy by the gut epithelial cells [68]. SCFAs also help maintain a healthy gut environment, improve gut motility, and reduce inflammation in the gut. A study conducted on rats fed with a high-fat diet showed that supplementation with *Lactobacillus plantarum* and *Lactobacillus curvatus* improved the absorption of iron in the liver by enhancing the expression of proteins involved in iron metabolism, such as transferrin and ferritin [60].

5.2.5. Benefits of probiotics for breaking down complex carbohydrates and fibers:

5.2.5.1. Result

Probiotics

⇩

Breakdown of fibers and oligosaccharides [69]

⇩

Degradation of resistant starch [70]

⇩

Production of short-chain fatty acids [68]

⇩

Improved gut barrier function [71]

⇩

Growth of other beneficial bacteria [72]

⇩

Increased production of enzymes for carbohydrate and fiber digestion [73]

⇩

Improved nutrient absorption [74]

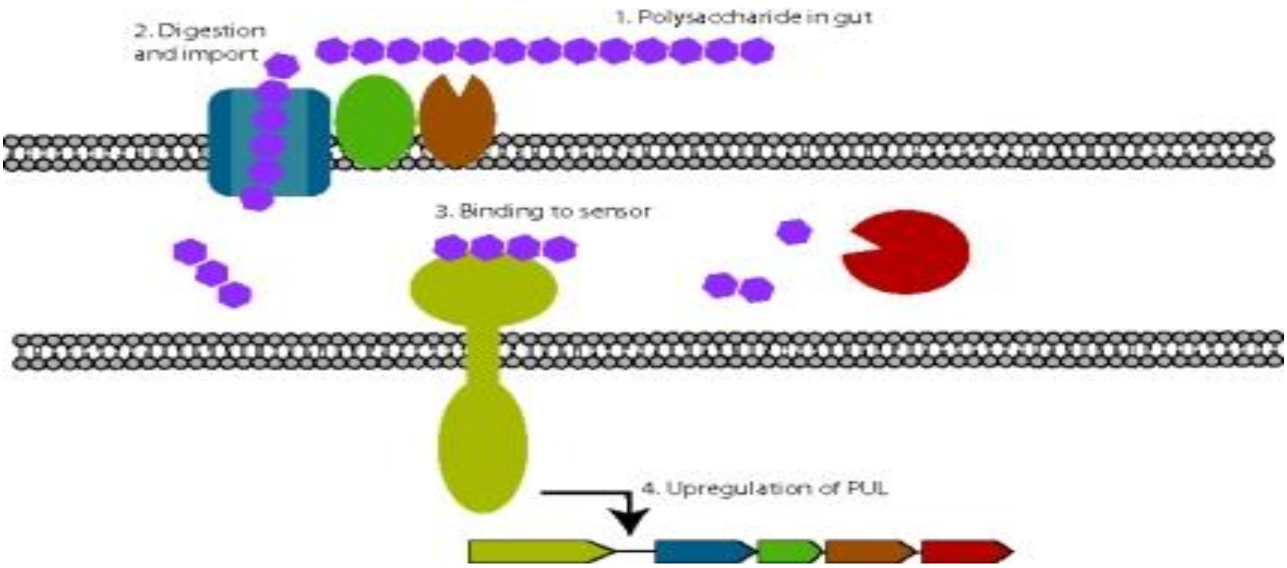

Figure 4: Gut bacteria are able to detect and break down particular plant cell wall polysaccharides and improve human digestive abilities due to the presence of specialized membrane protein complexes [75].

5.2.5.2. Discussion:

Research has shown that probiotics, such as Lactobacillus and Bifidobacterium species, can break down different types of fibers and oligosaccharides, including fructooligosaccharides (FOS) and galactooligosaccharides (GOS) [69]. Additionally, probiotics can also degrade resistant starch, a type of complex carbohydrate that escapes digestion in the small intestine and reaches the colon intact. Resistant starch can be found in foods such as legumes, whole grains, and green bananas [70]. Besides, probiotics have been found to increase the production of enzymes involved in the breakdown of carbohydrates and fibers. For example, *Bifidobacterium infantis* has been shown to enhance the activity of α-glucosidase, an enzyme that breaks down carbohydrates, resulting in improved digestion and absorption of nutrients [76]. In short, probiotics play a significant role in breaking down complex carbohydrates and fibers that are not fully digested by humans. This process results in the production of SCFAs that provide numerous benefits to the colon's health [68], including improved gut barrier function and the growth of other beneficial bacteria. Additionally, probiotics can increase the production of enzymes involved in carbohydrate and fiber digestion, further promoting nutrient absorption [73] [74].

5.2.6. Beneficial effects of probiotics in gut microbiota composition:

5.2.6.1. Result:

Table- 4: Examples of probiotic strains and their benefits on the gut microbiota

Probiotic strain	**Benefits on the gut microbiota**
Lactobacillus acidophilus	Increases bifidobacteria and lactobacilli [77].
Lactobacillus rhamnosus GG	Increases lactobacilli and bifidobacteria, decreases enterobacteria and clostridia [78].
Saccharomyces boulardii	Increases beneficial bacteria, decreases pathogenic bacteria [79]
Streptococcus thermophilus	Increases lactobacilli, bifidobacteria, and other beneficial bacteria [80]

5.2.6.2. Discussion:

The human gut is colonized by a complex community of microorganisms that together make up the gut microbiota. The gut microbiota consists of trillions of microorganisms, including bacteria, archaea, viruses, and fungi, which reside in the lumen of the intestine, as well as in the mucus layer and the intestinal epithelium. The gut microbiota is involved in various physiological processes, such as digestion, nutrient metabolism, immune system development, and protection against pathogens [63] [81]. The composition of the gut microbiota is influenced by various factors, such as diet, genetics, age, and lifestyle. A disruption in the gut microbiota, called dysbiosis, has been linked to various diseases, such as inflammatory bowel disease, obesity, type 2 diabetes, and colorectal cancer [82]. Therefore, maintaining a healthy gut microbiota is crucial for overall health. Probiotics, as live microorganisms, can positively influence the gut microbiota and improve gut health. Probiotics can modify the gut microbiota by colonization, transient interactions, or metabolic activity, resulting in changes in the composition and metabolic function of the gut microbiota [83].

5.2.7. Beneficial effects of probiotics in the absorption of specific nutrients:

5.2.7.1. Result:

The **(Table-5)** below summarizes the probiotic strains, mechanisms, and studies related to the enhancement of nutrient absorption.

Table-5: Summary of the probiotic strains, mechanisms, and studies related to the enhancement of nutrient absorption

Nutrient	Probiotic Strains	Mechanism	Study
Calcium	*Lactobacillus acidophilus, Bifidobacterium lactis*	Increase expression of calcium-binding proteins and activity of alkaline phosphatase	[84]
Iron	*Lactobacillus plantarum, Lactobacillus fermentum*	Increase expression of iron transporters	[85]
Magnesium	*Lactobacillus acidophilus, Bifidobacterium lactis*	Increase expression of magnesium transporters	[86]

5.2.7.2. Discussion:

Probiotics such as *Lactobacillus acidophilus, Bifidobacterium lactis, Lactobacillus plantarum,* and *Lactobacillus fermentum* have been shown to enhance the absorption of calcium, iron, and magnesium, which are essential minerals required for various physiological processes. Probiotics increase the expression of transporters and enzymes required for absorption, leading to increased serum levels of these minerals. However, more research is needed to identify the specific strains and doses of probiotics required for optimal nutrient absorption. [84] [85] [86]

5.2.8. Beneficial effects of probiotics in oral drug bioavailability:

5.2.8.1. Result:

The activity of microbial enzymes in the gut microbiota can affect the absorption and transport of orally administered drugs, as well as alter gastrointestinal properties. This information can help prevent potential drug interactions and inform the design of drug delivery systems **(Figure-5) and (Table-6)** [87]**.**

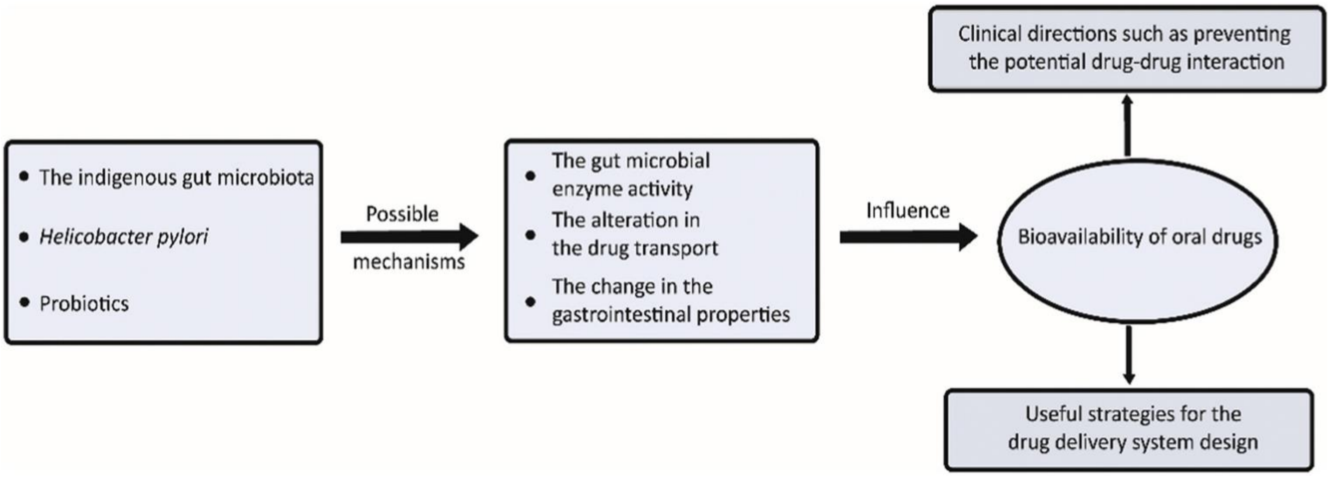

Figure 5: Graphical representation of the gut microbiota may influence the bioavailability of oral drugs [87]

Table-6. The influence of gut microbiota on bioavailability of oral drugs [87].

Drug Class	**Examples of Drugs**	**Influence of Gut Microbiota**
Analgesics	Morphine, Tramadol	Gut microbiota affects analgesic efficacy and toxicity
Antidiabetic	Metformin, Acarbose	Gut microbiota affects drug efficacy and glucose-lowering effect
Cardiovascular	Digoxin, Propranolol	Gut microbiota affects drug metabolism and bioavailability
Chemotherapy	Cyclophosphamide	Gut microbiota affects drug metabolism and toxicity
Immunomodulatory	Tacrolimus, Sirolimus	Gut microbiota affects drug metabolism and bioavailability
NSAIDs	Celecoxib, Naproxen	Gut microbiota affects drug metabolism and toxicity
Steroids	Prednisolone, Dexamethasone	Gut microbiota affects drug metabolism and toxicity
Antibiotics	Penicillin, Amoxicillin	Antibiotics alter gut microbiota composition and drug efficacy
Probiotics	*Lactobacillus acidophilus, Bifidobacterium bifidum*	Can interact with drugs and alter their bioavailability

5.2.8.2. Discussion:

Probiotic strains have been shown to impact the bioavailability of several nutrients, including vitamins and minerals. For instance, Lactobacillus acidophilus has been shown to enhance the bioavailability of vitamins B1, B2, B6, B12, and folate by increasing their production and absorption in the gut [88]. In addition, probiotic strains such as *Bifidobacterium bifidum* and *Lactobacillus reuteri* have been shown to enhance the bioavailability of vitamin D by promoting its synthesis and absorption in the gut [89].

5.2.9. Beneficial effects of probiotics in immune function:

5.2.9.1. Result:

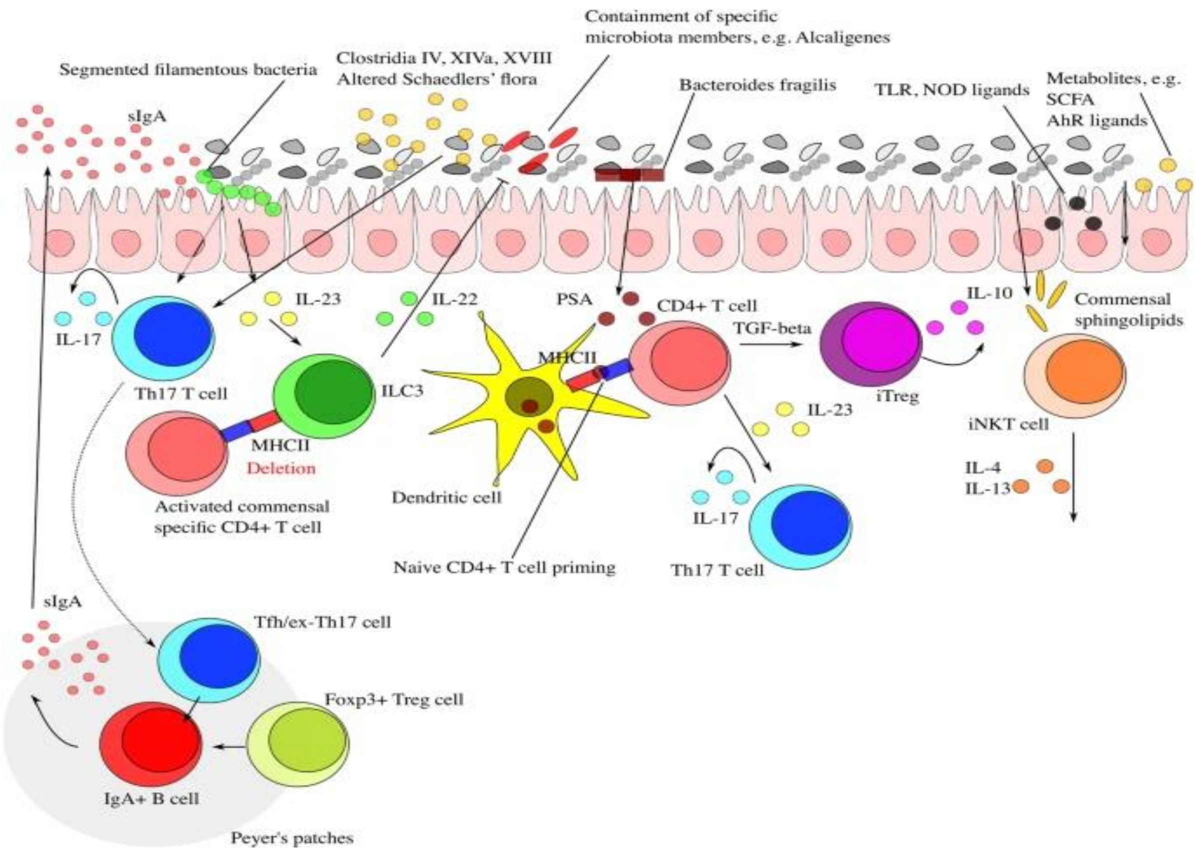

Figure 6: Intestinal microbiota-immunity interplay in homeostasis [90].

Table- 7: Examples of Probiotics and their Impact on the Immune System

Probiotic Strain	Impact on Immune System
Lactobacillus rhamnosus GG	Increases production of IgA antibodies and reduces inflammation [91]
Bifidobacterium lactis BB-12	Increases the production of cytokines and enhances immune function [91]
Lactobacillus casei Shirota	Enhances natural killer cell activity and reduces inflammation [92]
Saccharomyces boulardii	Enhances mucosal immunity and reduces the risk of infectious diseases [93]

5.2.9.2 . Discussion:

Commensal microbes colonize the host's mucosal surfaces during early life, which is crucial for the maturation of the immune system. The microbiota composition displays high variability in the first few years of life before reaching a stable configuration around age three. This variability creates a window of opportunity for environmental incursions to the microbiota, which may have long-lasting harmful impacts on immunity. Newborns and infants have an immature immune system, making them more susceptible to various infectious pathogens and leading to infectious diseases as the leading cause of mortality in children. Premature infants are more prone to excessive inflammation, leading to the potentially devastating disorder necrotizing enterocolitis. Germ-free animal models have shown that the absence of commensal microbes is associated with profound intestinal defects of lymphoid tissue architecture and immune functions. The intestinal mucosa is the best-studied interface for host-microbiota interactions. In a healthy state, the host's immune response to the intestinal microbiota is compartmentalized to the mucosal surface, where mechanisms such as the dense mucus layer, tight junctions, and enteric dendritic cells are employed to achieve microbiota compartmentalization. The host immune system establishes immune tolerance towards an enormous and constantly changing wealth of harmless microorganisms while preserving immune responses against pathogenic infection or commensal intrusion into the sterile body milieu. [90]. Moreover Probiotics have a positive impact on the immune system by modulating the immune response, enhancing immune function, and reducing the risk of infectious diseases. Different probiotic strains may have different beneficial effects on the immune system, and the specific mechanisms by which they exert their beneficial effects are still being investigated. Nevertheless, the evidence suggests that probiotics can be a useful tool for improving immune function and preventing infectious diseases. [90] [91]

5.2.10. Beneficial effects of probiotics in immune cell function:

5.2.10.1. Result:

Probiotics have been shown to have a positive effect on immune cell function. **(Table-7)** summarizes some of the studies that have investigated the effect of probiotics on different immune cells.

Table-8. The beneficial effect of probiotics on immune cell function

Probiotic	**Immune cell type**	**Effect**
Lactobacillus casei Shirota	Natural killer cells	Enhanced activity [94]
Lactobacillus rhamnosus GG	IgA-producing cells	Increased production [95]
Bifidobacterium lactis HN019	T cells	Increased activity [96]
Lactobacillus acidophilus and *Bifidobacterium bifidum*	Macrophages	Increased phagocytic activity [97]

5.2.10.2 Discussion:

Probiotics have been shown to have a significant impact on immune cell function. Immune cells are crucial for defending the body against harmful pathogens and maintaining overall health. Several studies have shown that probiotics can enhance the activity of NK cells. For example, a study of healthy adults found that consuming *Lactobacillus casei Shirota* for 3 weeks resulted in a significant increase in NK cell activity compared to a placebo group. Another study found that daily consumption of a probiotic mixture containing *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium bifidum* for 12 weeks significantly increased NK cell activity in elderly individuals. A study found that consuming Lactobacillus acidophilus for 6 weeks increased the production of T cells in healthy adults. Another study found that daily consumption of a probiotic containing *Lactobacillus rhamnosus* for 6 months increased the production of regulatory T cells, which help to prevent autoimmune diseases. Probiotics have been shown to enhance the phagocytic activity of macrophages. For example, a study found that consuming *Lactobacillus fermentum* for 4 weeks increased the phagocytic activity of macrophages in healthy adults [96] [97] [98].

5.2.11. Beneficial effects of probiotics in immune signaling pathways:

5.2.11.1. Result:

Probiotics have been shown to modulate immune signaling pathways, which are crucial for regulating immune responses. These pathways involve a complex network of cytokines, chemokines, and other immune molecules that communicate between immune cells and tissues. Probiotics can stimulate the production of anti-inflammatory cytokines while suppressing pro-inflammatory cytokines, resulting in a balanced immune response.

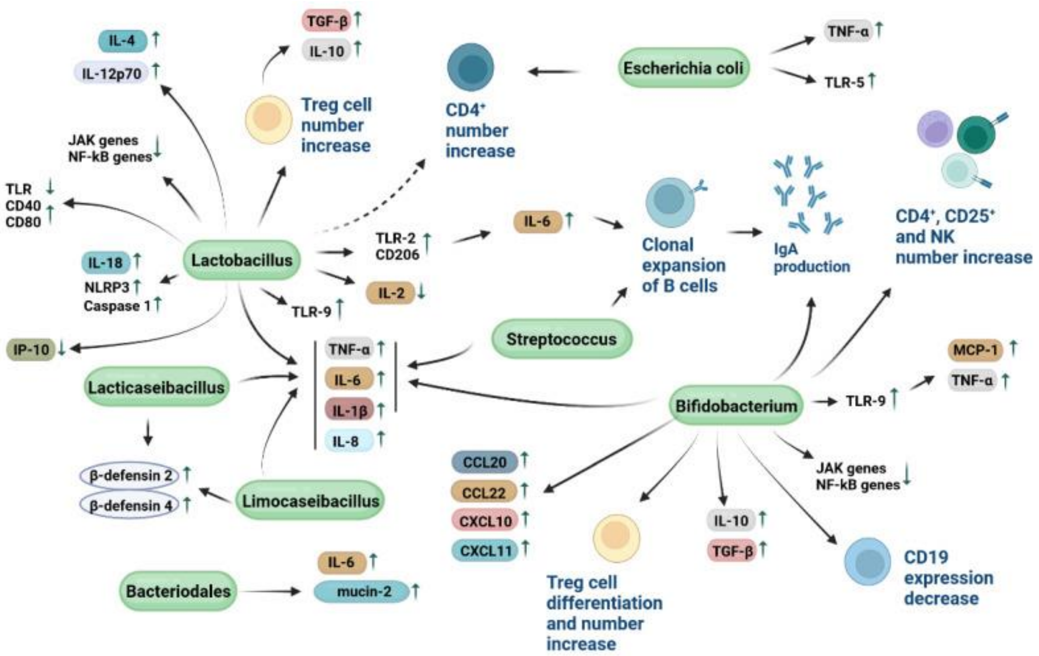

Figure 7: Impact of Probiotics on Immune Signaling Pathways [98].

5.2.11.2. Discussion:

Studies have shown that probiotics can modulate various immune signaling pathways, including Toll-like receptors (TLRs). Probiotics can modulate TLR signaling, which can lead to a reduction in inflammation and an increase in immune tolerance. For example, some strains of *Lactobacillus* and *Bifidobacterium* have been shown to downregulate TLR signaling, reducing the production of pro-inflammatory cytokines. Probiotics can modulate IL production, which can lead to a reduction in inflammation and an increase in immune tolerance. For example, some strains of *Lactobacillus* and *Bifidobacterium* have been shown to stimulate the production of anti-inflammatory cytokines, such as IL-10, while reducing the production of pro-inflammatory cytokines, such as IL-6.Probiotics can modulate NF-κB activation, which can lead to a reduction in inflammation. For example, some strains of Lactobacillus and *Bifidobacterium* have been shown to suppress NF-κB activation, reducing the production of pro-inflammatory cytokines. Probiotics can modulate STAT signaling, which can lead to a reduction in inflammation. For example, some strains of Lactobacillus and *Bifidobacterium* have been shown to modulate STAT3 signaling, reducing the production of pro-inflammatory cytokines. Again, some strains of Lactobacillus and *Bifidobacterium* have been shown to reduce the expression of pro-inflammatory cytokine receptors on immune cells, reducing the response to pro-inflammatory cytokines. [98]

5.2.12. Beneficial effects of probiotics in inflammatory bowel disease:

5.2.12.1. Result:

Probiotics have been extensively studied as a potential therapeutic option for IBD due to their ability to modulate the gut microbiota and immune system. Here are some examples of the impact of probiotics on IBD: **(Table-9)**

Table-9: The following table summarizes some of the key studies investigating the benefits of probiotics on IBD

Probiotic Strain	IBD Type	Study Design	Findings
Lactobacillus acidophilus	Crohn's Disease	Double-blind, placebo-controlled trial [99]	No significant effect on disease activity, but improved quality of life
Bifidobacterium bifidum, Lactobacillus acidophilus, Lactobacillus rhamnosus	Ulcerative Colitis	Randomized controlled trial [100]	Reduced disease activity and improved mucosal inflammation
VSL#3 (mixture of 8 probiotic strains)	Ulcerative Colitis	Randomized controlled trial [101]	Induced remission in active disease and maintained remission in quiescent disease
E. coli Nissle 1917	Ulcerative Colitis	Double-blind, placebo-controlled trial [102]	Induced and maintained remission
Lactobacillus rhamnosus GG	Ulcerative Colitis	Randomized controlled trial [103]	Reduced disease activity and improved mucosal inflammation
Lactobacillus plantarum 299v	Ulcerative Colitis	Randomized controlled trial [104]	Reduced disease activity and improved mucosal inflammation

5.2.12.2. Discussion:

The available evidence suggests that probiotics may have a beneficial effect on IBD. However, further research is needed to fully understand the mechanisms underlying these beneficial effects and to identify the most effective probiotic strains and dosages for the treatment of IBD. [104]

5.2.13. Beneficial effects of probiotics in the gut-brain axis:

5.2.13.1. Result:

Several studies have shown that probiotics have potential benefits in the prevention and treatment of metabolic disorders.

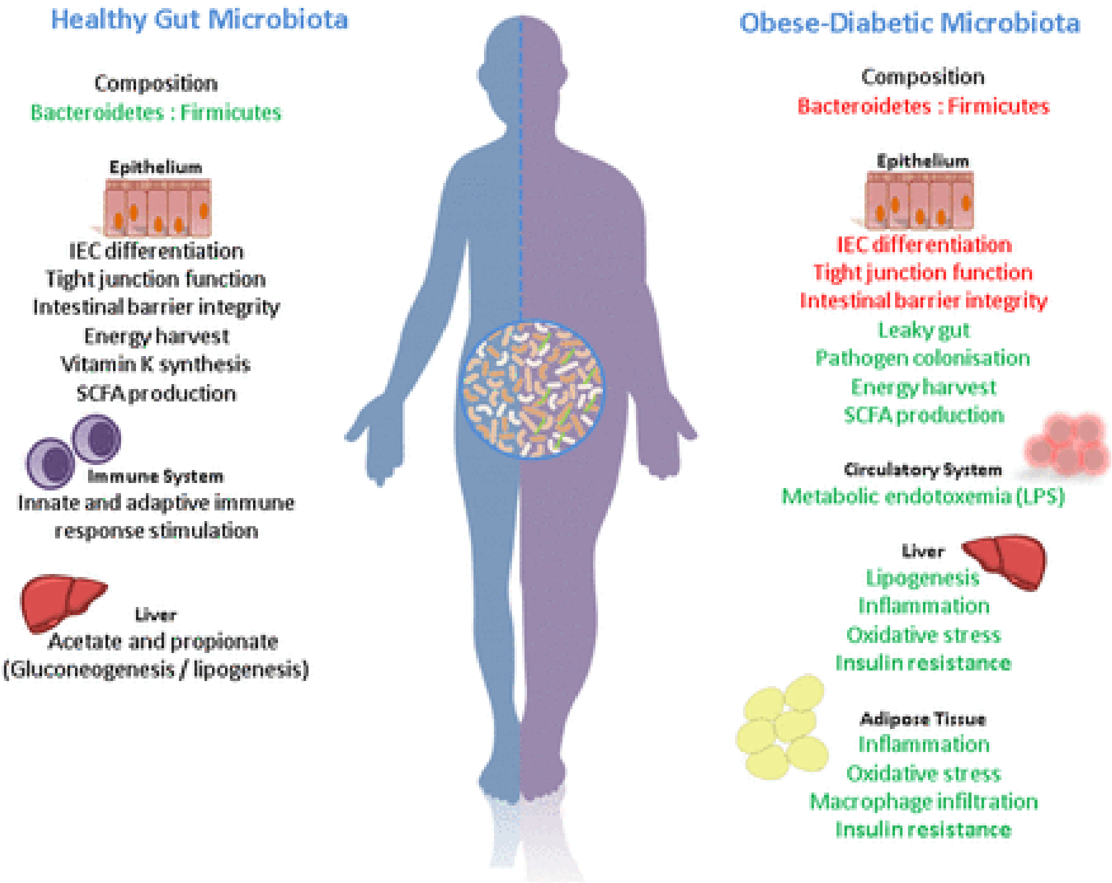

Figure-8: The gut microbiota of obese and diabetic individuals exhibit significant differences in their composition and function compared to healthy individuals [105].

5.2.13.2. Discussion:

One meta-analysis of randomized controlled trials found that probiotic supplementation significantly reduced body weight, body mass index (BMI), and fat percentage in overweight and obese adults [106]. Another meta-analysis showed that probiotics improved glucose metabolism, insulin sensitivity, and glycemic control in people with type 2 diabetes [107]. Probiotics have also shown promise in the prevention and treatment of NAFLD. A meta-analysis of clinical trials found that probiotics significantly improved liver enzymes, liver fat, and inflammation in people with NAFLD [108].

5.2.14. Beneficial effects of probiotics in the gut-brain axis:

5.2.14.1. Result:

The gut-brain axis refers to the bidirectional communication network between the gut and the brain. Some studies have found that certain probiotic strains can increase the production of neurotransmitters such as serotonin and GABA in the gut, which may have a positive impact on mood and behavior [109] [110]. Other studies have shown that probiotics can reduce levels of stress hormones such as cortisol, and may also have anti-inflammatory effects that can benefit both the gut and the brain [111].

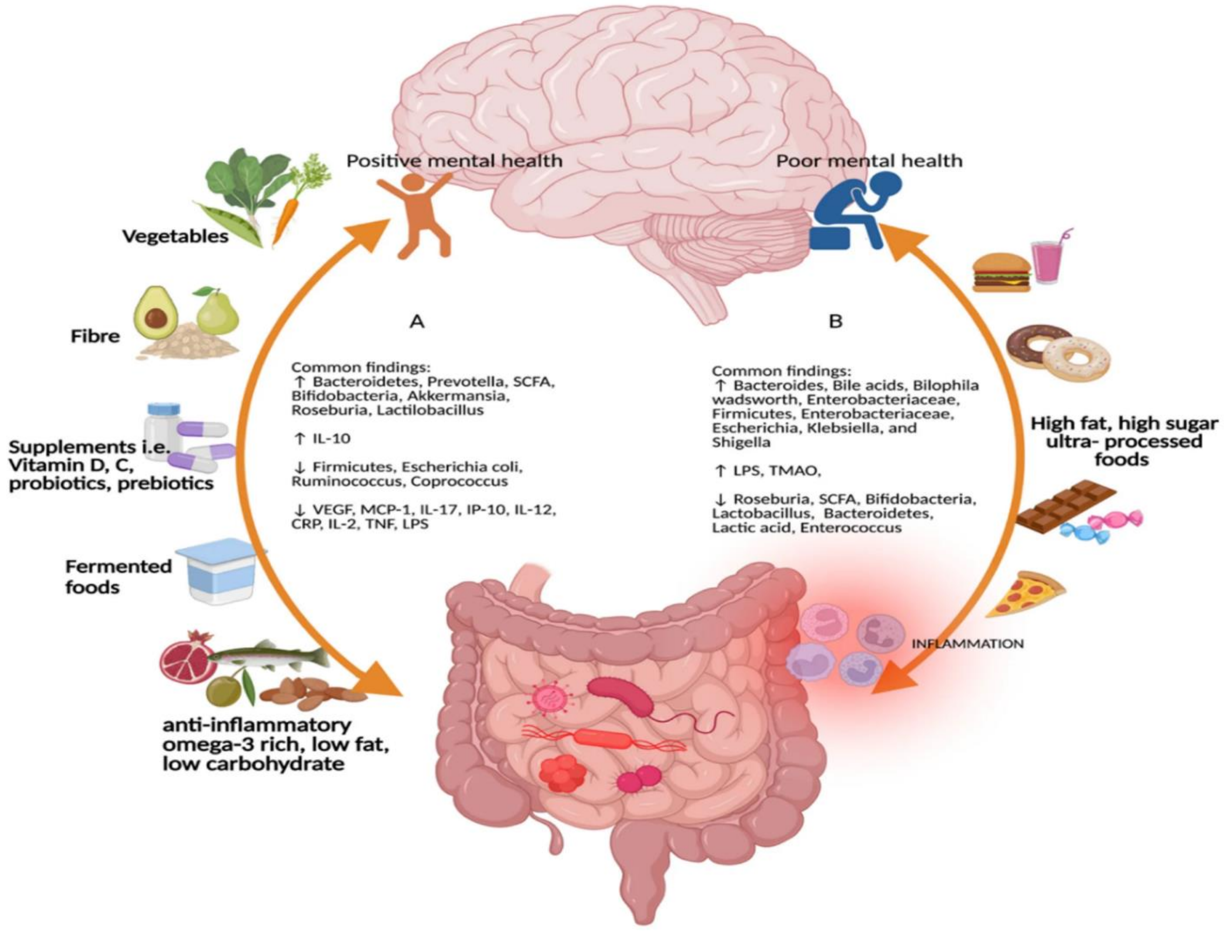

Figure-9: The figure shows the common findings for different types of diets on the gut-brain-microbiome axis [111].

5.2.14.2. Discussion:

The mechanisms underlying the beneficial effects of probiotics on the gut-brain axis are complex and not yet fully understood. However, several potential mechanisms have been proposed, including the Regulation of the hypothalamic-pituitary-adrenal (HPA) axis, which is a key regulator of the stress response, and dysregulation of this system has been implicated in the pathogenesis of stress-related disorders. Probiotics have been shown to modulate the HPA axis, reducing stress-induced activation of the axis and resulting in reduced anxiety- and depression-like behaviors [112] [113]. Probiotics can alter the levels of neurotransmitters such as serotonin and dopamine, which are involved in the regulation of mood and behavior [114] [115]. Again, the gut microbiota plays a crucial role in the development and function of the immune system, and dysregulation of the immune system has been linked to the pathogenesis of neuropsychiatric disorders. Probiotics can modulate the immune system, resulting in reduced inflammation and improved mental health outcomes [116] [117]. Additionally, *Lactobacillus* and *Bifidobacterium* strains have been found to increase the production of neurotransmitters such as serotonin, gamma-aminobutyric acid (GABA), and acetylcholine [110]. Some strains of probiotics may produce neurotransmitters directly [118].

5.2.15. Beneficial effects of probiotics in the gut-liver axis:

5.2.15.1. Result:

The gut microbiota plays a significant role in liver metabolism and homeostasis [119]. Dysbiosis, or an imbalance in gut microbiota, can lead to an increased risk of liver disease, including non-alcoholic fatty liver disease (NAFLD) and cirrhosis [108]. A study in patients with alcoholic cirrhosis found that a probiotic containing *Lactobacillus rhamnosus* and *Bifidobacterium lactis* improved liver function and reduced markers of inflammation [120].

Table-10: Probiotic strains and their benefits on the gut-liver axis

Probiotic Strain	**Benefits on Gut-Liver Axis**
Lactobacillus rhamnosus and Bifidobacterium lactis	Improved liver function and reduced markers of inflammation in patients with alcoholic cirrhosis [120].
Lactobacillus plantarum	Reduced liver damage and inflammation in animal models of liver disease [121].
Saccharomyces boulardii	Reduced liver damage and fibrosis in animal models of liver disease [122].

5.2.15.2. Discussion:

Certain probiotic strains, such as *Lactobacillus plantarum,* have been shown to reduce liver damage and inflammation in animal models of liver disease by promoting the production of enzymes involved in liver detoxification [123]. Probiotics have also been shown to improve liver function by modulating the gut microbiome composition. Studies have found that probiotics can reduce the levels of harmful bacteria in the gut, such as *Escherichia coli* and *Enterococcus*, and increase the levels of beneficial bacteria, such as *Lactobacillus* and *Bifidobacterium* [124]. This modulation of the gut microbiome can improve liver function by reducing inflammation and oxidative stress in the liver. In addition, a study found that treatment with the probiotic strain *Saccharomyces boulardii* improved liver function and reduced liver damage and fibrosis in animal models of liver disease [125].

5.3. Limitations and future directions:

5.3.1. Discussion of the limitations of the study:

5.3.1.1. Methodological limitations:

One of the main methodological limitations of studies investigating the beneficial effects of probiotics is the lack of standardization of the strains and doses used. The efficacy of a specific probiotic strain may differ depending on the dose and the population studied. Additionally, the beneficial effects of probiotics may also depend on the specific health condition and the duration of the intervention. Therefore, future studies should aim to use standardized doses of specific probiotic strains in well-designed randomized controlled trials.

5.3.1.2. Interpretational limitations:

Another limitation is the complexity of the gut microbiome and the gut-brain axis, which makes it challenging to establish clear causal relationships between probiotic interventions and their benefits on mental and metabolic health. Moreover, the heterogeneity of the study populations, the differences in study designs and outcome measures, and the lack of long-term follow-up data further complicate the interpretation of the results. Therefore, more studies are needed to elucidate the mechanisms of action of probiotics and to identify the specific subpopulations that may benefit the most from their use.

Overall, while the existing evidence suggests that probiotics may have promising effects on the gut-brain and gut-liver axes and on metabolic health, further studies are needed to overcome the limitations of current research and to establish their clinical relevance.

5.3.2. Recommendations for future research on the topic

5.3.2.1. The need for further research on the impact of probiotics on specific health outcomes:

While there is increasing evidence to suggest that probiotics can have a positive impact on health outcomes, the exact mechanisms and specific health benefits are not yet fully understood. Future research should focus on investigating the impact of probiotics on specific health outcomes, such as inflammatory bowel disease, irritable bowel syndrome, allergies, and mental health conditions, to better understand their potential benefits and mechanisms of action.

5.3.2.2. The need for studies investigating the beneficial effect of probiotics on different populations and age groups:

Most studies on probiotics have focused on healthy adults, and there is limited research on the effect of probiotics on different populations, such as children, older adults, and those with underlying health conditions. Future studies should investigate the impact of probiotics on different populations to determine whether there are any age-related or health-related differences in their effectiveness. Additionally, studies should investigate the optimal dose and duration of probiotic use for different populations and health outcomes.

CHAPTER-6

CONCLUSION

6. Conclusion:

In conclusion, probiotics have gained attention as a potential dietary supplement with numerous health benefits. The gut microbiome is a complex system that plays a crucial role in human health, and probiotics have shown promising results in regulating and maintaining a healthy gut microbiome. The reviewed literature suggests that probiotics can modulate the gut-brain axis, gut-liver axis, and metabolism, which in turn affects mental health, liver function, and insulin sensitivity. However, there are still methodological and interpretational limitations in the studies, indicating the need for further research. Therefore, it is recommended to conduct more randomized controlled trials investigating the beneficial effects of probiotics on specific health outcomes in different populations and age groups. Despite these limitations, the potential health benefits of probiotics suggest their inclusion in a healthy diet, and their use as a dietary supplement may prove to be an effective strategy for maintaining overall health and well-being.

CHAPTER-7

REFERENCES

7. References:

[1] C. Hill *et al.*, "The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic," *Nat. Rev. Gastroenterol. Hepatol. 2014 118*, vol. 11, no. 8, pp. 506–514, Jun. 2014, doi: 10.1038/nrgastro.2014.66.

[2] G. Gibson, R. Hutkins, … M. S.-N. reviews, and undefined 2017, "Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of," *nature.com*, vol. 8, pp. 491–502, Aug. 2017, Accessed: Mar. 30, 2023. [Online]. Available: https://www.nature.com/articles/nrgastro.2017.75

[3] National Institutes of Health (NIH), "Probiotics - Health Professional Fact Sheet," Jun. 02, 2022. https://ods.od.nih.gov/factsheets/Probiotics-HealthProfessional/ (accessed Mar. 30, 2023).

[4] L. M. Proctor, "The human microbiome project in 2011 and beyond," *Cell Host Microbe*, vol. 10, no. 4, pp. 287–291, Oct. 2011, doi: 10.1016/j.chom.2011.10.001.

[5] A. Madison, J. K.-G.-C. opinion in behavioral sciences, and undefined 2019, "Stress, depression, diet, and the gut microbiota: human–bacteria interactions at the core of psychoneuroimmunology and nutrition," *Elsevier*, vol. 28, pp. 105–10, Aug. 2019, Accessed: Mar. 30, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S2352154618301608

[6] I. Rowland *et al.*, "Gut microbiota functions: metabolism of nutrients and other food components," *Eur. J. Nutr.*, vol. 57, no. 1, Feb. 2018, doi: 10.1007/S00394-017-1445-8.

[7] M. Giron, M. Thomas, D. Dardevet, C. Chassard, and I. Savary-Auzeloux, "Gut microbes and muscle function: can probiotics make our muscles stronger?," *J. Cachexia. Sarcopenia Muscle*, vol. 13, no. 3, pp. 1460–1476, Jun. 2022, doi: 10.1002/JCSM.12964.

[8] B. J. Lee and Y. T. Bak, "Irritable Bowel Syndrome, Gut Microbiota and Probiotics," *J. Neurogastroenterol. Motil.*, vol. 17, no. 3, p. 252, Jul. 2011, doi: 10.5056/JNM.2011.17.3.252.

[9] S. Bibbò *et al.*, "Gut microbiota in anxiety and depression: Pathogenesis and therapeutics," *Front. Gastroenterol.*, vol. 1, p. 25, Oct. 2022, doi: 10.3389/FGSTR.2022.1019578.

[10] T. G. Dinan and J. F. Cryan, "Melancholic microbes: A link between gut microbiota and depression?," *Neurogastroenterol. Motil.*, vol. 25, no. 9, pp. 713–719, Sep. 2013, doi: 10.1111/NMO.12198.

[11] M. E. Segers and S. Lebeer, "Towards a better understanding of Lactobacillus rhamnosus GG - host interactions," *Microb. Cell Fact.*, vol. 13, pp. 1–6, Aug. 2014, doi: 10.1186/1475-2859-13-S1-S7.

[12] R. Sansanwal, U. Ahlawat, and R. Dhanker, "Yoghurt: A Predigested Food for Lactose-Intolerant People," *Int.J.Curr.Microbiol.App.Sci*, vol. 6, no. 12, pp. 1408–

1418, 2017, doi: 10.20546/ijcmas.2017.612.158.

[13] T. Kelesidis, C. P.-T. advances in, and undefined 2012, “Efficacy and safety of the probiotic Saccharomyces boulardii for the prevention and therapy of gastrointestinal disorders,” *journals.sagepub.com*, vol. 5, no. 2, pp. 111–125, Mar. 2012, doi: 10.1177/1756283X11428502.

[14] K. Chen *et al.*, “Efficacy of Bifidobacterium animalis subsp. lactis, BB-12® on infant colic – A randomised, double-blinded, placebo-controlled study,” *Benef. Microbes*, vol. 12, no. 6, pp. 531–540, Nov. 2021, doi: 10.3920/BM2020.0233.

[15] M. Fidanza, P. Panigrahi, and T. R. Kollmann, “Lactiplantibacillus plantarum–Nomad and Ideal Probiotic,” *Front. Microbiol.*, vol. 12, p. 2911, Oct. 2021, doi: 10.3389/FMICB.2021.712236/BIBTEX.

[16] E. M. M. Elleithy *et al.*, “Influence of dietary Bacillus coagulans and/or Bacillus licheniformis-based probiotics on performance, gut health, gene expression, and litter quality of broiler chickens,” *Trop. Anim. Health Prod.*, vol. 55, no. 1, p. 38, Feb. 2023, doi: 10.1007/S11250-023-03453-2.

[17] Creative Enzymes, “Classification of Probiotics | Creative Enzymes,” Jan. 01, 2023. https://probiotic.creative-enzymes.com/classification-of-probiotics.html (accessed Mar. 30, 2023).

[18] Cleveland Clinic, “Probiotics: What is it, Benefits, Side Effects, Food & Types,” 2023. https://my.clevelandclinic.org/health/articles/14598-probiotics (accessed Mar. 30, 2023).

[19] M. A. Bari, M. R. Islam, M. A. Bari, and M. R. Islam, “Probiotics: A New Horizon for Treating Childhood Diarrhea in Bangladesh,” *Food Nutr. Sci.*, vol. 8, no. 6, pp. 613–623, Jun. 2017, doi: 10.4236/FNS.2017.86043.

[20] B. R. Goldin, “Health benefits of probiotics,” *Br. J. Nutr.*, vol. 80, no. S2, pp. S203–S207, Jan. 1998, doi: 10.1017/S0007114500006036.

[21] H. S. Ejtahed, J. Mohtadi-Nia, A. Homayouni-Rad, M. Niafar, M. Asghari-Jafarabadi, and V. Mofid, “Probiotic yogurt improves antioxidant status in type 2 diabetic patients,” *Nutrition*, vol. 28, no. 5, pp. 539–543, May 2012, doi: 10.1016/J.NUT.2011.08.013.

[22] C. R. Kok and R. Hutkins, “Yogurt and other fermented foods as sources of health-promoting bacteria,” *Nutr. Rev.*, vol. 76, no. Suppl 1, pp. 4–15, Dec. 2018, doi: 10.1093/NUTRIT/NUY056.

[23] L. Kumar, L. Pugalenthi, M. Ahmad, S. R.- Cureus, and undefined 2022, “Probiotics in Irritable Bowel Syndrome: A Review of Their Therapeutic Role,” *cureus.com*, vol. 14, no. 4, Apr. 2022, Accessed: Mar. 30, 2023. [Online]. Available: https://www.cureus.com/articles/92454-probiotics-in-irritable-bowel-syndrome-a-review-of-their-therapeutic-role

[24] M. Noorifard, E. Ebrahimi, … A. M.-A. of M. and, and undefined 2020, “Effects of Probiotic Supplementation on Immune Response in Soldiers: A Randomized, Double-Blinded, Placebo-Controlled Trial,” *brieflands.com*, vol. 18, no. 3, Sep. 2020,

Accessed: Mar. 30, 2023. [Online]. Available: https://brieflands.com/articles/amhsr-100540.html

[25] Healthline, “8 Health Benefits of Probiotics,” 2023. https://www.healthline.com/nutrition/8-health-benefits-of-probiotics#heart-health (accessed Apr. 04, 2023).

[26] C. Hill, F. Guarner, G. Reid, … G. G.-N. reviews, and undefined 2014, “The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic,” *nature.com*, vol. 8, pp. 506–14, Aug. 2014, Accessed: Apr. 05, 2023. [Online]. Available: https://www.nature.com/articles/nrgastro.2014.66)

[27] F. Yan and D. B. Polk, “Probiotics and immune health,” *Curr. Opin. Gastroenterol.*, vol. 27, no. 6, pp. 496–501, Oct. 2011, doi: 10.1097/MOG.0B013E32834BAA4D.

[28] I. Sergeev, T. Aljutaily, G. Walton, E. H.- Nutrients, and undefined 2020, “Effects of synbiotic supplement on human gut microbiota, body composition and weight loss in obesity,” *mdpi.com*, vol. 12, no. 1, p. 222, Jan. 2020, doi: 10.3390/nu12010222.

[29] S. Park, J. B.-N. research, and undefined 2015, “Probiotics for weight loss: a systematic review and meta-analysis,” *Elsevier*, vol. 35, no. 7, pp. 566–75, Jul. 2015, Accessed: Apr. 04, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0271531715001037

[30] S. Fijan, “Microorganisms with claimed probiotic properties: An overview of recent literature,” *Int. J. Environ. Res. Public Health*, vol. 11, no. 5, pp. 4745–4767, May 2014, doi: 10.3390/IJERPH110504745.

[31] M. Jones, C. Martoni, S. P.-T. J. of Clinical, and undefined 2013, “Oral Supplementation With Probiotic L. reuteri NCIMB 30242 Increases Mean Circulating 25-Hydroxyvitamin D: A Post Hoc Analysis of a Randomized Controlled Trial,” *academic.oup.com*, vol. 98, no. 7, pp. 2944–51, Jul. 2013, Accessed: Apr. 05, 2023. [Online]. Available: https://academic.oup.com/jcem/article-abstract/98/7/2944/2537145

[32] L. V. McFarland, “Systematic review and meta-analysis of saccharomyces boulardii in adult patients,” *World J. Gastroenterol.*, vol. 16, no. 18, pp. 2202–2222, Nov. 2010, doi: 10.3748/WJG.V16.I18.2202.

[33] K. Dylag, … M. H.-M.-C., and undefined 2014, “Probiotics in the mechanism of protection against gut inflammation and therapy of gastrointestinal disorders,” *ingentaconnect.com*, vol. 20, no. 7, pp. 1149–56, Feb. 2014, Accessed: Apr. 05, 2023. [Online]. Available: https://www.ingentaconnect.com/content/ben/cpd/2014/00000020/00000007/art00013

[34] J. Plaza-Díaz, F. Ruiz-Ojeda, L. Vilchez-Padial, A. G.- Nutrients, and undefined 2017, “Evidence of the anti-inflammatory effects of probiotics and synbiotics in intestinal chronic diseases,” *mdpi.com*, vol. 9, no. 6, p. 555, Jun. 2017, doi: 10.3390/nu9060555.

[35] G. Fabbrocini, M. Bertona, Picazo, H. Pareja-Galeano, G. Monfrecola, and E. Emanuele, “Supplementation with Lactobacillus rhamnosus SP1 normalises skin expression of genes implicated in insulin signalling and improves adult acne,” *Benef.*

Microbes, vol. 7, no. 5, pp. 625–630, Nov. 2016, doi: 10.3920/BM2016.0089.

[36] Q. Zhang, Y. Wu, X. F.- Medicina, and undefined 2016, "Effect of probiotics on glucose metabolism in patients with type 2 diabetes mellitus: A meta-analysis of randomized controlled trials," *mdpi.com*, vol. 52, no. 1, pp. 28–34, Feb. 2016, doi: 10.1016/j.medici.2015.11.008.

[37] H. Ejtahed, J. Mohtadi-Nia, A. H.-R.- Nutrition, and undefined 2012, "Probiotic yogurt improves antioxidant status in type 2 diabetic patients," *Elsevier*, vol. 28, no. 5, pp. 539–43, May 2012, Accessed: Apr. 05, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0899900711003108

[38] Z. Asemi, Z. Zare, H. Shakeri, … S. S.-A. of nutrition and, and undefined 2013, "Effect of multispecies probiotic supplements on metabolic profiles, hs-CRP, and oxidative stress in patients with type 2 diabetes," *karger.com*, vol. 63, no. 1–2, pp. 1–9, 2013, Accessed: Apr. 05, 2023. [Online]. Available: https://www.karger.com/Article/Abstract/349922

[39] K. Banach, P. Glibowski, and P. Jedut, "The effect of probiotic Yogurt containing lactobacillus acidophilus LA-5 and bifidobacterium lactis BB-12 on selected anthropometric parameters in obese individuals on an energy-restricted diet: A randomized, controlled trial," *Appl. Sci.*, vol. 10, no. 17, p. 5830, Sep. 2020, doi: 10.3390/APP10175830.

[40] Y. Kadooka, A. Ogawa, K. Ikuyama, M. S.-I. dairy journal, and undefined 2011, "The probiotic Lactobacillus gasseri SBT2055 inhibits enlargement of visceral adipocytes and upregulation of serum soluble adhesion molecule (sICAM-1) in rats," *Elsevier*, vol. 21, no. 9, pp. 623–7, Sep. 2011, Accessed: Apr. 05, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0958694611000410

[41] P. Wang *et al.*, "Gut microbiota involved in desulfation of sulfated progesterone metabolites: A potential regulation pathway of maternal bile acid homeostasis during pregnancy," *Front. Microbiol.*, vol. 13, p. 4194, Oct. 2022, doi: 10.3389/FMICB.2022.1023623/PDF.

[42] R. Rao Ambati, R. Krishna Kota, A. Kumar Yalakurthi, K. Srirama, and P. Narayana Reddy, "Recent advances in probiotics as live biotherapeutics against gastrointestinal diseases," *ingentaconnect.com*, vol. 24, no. 27, pp. 3162–71, Aug. 2018, doi: 10.2174/1381612824666180717105128.

[43] H. Dale, S. Rasmussen, Ö. Asiller, G. L.- Nutrients, and undefined 2019, "Probiotics in irritable bowel syndrome: an up-to-date systematic review," *mdpi.com*, vol. 9, p. 2048, Sep. 2019, doi: 10.3390/nu11092048.

[44] Y. Zhao, B. R. Dong, and Q. Hao, "Probiotics for preventing acute upper respiratory tract infections," *Cochrane Database Syst. Rev.*, vol. 2022, no. 8, Aug. 2022, doi: 10.1002/14651858.CD006895.PUB4/ABSTRACT.

[45] D. G. de Llano, M. Moreno-Arribas, B. B.- Molecules, and undefined 2020, "Cranberry polyphenols and prevention against urinary tract infections: relevant considerations," *mdpi.com*, vol. 25, no. 15, p. 3523, Aug. 2020, doi: 10.3390/molecules25153523.

[46] C. Hill *et al.*, "The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic," *Nat. Rev. Gastroenterol. Hepatol. 2014 118*, vol. 11, no. 8, pp. 506–514, Jun. 2014, doi: 10.1038/nrgastro.2014.66.

[47] M. Giron, M. Thomas, D. Dardevet, C. Chassard, and I. Savary-Auzeloux, "Gut microbes and muscle function: can probiotics make our muscles stronger?," *J. Cachexia. Sarcopenia Muscle*, vol. 13, no. 3, pp. 1460–1476, Jun. 2022, doi: 10.1002/JCSM.12964.

[48] Q. Gu, P. Li, Q. Gu, and P. Li, "Biosynthesis of Vitamins by Probiotic Bacteria," *Probiotics Prebiotics Hum. Nutr. Heal.*, Jul. 2016, doi: 10.5772/63117.

[49] L. Steenbergen, R. Sellaro, S. van H.- Brain, undefined behavior, undefined and, and undefined 2015, "A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood," *Elsevier*, vol. 48, pp. 258–64, Aug. 2015, Accessed: Apr. 04, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0889159115000884

[50] D. Benton, C. Williams, A. B.-E. journal of clinical nutrition, and undefined 2007, "Impact of consuming a milk drink containing a probiotic on mood and cognition," *nature.com*, vol. 61, no. 3, pp. 365–61, Mar. 2007, Accessed: Apr. 02, 2023. [Online]. Available: https://www.nature.com/articles/1602546

[51] M. Messaoudi, N. Violle, J.-F. Bisson, D. Desor, H. Javelot, and C. Rougeot, "Beneficial psychological effects of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in healthy human volunteers," *Taylor Fr.*, vol. 2, no. 4, pp. 256–61, Jul. 2011, doi: 10.4161/gmic.2.4.16108.

[52] A. V. Rao *et al.*, "A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome," *Gut Pathog.*, vol. 1, no. 1, pp. 1–6, Dec. 2009, doi: 10.1186/1757-4749-1-6.

[53] R. Slykerman, F. Hood, K. Wickens, J. T.- EBioMedicine, and undefined 2017, "Effect of Lactobacillus rhamnosus HN001 in pregnancy on postpartum symptoms of depression and anxiety: a randomised double-blind placebo-controlled," *Elsevier*, vol. 24, pp. 159–65, Oct. 2017, Accessed: Apr. 02, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S2352396417303663

[54] R. Huang, K. Wang, J. H.- Nutrients, and undefined 2016, "Effect of probiotics on depression: a systematic review and meta-analysis of randomized controlled trials," *mdpi.com*, vol. 8, p. 483, Aug. 2016, Accessed: Apr. 02, 2023. [Online]. Available: https://www.mdpi.com/2072-6643/8/8/483/htm?utm_source=deleted&utm_medium=deleted&utm_term=deleted&utm_content=deleted&utm_campaign=deleted&gclid=deleted

[55] H. Wang, I. Lee, C. Braun, … P. E. neurogastroenterology and, and undefined 2016, "Effect of probiotics on central nervous system functions in animals and humans: a systematic review," *ncbi.nlm.nih.gov*, vol. 4, p. 589, Oct. 2016, Accessed: Apr. 04, 2023. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5056568/

[56] Creative Biolabs, "Probiotics on Central Nervous System Functions - Creative Biolabs," 2023. https://www.creative-biolabs.com/immuno-oncology/probiotics-on-

central-nervous-system-functions.htm (accessed Apr. 04, 2023).

[57] A. A. Mohammadi *et al.*, "The effects of probiotics on mental health and hypothalamic–pituitary–adrenal axis: A randomized, double-blind, placebo-controlled trial in petrochemical workers," *Nutr. Neurosci.*, vol. 19, no. 9, pp. 387–395, Nov. 2016, doi: 10.1179/1476830515Y.0000000023.

[58] G. Akkasheh, Z. Kashani-Poor, M. T.-E.- Nutrition, and undefined 2016, "Clinical and metabolic response to probiotic administration in patients with major depressive disorder: a randomized, double-blind, placebo-controlled trial," *Elsevier*, vol. 32, no. 3, pp. 315–20, Mar. 2016, doi: 10.1016/j.clnu.2016.08.015.

[59] M. Dubey, V. P.-T. open nutrition journal, and undefined 2018, "Probiotics: A promising tool for calcium absorption," *benthamopen.com*, vol. 12, no. 1, Aug. 2018, Accessed: Apr. 02, 2023. [Online]. Available: https://benthamopen.com/ABSTRACT/TONUTRJ-12-59

[60] K. Skrypnik, … A. O.-S.-J. of F., and undefined 2022, "Influence of supplementation of probiotic bacteria Lactobacillus plantarum and Lactobacillus curvatus on selected parameters of liver iron metabolism in rats," *Elsevier*, vol. 96, p. 105205, Sep. 2022, Accessed: Apr. 04, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S1756464622002754

[61] C. Hill, F. Guarner, G. Reid, … G. G.-N. reviews, and undefined 2014, "The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic," *nature.com*, vol. 8, pp. 506–14, Aug. 2014, Accessed: Apr. 04, 2023. [Online]. Available: https://www.nature.com/articles/nrgastro.2014.66)

[62] Y. P. Silva, A. Bernardi, and R. L. Frozza, "The Role of Short-Chain Fatty Acids From Gut Microbiota in Gut-Brain Communication," *Front. Endocrinol. (Lausanne).*, vol. 11, pp. 11–25, Jan. 2020, doi: 10.3389/FENDO.2020.00025/FULL.

[63] G. Wang *et al.*, "Role of SCFAs in gut microbiome and glycolysis for colorectal cancer therapy," *J. Cell. Physiol.*, vol. 234, no. 10, pp. 17023–17049, Oct. 2019, doi: 10.1002/JCP.28436.

[64] C. Hedin, K. Whelan, J. L.-P. of the N. Society, and undefined 2007, "Evidence for the use of probiotics and prebiotics in inflammatory bowel disease: a review of clinical trials," *cambridge.org*, vol. 66, no. 3, pp. 307–15, Aug. 2007, doi: 10.1017/S0029665107005563.

[65] J. Plaza-Díaz, F. Ruiz-Ojeda, L. Vilchez-Padial, A. G.- Nutrients, and undefined 2017, "Evidence of the anti-inflammatory effects of probiotics and synbiotics in intestinal chronic diseases," *mdpi.com*, vol. 9, no. 6, p. 555, May 2017, doi: 10.3390/nu9060555.

[66] R. Sender, S. Fuchs, and R. Milo, "Revised Estimates for the Number of Human and Bacteria Cells in the Body," *PLoS Biol.*, vol. 14, no. 8, p. 1e1002533, Aug. 2016, doi: 10.1371/JOURNAL.PBIO.1002533.

[67] N. Delzenne, & P. C.-C. O. in C. N., and undefined 2005, "A place for dietary fibre in the management of the metabolic syndrome," *journals.lww.com*, vol. 8, no. 6, pp. 636–40, Nov. 2005, Accessed: Apr. 04, 2023. [Online]. Available:

https://journals.lww.com/co-clinicalnutrition/Fulltext/2005/11000/Effect_of_dietary_fiber_intake_on_blood_pressure_.00010.aspx

[68] D. Ríos-Covián, P. Ruas-Madiedo, A. Margolles, M. Gueimonde, C. G. De los Reyes-Gavilán, and N. Salazar, “Intestinal short chain fatty acids and their link with diet and human health,” *Front. Microbiol.*, vol. 7, no. FEB, p. 185, Feb. 2016, doi: 10.3389/FMICB.2016.00185/FULL.

[69] R. A. Rastall and G. R. Gibson, “Recent developments in prebiotics to selectively impact beneficial microbes and promote intestinal health,” *Curr. Opin. Biotechnol.*, vol. 32, pp. 42–46, Apr. 2015, doi: 10.1016/J.COPBIO.2014.11.002.

[70] A. P. Nugent, “Health properties of resistant starch,” *Nutr. Bull.*, vol. 30, no. 1, pp. 27–54, Mar. 2005, doi: 10.1111/J.1467-3010.2005.00481.X.

[71] H. Gou, Y. Zhang, L. Ren, … Z. L.-F. in, and undefined 2022, “How do intestinal probiotics restore the intestinal barrier?,” *ncbi.nlm.nih.gov*, vol. 13, 2022, Accessed: Apr. 18, 2023. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9330398/

[72] M. El-Saadony, M. Alagawany, A. Patra, … I. K.-F. & S., and undefined 2021, “The functionality of probiotics in aquaculture: An overview,” *Elsevier*, pp. 36–52, Oct. 2021, Accessed: Apr. 18, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S1050464821001960

[73] J. N. Pugh *et al.*, “Probiotic supplementation increases carbohydrate metabolism in trained male cyclists: A randomized, double-blind, placebo-controlled crossover trial,” *Am. J. Physiol. - Endocrinol. Metab.*, vol. 318, no. 4, pp. E504–E513, Apr. 2020, doi: 10.1152/AJPENDO.00452.2019/ASSET/IMAGES/LARGE/ZH10042083180004.JPEG.

[74] P. O. Sheridan *et al.*, “focus issue on the impact of diet on gut microbiota composition and function and future opportunities for nutritional modulation of the gut microbiome to improve …,” *Taylor Fr.*, vol. 5, no. 1, pp. 74–82, Dec. 2014, doi: 10.4161/gmic.27252.

[75] M. Inman, “How bacteria turn fiber into food,” *PLoS Biol.*, vol. 9, no. 12, p. e1001227, Dec. 2011, doi: 10.1371/JOURNAL.PBIO.1001227.

[76] B. Sánchez, S. Delgado, A. Blanco-Míguez, A. Lourenço, M. Gueimonde, and A. Margolles, “Probiotics, gut microbiota, and their influence on host health and disease,” *Mol. Nutr. Food Res.*, vol. 61, no. 1, p. 1600240, Jan. 2017, doi: 10.1002/MNFR.201600240.

[77] M. Sanchez *et al.*, “Effect of Lactobacillus rhamnosus CGMCC1. 3724 supplementation on weight loss and maintenance in obese men and women,” *cambridge.org*, vol. 111, no. 8, pp. 1507–19, Apr. 2014, doi: 10.1017/S0007114513003875.

[78] J. Flach, M. B. Van Der Waal, A. F. M. Kardinaal, J. Schloesser, R. M. A. J. Ruijschop, and E. Claassen, “Probiotic research priorities for the healthy adult population: A review on the health benefits of Lactobacillus rhamnosus GG and

Bifidobacterium animalis subspecies," *Taylor Fr.*, vol. 4, no. 1, p. 1452839, Jan. 2018, doi: 10.1080/23311932.2018.1452839.

[79] L. V. McFarland, "Systematic review and meta-analysis of saccharomyces boulardii in adult patients," *World J. Gastroenterol.*, vol. 32, no. 8, pp. 1069–79, Nov. 2010, doi: 10.3748/WJG.V16.I18.2202.

[80] J. De Paula, E. Carmuega, R. W.-A. Gastroenterologica, and undefined 2008, "Effect of the ingestion of a symbiotic yogurt on the bowel habits of women with functional constipation," *redalyc.org*, vol. 38, no. 1, pp. 16–25, 2008, Accessed: Apr. 04, 2023. [Online]. Available: https://www.redalyc.org/pdf/1993/199318017005.pdf

[81] R. Sender, S. Fuchs, and R. Milo, "Revised Estimates for the Number of Human and Bacteria Cells in the Body," *PLoS Biol.*, vol. 14, no. 8, p. e1002533., Aug. 2016, doi: 10.1371/JOURNAL.PBIO.1002533.

[82] S. V. Lynch and O. Pedersen, "The Human Intestinal Microbiome in Health and Disease," *N. Engl. J. Med.*, vol. 375, no. 24, pp. 2369–2379, Dec. 2016, doi: 10.1056/NEJMRA1600266.

[83] R.-O. F. Plaza-Diaz J and G. A. Gil-Campos M, "Plaza-Díaz J, Ruiz-Ojeda FJ, Gil-Campos M, Gil A.... - Google Scholar." https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=Plaza-Díaz+J%2C+Ruiz-Ojeda+FJ%2C+Gil-Campos+M%2C+Gil+A.+Mechanisms+of+action+of+probiotics.+Adv+Nutr.+2019+Jan+1%3B10%28suppl_1%29%3AS49-S66.&btnG=#d=gs_cit&t=1680603291451&u=%2Fscholar%3Fq%3Dinfo%3ADXN1bg91XgAJ%3Ascholar.google.com%2F%26output%3Dcite%26scirp%3D0%26hl%3Den (accessed Apr. 04, 2023).

[84] M. Kumar *et al.*, "Probiotic Lactobacillus rhamnosus GG and Aloe vera gel improve lipid profiles in hypercholesterolemic rats," *Elsevier*, vol. 29, no. 3, pp. 574–9, Mar. 2013, doi: 10.1016/j.nut.2012.09.006.

[85] M. Zimmermann, R. H.-T. lancet, and undefined 2007, "Nutritional iron deficiency," *Elsevier*, vol. 370, no. 9586, p. 511, Aug. 2007, Accessed: Apr. 04, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0140673607612355

[86] J. Suliburska, I. A. Harahap, K. Skrypnik, and P. Bogdański, "The Impact of Multispecies Probiotics on Calcium and Magnesium Status in Healthy Male Rats," *Nutr. 2021, Vol. 13, Page 3513*, vol. 13, no. 10, p. 3513, Oct. 2021, doi: 10.3390/NU13103513.

[87] X. Zhang, Y. Han, W. Huang, M. Jin, Z. G.-A. P. S. B, and undefined 2021, "The influence of the gut microbiota on the bioavailability of oral drugs," *Elsevier*, vol. 11, no. 7, pp. 1789–812, Jul. 2021, Accessed: Apr. 05, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S2211383520307279

[88] B. Barkhidarian, L. Roldos, M. M. Iskandar, A. Saedisomeolia, and S. Kubow, "Probiotic supplementation and micronutrient status in healthy subjects: A systematic review of clinical trials," *mdpi.com*, vol. 13, no. 9, p. 3001, Aug. 2021, doi: 10.3390/nu13093001.

[89] M. Abboud, R. Rizk, F. Alanouti, D. Papandreou, S. Haidar, and N. Mahboub, "The health effects of vitamin D and probiotic co-supplementation: A systematic review of randomized controlled trials," *mdpi.com*, vol. 13, no. 1, p. 111, Dec. 2020, doi: 10.3390/nu13010111.

[90] D. Zheng, T. Liwinski, E. E.-C. research, and undefined 2020, "Interaction between microbiota and immunity in health and disease," *nature.com*, vol. 6, pp. 492–506, Jun. 2020, Accessed: Apr. 05, 2023. [Online]. Available: https://www.nature.com/articles/s41422-020-0332-7

[91] H. Guo, L. Yu, F. Tian, W. Chen, Q. Z.- Foods, and undefined 2023, "The Potential Therapeutic Role of Lactobacillaceae rhamnosus for Treatment of Inflammatory Bowel Disease," *mdpi.com*, vol. 12, no. 4, p. 692, Feb. 2023, Accessed: Apr. 02, 2023. [Online]. Available: https://www.mdpi.com/2304-8158/12/4/692

[92] Speranta Avram. Maria Mernea. Dan Mihailescu, "Advanced QSAR Methods Evaluated Polycyclic Aromatic Compounds Duality as Drugs and Inductors in Psychiatric Disorders | Request PDF," *Current Organic Chemistry*, Dec. 2013. https://www.researchgate.net/publication/285626395_Advanced_QSAR_Methods_Evaluated_Polycyclic_Aromatic_Compounds_Duality_as_Drugs_and_Inductors_in_Psychiatric_Disorders (accessed May 17, 2021).

[93] Andrés Gerique, "An Introduction to ethnoecology and ethnobotany. Theory and Methods - Integrative assessment and planning methods for sustainable agroforestry in humid and semiarid regions," *Advanced Scientific Training*, Jan. 2006. https://www.researchgate.net/publication/239591352_An_Introduction_to_ethnoecology_and_ethnobotany_Theory_and_Methods_-_Integrative_assessment_and_planning_methods_for_sustainable_agroforestry_in_humid_and_semiarid_regions (accessed May 17, 2021).

[94] H. S. Gill, K. J. Rutherfurd, and M. L. Cross, "Dietary probiotic supplementation enhances natural killer cell activity in the elderly: An investigation of age-related immunological changes," *J. Clin. Immunol.*, vol. 21, no. 4, pp. 264–271, Jul. 2001, doi: 10.1023/A:1010979225018.

[95] K. Kailasapathy and J. Chin, "Survival and therapeutic potential of probiotic organisms with reference to Lactobacillus acidophilus and Bifidobacterium spp.," *Immunol. Cell Biol.*, vol. 78, no. 1, pp. 80–88, Feb. 2000, doi: 10.1046/J.1440-1711.2000.00886.X.

[96] L. Miller, L. Lehtoranta, M. L.- Nutrients, and undefined 2017, "The Effect of Bifidobacterium animalis ssp. lactis HN019 on Cellular Immune Function in Healthy Elderly Subjects: Systematic Review and Meta-Analysis," *mdpi.com*, vol. 9, no. 3, p. `191, Feb. 2017, doi: 10.3390/nu9030191.

[97] H. Sadrzadeh-Yeganeh, I. Elmadfa, A. Djazayery, M. Jalali, R. Heshmat, and M. Chamary, "The effects of probiotic and conventional yoghurt on lipid profile in women," *cambridge.org*, vol. 103, no. 12, pp. 1778–83, Jun. 2010, doi: 10.1017/S0007114509993801.

[98] C. Mazziotta, M. Tognon, F. Martini, E. Torreggiani, and J. C. Rotondo, "Probiotics Mechanism of Action on Immune Cells and Beneficial Effects on Human Health," *Cells*, vol. 12, no. 1, p. 184, Jan. 2023, doi: 10.3390/CELLS12010184.

[99] R. Bibiloni, R. Fedorak, … G. T.-O. journal of the, and undefined 2005, "VSL# 3 probiotic-mixture induces remission in patients with active ulcerative colitis," *journals.lww.com*, vol. 100, no. 7, pp. 1539–46, Jul. 2005, Accessed: Apr. 02, 2023. [Online]. Available: https://journals.lww.com/ajg/Fulltext/2005/07000/VSL_3_Probiotic_Mixture_Induces_Remission_in.20.aspx

[100] K. Kato *et al.*, "Randomized placebo-controlled trial assessing the effect of bifidobacteria-fermented milk on active ulcerative colitis," *Aliment. Pharmacol. Ther.*, vol. 20, no. 10, pp. 1133–1141, Nov. 2004, doi: 10.1111/J.1365-2036.2004.02268.X.

[101] E. Miele, F. Pascarella, E. Giannetti, L. Quaglietta, R. N. Baldassano, and A. Staiano, "Effect of a probiotic preparation (VSL#3) on induction and maintenance of remission in children with ulcerative colitis," *Am. J. Gastroenterol.*, vol. 104, no. 2, pp. 437–443, Feb. 2009, doi: 10.1038/AJG.2008.118.

[102] W. Kruis *et al.*, "Maintaining remission of ulcerative colitis with the probiotic Escherichia coli Nissle 1917 is as effective as with standard mesalazine," *gut.bmj.com*, vol. 53, no. 11, pp. 1617–1623, Nov. 2004, doi: 10.1136/gut.2003.037747.

[103] R. Fedorak, D. D.-G. Clinics, and undefined 2012, "Probiotic bacteria in the prevention and the treatment of inflammatory bowel disease," *gastro.theclinics.com*, vol. 41, no. 4, pp. 821–842, Dec. 2012, doi: 10.1016/j.gtc.2012.08.003.

[104] K. Kaźmierczak-Siedlecka, A. Daca, M. Folwarski, J. M. Witkowski, E. Bryl, and W. Makarewicz, "The role of Lactobacillus plantarum 299v in supporting treatment of selected diseases," *Cent. J. Immunol.*, vol. 45, no. 4, p. 488, Jan. 2020, doi: 10.5114/CEJI.2020.101515.

[105] E. E. Patterson *et al.*, "Gut microbiota, obesity and diabetes," *Postgrad. Med. J.*, vol. 92, no. 1087, pp. 286–300, May 2016, doi: 10.1136/POSTGRADMEDJ-2015-133285.

[106] H. Borgeraas, L. K. Johnson, J. Skattebu, J. K. Hertel, and J. Hjelmesaeth, "Effects of probiotics on body weight, body mass index, fat mass and fat percentage in subjects with overweight or obesity: a systematic review and meta-analysis of," *Wiley Online Libr.*, vol. 19, no. 2, pp. 219–232, Feb. 2017, doi: 10.1111/obr.12626.

[107] Q. Zhang, Y. Wu, X. F.- Medicina, and undefined 2016, "Effect of probiotics on glucose metabolism in patients with type 2 diabetes mellitus: A meta-analysis of randomized controlled trials," *mdpi.com*, vol. 52, no. 1, pp. 28–34, Feb. 2016, doi: 10.1016/j.medici.2015.11.008.

[108] J. Boursier *et al.*, "The severity of nonalcoholic fatty liver disease is associated with gut dysbiosis and shift in the metabolic function of the gut microbiota," *Hepatology*, vol. 63, no. 3, pp. 764–775, Mar. 2016, doi: 10.1002/HEP.28356.

[109] J. Yano, K. Yu, G. Donaldson, G. Shastri, P. A.- Cell, and undefined 2015, "Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis," *Elsevier*, vol. 161, no. 2, pp. 264–76, Apr. 2015, Accessed: Apr. 03, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0092867415002482

[110] J. A. Bravo *et al.*, "Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve," *Proc. Natl. Acad.*

Sci. U. S. A., vol. 108, no. 38, pp. 16050–16055, Oct. 2011, doi: 10.1073/PNAS.1102999108.

[111] A. Mohammadi, … S. J.-… journal of preventive, and undefined 2015, "Effects of probiotics on biomarkers of oxidative stress and inflammatory factors in petrochemical workers: a randomized, double-blind, placebo-controlled trial," *ncbi.nlm.nih.gov*, vol. 6, 2015, Accessed: Apr. 03, 2023. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4587074/

[112] S. O'Mahony, J. Marchesi, P. Scully, … C. C.-B., and undefined 2009, "Early life stress alters behavior, immunity, and microbiota in rats: implications for irritable bowel syndrome and psychiatric illnesses," *Elsevier*, vol. 65, no. 3, pp. 263–7, Feb. 2009, Accessed: Apr. 05, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0006322308008019

[113] A. Bharwani, M. Mian, J. Foster, … M. S.-, and undefined 2016, "Structural & functional consequences of chronic psychosocial stress on the microbiome & host," *Elsevier*, vol. 63, pp. 217–27, Jan. 2016, Accessed: Apr. 05, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0306453015009348

[114] P. Bercik *et al.*, "The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice," *Elsevier*, vol. 141, no. 2, pp. 599–609, Aug. 2011, Accessed: Apr. 05, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S001650851100607X

[115] L. Desbonnet, L. Garrett, G. Clarke, B. Kiely, J. C.- Neuroscience, and undefined 2010, "Effects of the probiotic Bifidobacterium infantis in the maternal separation model of depression," *Elsevier*, vol. 170, no. 4, pp. 1179–88, Nov. 2010, Accessed: Apr. 05, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0306452210010729

[116] H. J. Wu and E. Wu, "The role of gut microbiota in immune homeostasis and autoimmunity," *Gut Microbes*, vol. 3, no. 1, p. 4, Jan. 2012, doi: 10.4161/GMIC.19320.

[117] F. Yan, D. P.-C. opinion in gastroenterology, and undefined 2011, "Probiotics and immune health," *ncbi.nlm.nih.gov*, vol. 6, p. 496, Oct. 2011, Accessed: Apr. 05, 2023. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4006993/

[118] R. Huang, K. Wang, J. H.- Nutrients, and undefined 2016, "Effect of probiotics on depression: a systematic review and meta-analysis of randomized controlled trials," *mdpi.com*, vol. 8, p. 483, Aug. 2015, Accessed: Apr. 05, 2023. [Online]. Available: https://www.mdpi.com/2072-6643/8/8/483/htm?utm_source=deleted&utm_medium=deleted&utm_term=deleted&utm_content=deleted&utm_campaign=deleted&gclid=deleted

[119] T. Pereira, L. Côco, A. Ton, S. M.- Antioxidants, and undefined 2021, "The emerging scenario of the gut–brain axis: the therapeutic actions of the new actor kefir against neurodegenerative diseases," *mdpi.com*, vol. 11, p. 1845, Nov. 2021, Accessed: Apr. 03, 2023. [Online]. Available: https://www.mdpi.com/1368308

[120] R. Dhiman, B. Rana, S. Agrawal, A. Garg, M. C.- Gastroenterology, and undefined 2014, "Probiotic VSL# 3 reduces liver disease severity and hospitalization in patients

with cirrhosis: a randomized, controlled trial," *Elsevier*, vol. 147, no. 6, pp. 1327–37, Dec. 2014, Accessed: Apr. 04, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0016508514010701

[121] J. I. Riezu-Boj *et al.*, "Lactiplantibacillus plantarum DSM20174 Attenuates the Progression of Non-Alcoholic Fatty Liver Disease by Modulating Gut Microbiota, Improving Metabolic Risk Factors, and Attenuating Adipose Inflammation," *Nutrients*, vol. 14, no. 24, p. 5212, Dec. 2022, doi: 10.3390/NU14245212/S1.

[122] B. Cui, L. Lin, B. Wang, W. Liu, C. S.-P. Research, and undefined 2022, "Therapeutic potential of Saccharomyces boulardii in liver diseases: from passive bystander to protective performer?," *Elsevier*, vol. 175, p. 106022, Jan. 2022, Accessed: Apr. 04, 2023. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S104366182100606X

[123] R. Aller, D. De Luis, O. Izaola, … R. C.-E. R. M., and undefined 2011, "Effect of a probiotic on liver aminotransferases in nonalcoholic fatty liver disease patients: a double blind randomized clinical trial," *europeanreview.org*, vol. 15, no. 9, pp. 1090–5, Sep. 2011, Accessed: Apr. 05, 2023. [Online]. Available: https://www.europeanreview.org/wp/wp-content/uploads/1039.pdf

[124] Q. Liu *et al.*, "Role and effective therapeutic target of gut microbiota in NAFLD/NASH," *Exp. Ther. Med.*, vol. 18, no. 3, p. 1935, Jul. 2019, doi: 10.3892/ETM.2019.7781.

[125] Y. Wang, Y. Liu, I. Kirpich, C. McClain, and W. Feng, "Lactobacillus rhamnosus GG treatment potentiates intestinal hypoxia-inducible factor, promotes intestinal integrity, prevents inflammation, and ameliorates alcohol-induced liver injury," *FASEB J.*, vol. 26, no. S1, pp. 2866–75, Apr. 2012, doi: 10.1096/FASEBJ.26.1_SUPPLEMENT.673.17.