Role of Probiotics in Advancement of Physical Abnormalities and Disease Control: A Systematic Review

Comment [RJ1]: Check the title. . this read like probiotics will increase the abnormalities

ABSTRACT

Probiotics are live microorganisms, primarily bacteria that give the host health benefits when given in sufficient amounts. It works in various defensive mechanisms, including releasing antimicrobial compounds, competitive adhesion to the mucosa and epithelium, fortifying the gut epithelial barrier and regulating the immune system. Probiotics have a considerable effect in reducing allergies and gastrointestinal problems like diarrhoea and ulcers. Probiotics are quite beneficial for managing and preventing complex diseases including diabetes, cardiovascular diseases, anemia, urogenital diseases, dental caries, URTI, cancers and various abnormalities like obesity, depression, etc. Nowadays, Antibiotic resistance is a global challenge associated with high morbidity and mortality. The current lack of efficacious treatments necessitates the creation of innovative therapeutic approaches and substitute antimicrobial therapies. So, natural products or probiotics would be a better treatment for human health. However, Probiotics have already gained popularity as a successful therapeutic intervention strategy among physicians. This investigation covers a comprehensive overview of the current state of probiotic research which comprises a wide range of topics including sourcing, mode of action, probiotic strains, isolating procedures and the role of probiotics.

Comment [RJ2]: How can it be a treatment for human health.? Chk sentence.

Keywords: Probiotics, Defensive Mechanism, Bacteria, Diseases, Abnormality.

1. Introduction

Antibiotics have been widely employed in managing bacterial infections because of their capacity to either stop the growth or eradicate living microbes [1]. However, the spread of antibiotic-resistance genes into harmful bacteria has sparked worries about the short-term efficacy of the current antibiotic inventory [2]. Due to the global expansion of antibiotic and antimicrobial resistance, the World Health Organization has classified these concerns as an unanticipated global health danger with wide-ranging effects on the safety of humans, animals, food, and the environment across numerous sectors [2]. Thus, Probiotics are considered one of the substitute treatments [3]. German physicist Werner Kollath first used the term "probiotic" in 1953 [4]. It is a combination of the Latin word "pro" and the Greek word "βιοσ," which means "for life" [4]. This word is used by Kollath to describe the "active substances" that are essential to the healthy growth and well-being of living things [4]. According to the definition given to probiotics in 1965, they are chemicals secreted by microbes that encourage the growth of other microorganisms [5]. Probiotics are defined by the World Health Organization (WHO) as "living microorganisms that, when administered in adequate amounts, confer benefits to the host's health" [6].

Probiotics which can exist in food, supplements, and the intestine, are a significant class of advantageous bacteria that are taken or added to diets [7]. These bacteria are capable of colonizing the intestine and competing with dangerous microorganisms. Additionally, these bacteria produce certain enzymes that aid in feed breakdown. Probiotics can enhance immune activities by interacting with various immune cells and altering the composition of gut bacteria when ingested [8][9][10]. Fundamental selection criteria should generally be used in the selection and characterization of novel probiotic strains [11]. The Food and Agriculture Organization (FAO) and the World Health Organization (WHO) of the United Nations released guidelines in 2002 outlining the various factors that need to be considered when choosing probiotic microorganisms [11]. These factors include antimicrobial activity, the ability to adhere to epithelial tissues, resistance to harsh conditions inside the human body, and safety for use [11]. Furthermore, a probiotic must possess a high ability to endure under intestinal circumstances, such as acidic pH, enzymes, bile saltsetc[12]. They have no harmful side effects, are not poisonous, and are not pathogenic [13]. To preserve the intended qualities, they are also appropriately labelled and compatible with the product matrix, processing, and storage circumstances [13]. It has been demonstrated that consuming 10^9–10^{10} viable colony-forming units (CFU) per day improves host health [14]. So, probiotics are frequently prescribed to enhance health in nations like Canada, Switzerland and Japan [15]. This paper provides a review of available information and summarizes the current knowledge about probiotics, their defensive mechanism, sources, isolation techniques and the effect of various diseases on human health.

Table 1. List of some probiotic bacteria (gram-positive and gram-negative)

Comment [RJ3]: This list is incomplete

Bacteria type	Bacteria name	References
Gram-positive	*Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus fermentum, Lactobacillus gasseri, Lactobacillus johnsonii, Lactobacillus paracasei, Lactobacillus plantarum, Lactobacillus salivarius, Bifidobacterium adolescentis, Bifidobacterium animalis, Bifidobacterium bifidum, Leuconostoc, Enterococcus, Streptococcus salivarius*	[16][17][18][19]
Gram-negative	*Escherichia coli*	[20][21]

1.1 Mode of Action of Probiotics

Though their exact processes are unclear, probiotics are thought to have several positive impacts [13]. Probiotics work against various pathogens in several ways, including releasing antimicrobial compounds, competitive adhesion to the mucosa and epithelium, fortifying the gut epithelial barrier, and regulating the immune system (Fig. 1) [13]. Probiotics can increase the intestinal defence system through various strategies, including acting as an antagonist against pathogens, enhancing the intestinal epithelial layer, producing neurotransmitters, increasing innate immunity, and supporting adaptive immunity (Fig. 1) [22][23]. One important defence mechanism that keeps the organism safe from the environment and preserves epithelial integrity is the intestinal barrier [24]. The mucous layer, antimicrobial peptides, secretory IgA, and the epithelial junction adhesion complex are the intestinal barrier's defences[24]. When this barrier function is damaged, food antigens and bacteria can enter the submucosa and cause inflammatory reactions that could lead to digestive problems. Concerning their role in maintaining this barrier, probiotic microorganisms have been thoroughly investigated. Mucin glycoproteins, often known as mucins, are important macromolecules that make up epithelial mucus and have been linked to both health and illness. Probiotics may increase mucus secretion as a means of enhancing barrier performance and pathogen exclusion (Fig 1) [18].

Comment [RJ4]: Check sentence

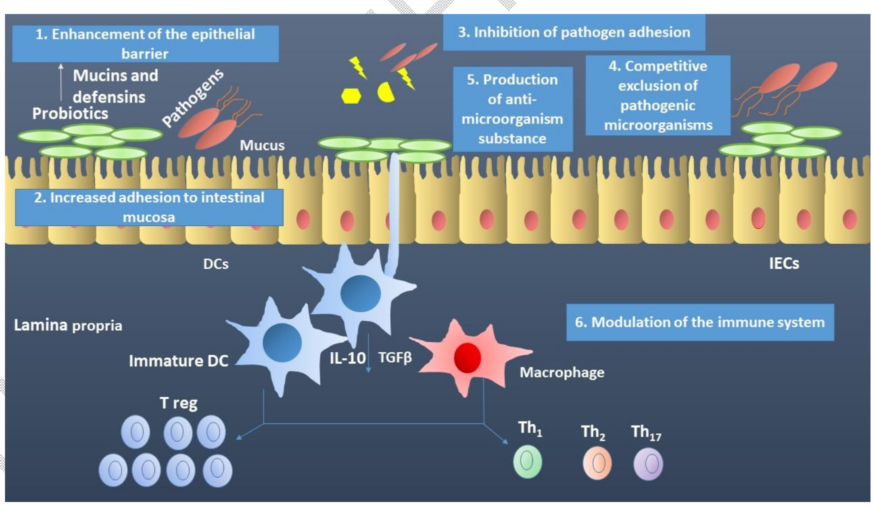

Fig 1. Major mechanisms of action of probiotics [16] [17] [18].

It is thought that adhesion to intestinal mucosa is necessary for colonization and plays a crucial role in the relationship between probiotic strains and their host. The particular interaction has suggested a potential link between probiotic bacterial surface proteins and pathogens' competitive removal from mucus [25][26]. Additionally, probiotics control the innate and adaptive immune response by influencing B and T lymphocytes, dendritic cells (DC), and macrophages [27]. Probiotics interact with intestinal epithelial cells and draw macrophages and mononuclear cells, which in turn increases the generation of anti-inflammatory cytokines [27]. Additionally, probiotics can use the gut-brain axis to create neurotransmitters in the gut. The amounts of serotonin, gamma-aminobutyric acid (GABA), and dopamine can be modulated by some probiotic strains, which can impact mood, behaviour, gut motility and stress-related pathways [28][29][30].

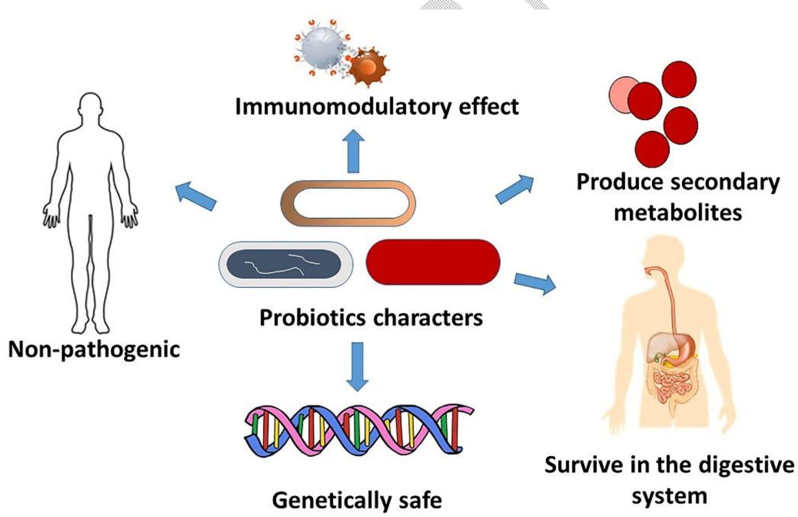

Fig 2. Features of probiotics [21] [22] [23] [24]

1.2 Sources of probiotics

Probiotic foods are the subject of intense interest due to their positive effects on human health [31]. Thus, there is a corresponding increase in the study of probiotic microbes [31].

Consequently, probiotics may be present in many ecological niches besides humans [32]. Probiotics are becoming more and more common in the food, pharmaceutical, and fermentation industries, where customers generally accept them favourably[32]. Besides, probiotic-rich foods include dairy and dairy-related products [33]. The primary supplies could come from human origins, such as breast milk or the large or small intestine of humans [33]. Milk serves as an excellent medium for both good and bad microbes due to its high nutritional content [34]. Moreover, the best source of probiotics for human consumption has been determined to be the feces of newborns, kids and adults [35]. Their capacity to withstand gastrointestinal transit and colonize the intestines for beneficial purposes is the reason behind this [35]. Additionally, foods of animal origin (milk, fish, dairy, meat products and honey) and foods of plant origin (fruits, vegetables, grains/cereals and non-fermented foods) may provide additional sources for isolating probiotic strains [36]. However, Supplements containing probiotics are also offered [37]. The bacterial strains found in probiotic foods and supplements should be essential for the following processes: lowering and metabolism of cholesterol; colonization of the intestinal, respiratory, and urogenital tracts; inhibition of carcinogenesis, either directly or indirectly, through immune system stimulation; lactose metabolism; calcium absorption and vitamin synthesis potential; reductive potential of yeast and vaginal infection; reduction of constipation and diarrheal disorders; mitigation of gastritis and ulcers; reduction of acne, rash face, and skin issues; and the synthesis of natural antimicrobials [38][39].

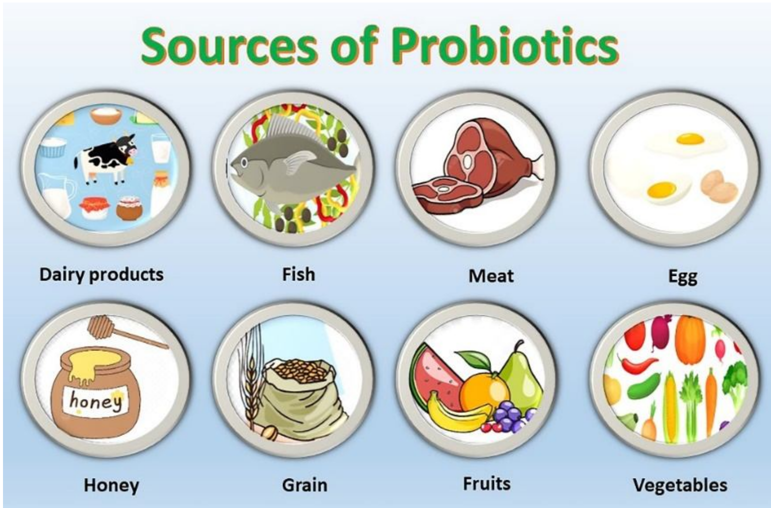

Fig 3. Probiotic sources and selection criteria to apply in both humans and animals [30].

Comment [RJ5]: This fig is too basic

1.3 Isolation of probiotics

According to FAO/WHO guidelines, the first step is to isolate possible probiotic strains [40]. Researchers have determined that new probiotic bacterial strains are still needed for certain therapeutic applications [40]. The probiotics derived from dairy products differ in several ways from the probiotics isolated from the intestines of people and animals [41]. A prominent distinction between these probiotics is their adherence. The adhesion activity of intestinal isolates is often higher than that of dairy isolates [41]. To extract probiotic strains from dairy products, samples were gathered from a variety of sources, including camel milk, sheep yogurt, cow yogurt, goat milk, and native buttermilk [42]. Also, the sample was taken from clinical samples, which included blood, urine, respiratory, pericardial, abdominal and cerebral fluid (CSF) [43]. These samples were cultured on agar and broth media and incubated for 24 to 48 hours at 37°C [42]. The strains were identified using a variety of tests, such as Gram staining, catalase testing, growth at temperatures between 15°C and 45°C, production of acid and gas from glucose, production of ammonia from arginine, and fermentation of sugars (arabinose, cellobiose, mannitol, mannose, melibiose, raffinose, ribose, salicin, rhamnose and xylose) [42][43][44].

2. Methodology

Different sources were generated for article searches including Google Scholar, PubMed, Science Direct, Jstor and Base. The information mainly searches in several articles from 2000 to 2024. The keywords that were used for searches included probiotics, advancements and disease management. The articles that were obtained were either full text or just the title and abstract. Some criteria followed to search the articles included Probiotics, Sources of probiotics, Mechanism of action of probiotics, Probiotics in human health, Role of probiotics in different diseases (probiotics and allergy, probiotics and diabetes, probiotics and cancer, probiotics and probiotics and cardiovascular diseases, probiotics and diarrhoea, probiotics and anaemia, probiotics and ulcers, probiotics and obesity). The articles that met the requirements for inclusion in this review were either published in peer-reviewed journals, reviewed, or authored in English. Only studies about human health were included in the review. The exclusion criteria were as follows: no conference publications or book chapters, no mention of animals like aquaculture, no article searches in other languages, and yeast or fungus strains not acting as probiotics.

3. Role of probiotics in various diseases and abnormalities of the human body

3.1 Prevention of allergies

Probiotics help allergies by healing the digestive tract [45]. As a result of this intervention, the immune system stabilizes, the intestinal epithelial barrier is strengthened, and inflammation is reduced. Immunological processes cause hypersensitivity reactions, which are the outward manifestation of allergies [46]. Probiotics can rearrange antigens, which lessens their capacity to elicit an immunological response [46]. This ultimately results in a reduction of intestinal permeability and the class of pro-inflammatory compounds. People who suffer from various allergies often experience these symptoms. Research indicates that *L. rhamnosus*GG, a probiotic bacteria, may lessen the intensity of allergic reactions and ease the symptoms associated with food allergies [45][46]. According to a more contemporary hygiene hypothesis, certain organisms—such as *helminths*—as well as microorganisms—such as *bifidobacteria,lactobacilli*, and *saprophytic mycobacteria*—are necessary for the healthy development of the human immune system. To support immunological tolerance, these microorganisms are believed to have coevolved with the human immune system as part of our microbiota during human evolution. This involves the production of regulatory T cells (Treg) and the regulation of the balance between Th2 and Th1, which help to avoid the development of autoimmune and allergic diseases [47][48].

3.2 Antimicrobial effect

One possible strategy to stop the spread of bacteria resistant to antibiotics is the use of probiotics [49]. Probiotics use several important antimicrobial pathways to accomplish this, including as immune system modulation, mucin and tight junction protein production, competitive exclusion, and improved intestinal barrier function [50]. Antimicrobial peptides, which are essential for competitively excluding microorganisms, are produced by probiotics and are a major factor in their antimicrobial effectiveness. The antibacterial activity of *Lactobacillus* strains such as *S. aureus, P. aeruginosa, Shigella sp., Clostridium difficile, Klebsiella* sp. and *E. coli* has been particularly effective against a range of infections [51]. They produce lactic acid, bacteriocin and hydrogen peroxide, which prevent the attachment of harmful bacteria to the mucosa and enhance the immune response, among other efforts to outcompete and suppress these pathogenic bacteria [52]. The release of chemicals known as bacteriocins is the main way that *Lactobacillus* strains demonstrate antibacterial activity [53]. Antimicrobial peptides known as bacteriocins fight both Gram-positive and Gram-negative bacteria. It's interesting to note that the bacteria that make these bacteriocins have evolved defense mechanisms against the effects of their antimicrobial peptides [54]. It is also known that certain strains of *Lactobacillus* and *Bifidobacterium* produce bacteriocins. The antimicrobial peptides exhibit multiple modes of action, such as blocking the creation of peptidoglycan and pore formation, as well as inhibiting lipid II, an essential constituent of bacterial cell membranes [55].

3.3 Prevention of diarrhoea

Numerous clinical investigations have evaluated the probiotics' effectiveness in preventing acute diarrheal illness [56]. The prevalent side effect of repeated short- and long-term antibiotic usage is diarrhoea[56]. To stop antibiotic-associated diarrhea, two meta-analyses utilizing the strains *Lactobacillus acidophilus*, *Lactobacillus rhamnosus* strain GG, *Lactobacillus bulggaricus* and yeast *Saccharomyces boulardii* could be employed [56]. Nosocomial diarrhoea is a major issue in pediatric hospitals and is a global problem. Probiotics (*Streptococcus thermophiles*, *Bifidobacterium bifidum*, *and L rhamnosus*starin GG) can be used prophylactically to prevent acute diarrhoea, especially in babies [56].

Comment [RJ6]: There are many more studies which is done

3.4 Prevention of obesity

Comment [RJ7]: Prevention is a very strong word to be used until claimed by clinical trial

Human studies that examined the benefits of probiotic use included changes in lipid profiles, namely lower levels of total cholesterol, LDL cholesterol, and plasma TG and higher levels of HDL cholesterol [57]. During 4 to 6 weeks of intake, the majority of research indicates the anti-obesity advantages of some types of probiotics, such as *Lactobacillus* (primarily *Lactobacillus casei* strain Shirota (LAB13), *Lactobacillus gasseri*, *Lactobacillus rhamnosus*, and *Lactobacillus plantarum*) and *Bifidobacterium* (particularly *Bifidobacterium infantis*, *Bifidobacterium longum*, and *Bifidobacterium breve* B3) [58][59]. Additionally, probiotics with anti-obesogenic properties, including *L. rhamnosus* CGMCC1.3724, help prevent issues connected to obesity [60].

3.5 Prevention of diabetes

Comment [RJ8]: Here too

Patients with type 2 diabetes may have changed gut microbial composition. This implies that altering the gut microbiota by probiotic medication could be a strategy for controlling the metabolism of glucose. Probiotics may have a hypoglycemic effect, according to numerous studies, but the exact processes behind this are still up for debate because the etiology of type 2 diabetes is so complicated [61]. Probiotics may help to mitigate several metabolic syndrome components, many of which are connected to type 2 diabetes [62]. The preservation of a range of mucosal immune cells may inhibit potential pathogens; pro-inflammatory cytokines (TNF-α and interleukin-6) may be reduced; delayed glucose absorption in the gut may contribute to these improvements; and rate-controlling enzymes of gluconeogenesis, such as glucose-6-phosphatase (G-6-Pase) and phosphoenolpyruvate carboxykinase (PEPCK), may be suppressed. In patients with type 2 diabetes, unchecked gluconeogenesis results in hyperglycemia. Thus, probiotic therapy that inhibits G6Pase and PEPCK lowers glycaemia by reducing the amount of glucose released into the bloodstream from the liver [63].

3.6 Prevention of anemia

Numerous researches have demonstrated a strong correlation between iron deficiency and gut microbiota. Moreover, studies have demonstrated the positive effect of probiotic bacteria on improving iron absorption and the reciprocal association between gut microbiota composition and iron insufficiency [64][65]. Probiotic bacteria such as *Lactobacillus cerevisiae, Lactobacillus cremoris, B. pseudocatenulatum, Candida famata, B. adolescentis, Candida glabrata, Candida guilliermondii, S. cerevisiae, Yarrowialipolytica and Pichia glucozyma* are the source of folic acid, a water-soluble B vitamin that is essential for treating and managing anemia. These microbes are used to improve folic acid absorption through the intestines. *P. denitrificans and P. shermanii* have also been discovered to be effective in the treatment of vitamin B12 insufficiency. Foods fermented with lactic acid have a crucial role in boosting the absorption of iron and are utilized in the treatment of anaemia in patients. They aid in regulating the digestive tract's pH and stimulate the phytase enzyme, which aids in the absorption of nutrients. Moreover, megaloblastic anaemia has been treated by adding a mix of probiotic bacteria to the diet. These probiotics mitigate the negative effects of antibiotics and encourage intestinal fermentation [66].

Table 2. Different studies on the treatment of anaemia using probiotics.

Subject	Number of patients	Study duration	Observation	References
Healthy woman	Study 1- 14; Study 2- 28	4 weeks	In the probiotics group: significant increase of iron in serum; In the placebo group: Changes are not significant	[67]
Healthy woman	20	1 week	Probiotics Group: Significant increase in iron	[68]
Children with anaemia	52	3 years	No significant differences in serum ferritin levels between the probiotics and control group	[69]

3.7 Prevention of urogenital disease

According to recent research, maintaining a lactobacilli-dominated microbiome is crucial for preserving women's quality of life as well as preventing STDs and premature labour. It was questioned if artificial lactobacilli supplementation may reduce infection rates because women who are prone to vaginal and urinary infections lose lactobacilli organisms. However, uro-pathogens are becoming more resistant to common antibiotics (such as trimethoprim/sulfamethoxazole) and patients are turning increasingly to natural alternatives like cranberry juice, which seems to contain antiadhesive compounds that are effective against uro-pathogens and can help prevent UTIs. Probiotic therapy using lactobacilli has been explored as a non-chemotherapeutic way to maintain and repair a healthy urogenital tract. There is evidence that some strains of lactobacilli can be beneficial when inserted directly into the vagina or when ascending from the rectum after oral ingestion. Probiotic consumption regularly may be beneficial for all healthy women as well as those who experience recurrent urogenital infections to prevent serious infections and superinfections of the vaginal mucosa. Probiotics have been shown to help keep the vaginal flora in balance, which protects against UTIs [70].

3.8 Prevention of dental caries

Dental caries is one of the most prevalent illnesses in the world, causing exorbitant expenses and being regarded as a public health issue in youngsters. Various therapies have been suggested to lower the prevalence of this illness, with probiotic supplementation being one of the main ones. According to recent studies, probiotic supplementation appears to lower the risk of dental caries [71][72][73]. *Streptococcus mutans* (SM), one of the several bacterial species found in saliva, is widely regarded as the pathogen primarily responsible for the early stages of tooth decay, whereas Lactobacillus plays a significant part in the disease's progression. The primary traits of *Streptococcus mutans'* pathogenicity include its acidogenicity, capacity to endure in acidic conditions, capacity to form biofilms, and capacity to cling to teeth. The probiotic *Lactobacillus paracasei* SD1 was introduced and used in the oral cavity, due to its well-known ability to prevent Streptococcus mutans from growing, lessen its acid production and adhere well to oral epithelial cells [74].

3.9 Prevention of depression

The gut-brain axis is the term for the reciprocal connections between the brain, intestinal microbiota, and the digestive system via immunological, neurological and endocrine pathways. The gut microbiota is very responsive to the physical and physiological strain that its host endures. Stress drastically reduces the amount of Firmicutes phylum, particularly in *Bifidobacterium and Lactobacilllaceae* family bacteria and is a major risk factor for depression. It also modifies the percentage and makeup of the gut microbiota. Stress weakens the brain's relationship with the gut microbiota, which can result in metabolic depression. However, Changes in brain activity in patients with depression are known to be caused by higher levels of cortisol in plasma and corticotrophin-releasing factor in the cerebrospinal fluid. Furthermore, when these factors are repeatedly activated, catecholamine levels (primarily those of norepinephrine and dopamine) rise. This raises the risk of various physiological problems, such as attention deficit disorder, balance and posture, cognitive function, emotions and sleep-wake cycles. *Bifidobacterium* baby restored the stress-induced drop in norepinephrine, indicating that probiotics influenced catecholamine metabolism [75].

3.10 Prevention of cardiovascular diseases

Cardiovascular problems that commonly affect the heart include arrhythmia, thromboembolic disease, cardiomyopathy and atherosclerosis. Globally, the prevalence of cardiovascular disorders is rising. Cardiovascular diseases accounted for 18 million fatalities in 2015, or over one-third of all deaths with documented causes. This number indicates a noteworthy increase of 12.5% when compared to the data from 2005. Predictions from the American Heart Association suggest that by 2030, around 43.9% of the US population will be suffering from cardiovascular disease. In the United States, 92.1 million persons currently suffer from cardiovascular disease. Atherosclerosis is a chronic inflammatory disease characterized by the creation and progression of lipid-fueled atherosclerotic plaques in the artery wall [76]. From spontaneously fermented mustard, researchers obtained the *Lactobacillus plantarum* DMDL 9010 strain (CGMCC No. 5172). The potential benefits of this strain in lowering cholesterol were examined using an in vivo model. The study's findings demonstrated that rats given 109 cells of *L. plantarum* DMDL

9010 daily experienced significant reductions in their levels of total cholesterol (TC), low-density lipoprotein cholesterol content (LDL-C), and atherosclerosis index (AI) of 23.03%, 28.00%, and 34.03%, respectively. After administering *L. plantarum* DMDL 9010, there was, however, no statistically significant alteration in blood triglyceride levels. Rat hepatocyte protection against steatosis was demonstrated by morphological and pathological alterations in the liver following *L. plantarum* DMDL 9010 therapy. Significant reductions in hepatic cholesterol (33.20%) and triglyceride levels (40.86%) were also observed upon administration of substantial dosages of *L. plantarum* DMDL 9010. Significant increases were also observed in bile acid (+70.18%) and fecal cholesterol (+31.07%). After receiving *L. plantarum* DMDL 9010 treatment, there was a reduction in blood and total hepatic cholesterol and triglyceride levels as well as an increase in bile acid excretion through stool. These outcomes seemed to depend on the dosage of *L. plantarum* DMDL 9010. Thus, Probiotic supplementation may help those who are susceptible to ischemic heart disease escape the devastation that comes with it [77].

3.11 Prevention of upper respiratory tract infections

The most prevalent illnesses are upper respiratory tract infections (URTIs), which also include tonsillitis, pharyngitis, laryngitis, sinusitis, and the common cold. Adults experience colds two to three times a year, and 17.2 billion URTIs are thought to have occurred globally in 2015 [78][79]. Numerous viruses, including the influenza virus, adenovirus, rhinovirus, and respiratory syncytial virus, are the primary cause of URTIs. The symptoms can include chills, fever, headache, body aches, sore throat, runny or stuffy nose, cough and so on [80][81]. Retaining the immune system in a healthy, normal state reduces the likelihood of recurrent infections. Salivary immunoglobulin A (IgA) and NK cell activity are thought to be crucial in the prevention of URTIs. The immune system can be weakened by several environmental variables, such as leading a stressful lifestyle, which could raise the risk of URTIs. There is evidence that certain probiotic strains increase salivary IgA levels and activate NK cells again. Therefore, regular use of a probiotic beverage may help to regulate URTIs and preserve normal immunological function. A probiotic known as *Lactobacillus casei* strain Shirota (LcS) can survive in the digestive system and restore a balanced gut flora. Numerous studies have been conducted on human and animal models to examine the strain's immunomodulatory properties. Research involving healthy individuals with low NK cell activity revealed that consumption of LcS-fermented milk (LcS-FM) increased the activity [82].

3.12 Prevention of ulcers

The sores that form on the skin's surface that are painful and inflammatory are called ulcers. Clinical characteristics determine whether the illness is considered mild, substantial or herpetiform. Many theories have been put out to explain the illness, including immunologic abnormalities, viral infections and environmental and psychological stress. However, the etiology of the disorder is still unknown and up for debate. Probiotics given in sufficient amounts have been shown to improve host health. One way that probiotics help to reduce sickness is by enhancing and modulating the immune system. Probiotics can produce a variety of substances, such as peptides, bacteriocins and organic acids. Consequently, there is a decreased chance of harmful germs colonizing [83]. A very common oral ailment that is distinguished by a high degree of complexity, diversity and frequency is oral ulcers. Several etiological factors, such as allergic reactions, traumatic experiences and infectious agents, can result in oral ulcers. The loss of connective tissue and the development of crater-like depressions brought on by persistent disruption or damage to the integrity of the mouth epithelium are the hallmarks of mouth ulcers. Bacteria that are resistant to infections and benign are known as probiotics. In addition to strengthening immunity and preventing infection by fighting harmful bacteria, they may also improve digestion and make it easier for the host to absorb nutrients. Both immune system regulation and tissue healing are influenced by them. It may be possible to increase the effectiveness of probiotics in aiding the healing process of ulcers by using fucoidan (FD), a prebiotic obtained from marine sources. Probiotics can create a biofilm in the oral cavity that is capable of successfully competing with periodontal and cancer-causing bacteria. Additionally, they help to prevent diseases by enhancing immune system performance and modulating the host's immunological response. There is a significant improvement in dental health while using oral probiotics [84][85].

The development of peptic ulcers in the duodenum or stomach is known as peptic ulcer disease. The main risk factors for gastric and duodenal ulcers are the use of aspirin or nonsteroidal anti-inflammatory medicines (NSAIDs) and the existence of an H. pylori infection. The function of the barrier may be improved by probiotics. The primary defence against pathogenic bacteria is the acid and mucus barrier found in the stomach's gastric mucosa. Some probiotics can increase the upregulation of fitting linked proteins and promote the secretion of mucus and mucin, which strengthens the mucus secretion process and improves the protective capacity of the stomach mucosal barrier. Furthermore, some probiotic bacteria can create antimicrobial substances such hydrogen peroxide, lactic acid, short-chain fatty acids (SCFAs) and bacteriocins. Short-chain fatty acids (SCFAs) and lactic acid both show signs of partial dissociation and when these organic acids are in their dissociated stages, *H. pylori* is negatively impacted [86][87].

3.13 Prevention of breast cancer

Breast cancer makes for 29.0 % of all cancer cases identified in women, making it the most frequent cancer among them. An estimated 2.5 million instances of breast cancer were reported in 2016 [88].It was previously believed that disparities in hormonal components, reproductive patterns, and detection techniques at various stages were the causes of the wide variances in breast cancer incidence [89][90]. Breast cancer mortality has continuously dropped as a result of advancements in breast cancer detection and treatment. It was previously believed that probiotic supplements could lower the incidence of breast cancer in perimenopausal women. Bacteria believed to have anticancer properties include *Lactococcus and Streptococcus*, which are more common in healthy breast tissue. To see whether they may cause DNA damage, bacteria from malignant females were cultivated on human breast cancer cells. Triple-stranded DNA breaks generated by *Enterobacteriaceae*, *Escherichia coli*, and *Staphylococcus* bacteria were alarmingly visible throughout the proliferation of these malignant cells. Carcinogens can be broken down by the probiotic bacterium *Lactobacillus*. The probiotic *S. thermophilus* strain produces antioxidants that reduce DNA damage [91]. Moreover, Research has indicated that *Lactobacillus crispatus* and *Lactobacillus acidophilus* exhibit antiproliferative properties against breast cancer cells. Furthermore, four distinct cancer-testis antigens' transcriptional activity can be decreased by lactobacilli. It has been revealed that epigenetic controls have a role in the expression of cancer-testis antigens. Thus, its expression may be epigenetically downregulated by *lactobacilli*. A new era of clinical research applications could be enabled by lactobacilli-mediated expressional downregulation of cancer-testis antigens, as these antigens have been associated with high-grade malignancies and poor prognosis [92].

3.14 Prevention of blood cancer

Most hematopoietic malignancies, often known as blood cancers, start in the bone marrow, which is where blood cells are made. Research indicates that probiotics may be useful in the treatment of cancer. A study found a correlation between chronic myeloid leukemia and the therapeutic effects of heat-inactivated *Lactobacillus casei and Lactobacillus paracasei*on the K562 cell line. Bacteria were cultivated in an oxygen-free environment using a particular medium, and their cells were then exposed to a temperature of 100°C to induce cell death.

Lyophilization was used to extract moisture from the dead cells, and autoclaving was used to sterilize them thereafter. The next step involved creating several heat-inactivated bacterial suspensions at different concentrations (125.0, 250.0, 500.0, 1000.0, and 2000.0 g/ml). Three distinct time points—24, 48, and 72 hours—were used to evaluate the in vitro anticancer qualities of heat-killed bacteria using the MTT test. The results showed that *L. casei and L. paracasei* heat-killed cells have anticancer properties in K562 cells. Moreover, the anticancer activities of heat-killed cells are closely correlated with their concentration. In summary, heat-inactivated *Lactobacillus* has great potential and should be investigated further in the field of treatments for chronic myeloid leukaemia[46].

3.15 Prevention of colorectal cancer

One of the most prevalent cancers in the world and the primary cause of cancer-related mortality is colorectal cancer (CRC) [93]. The development of colorectal cancer and its incidence are intimately correlated with the gut microbiota. The altered gut microbiota can initiate carcinogenesis through modifications to the immune system, epithelial hemostasis, metabolic profile and activity, DNA damage and aberrant cellular and molecular activities in colonocytes. Numerous unfavourable treatment-associated side effects negatively impact the quality of life and although multiple cutting-edge medical methods (such as immunotherapy, surgery, chemotherapy, and radiation therapy) are available for the treatment of colorectal cancer, the survival rates are poor [94][95]. So, One well-known bioactive option for treating several illnesses and disorders is probiotics [96][97]. A powerful probiotic strain can help prevent tumorigenesis, including colorectal cancer (CRC), by competing for adhesion sites, producing microbicidal agents like bacteriocin, improving intestinal permeability, releasing bioactive metabolites, regulating immune pathways, and stimulating cell protective responses [95]. Despite several attempts to elucidate the mechanism behind probiotics' anticarcinogenic properties, a definitive explanation explaining probiotics' anti-CRC action remains to be discovered [98][99]. The production of carcinogenic compounds, such as cresols, ammonia, phenols, aglycones, and N-nitroso compounds, is linked to certain bacterial enzymes, including nitrate reductase, azoreductase, β-glucosidase, β-glucuronidase and 7-α-dehydroxylase. These compounds also induce antiapoptotic pathways, which contribute to the development of colorectal cancer [100][101]. Research demonstrated that adding probiotics to the diet dramatically decreased the activity of bacterial enzymes [102][103][104]. The carcinogenic chemicals are released through faeces after binding with peptidoglycan, which is found in the probiotic microorganisms' cell walls. Certain probiotic strains can metabolize carcinogenic substances, particularly amines and N-nitroso substances. Probiotic supplementation has been shown to reduce the incidence of colorectal cancer (CRC) through a variety of mechanisms, including altered metabolic activity of intestinal microbiota (i.e., decreased endogenous generation of carcinogenic chemicals), and the binding and destruction of carcinogens [105].

3.16 Prevention of liver cancer

The second greatest death rate globally is from primary liver cancer. There are various types of malignant tumours in this condition, which can include fibrolamellar HCC (FLC), pediatric neoplasm hepatoblastoma, mixed hepatocellular cholangiocarcinoma (HCC-CAA [106]), intrahepatic cholangiocarcinoma (iCAA), and HCC. Of all primary liver malignancies, HCC accounts for 75.0 –85.0 % of cases [106][107]. The more aggressive proliferative variant of HCC is linked to elevated serum levels of α-fetoprotein (AFP), progenitor cell phenotype expression, mutations in tumour protein 53 (TP53) and activation of the transforming growth factor β (TGF-β), hepatocyte growth factor receptor (MET), protein kinase B (AKT), and insulin-like growth factor (IGF) 2 pathways [108]. The prognosis for HCC patients is still not good generally, despite advances in treatment such as immune therapy, multi-kinase inhibitors, and intra-arterial therapy [109]. Pathogenesis of HCC is connected to adverse changes in the gut microbiota because the hepatic portal circulation connects the liver and the intestines directly [110]. According to this anatomical link, probiotic bacteria may be able to reverse the dysbiosis linked with HCC by reestablishing the complexity and colonization resistance of the gut flora [111]. The expression of tight junction proteins is upregulated by probiotic metabolites and probiotic cell components, which improve gut epithelial integrity. The integrity of the gut epithelium can be preserved by the probiotic bacteria's cell surface proteins, which can reduce gut epithelial cell inflammation and prevent epithelial cell apoptosis. Additionally, probiotics also shield the gut epithelium from harmful bacteria by increasing goblet cells' production of mucus and antimicrobial peptides [112]. Probiotic bacteria, particularly *Bifidobacterium spp. and Lactobacillus spp.,* can lessen fatty liver, lowering the risk of HCC [113].

3.17 Prevention of lung cancer

Lung cancer is the second most frequent type of cancer and the primary cause of cancer-related mortality [114] . According to estimates, smoking is the primary cause of 90.0 % of lung cancer occurrences, and other known risk factors include tobacco smoke, air pollution, and other toxins. The precise mechanics, nevertheless, are not fully understood. Lungs offer a special chance to be exposed to germs and environmental hazards since they are the mucosa site with the biggest surface area in the body and an important interaction with the outside world. Despite being believed to be sterile, many microorganisms reside in the lungs. Introducing new bacteria, their removal by the body and immune system, and their ability to reproduce in the given environment all influence the prevalence of germs. Long-term obstructive pulmonary disease and cystic fibrosis are two lung conditions that seem to have dysregulated lung microbiome [115][116][117][118]. The connection between immunological response to medication and gut flora is one topic of research. Recent research indicates that the gut microbiota's composition may influence how effective immunotherapy is [119]. Probiotics may increase the effectiveness of immunotherapy and help to overcome some of its drawbacks by enhancing gut bacteria diversity and fostering a supportive immunological milieu [7].

4. Future of probiotics

The future of probiotic research is promising and multifaceted, with numerous important areas poised for significant advancements. Though antibiotic resistance is very common nowadays, so probiotics can be replaceable treatments for the future. Identifying and utilizing probiotics from diverse and sustainable sources, including soil, and marine environments, can provide new strains with unique benefits. This approach also supports biodiversity and environmental sustainability. Innovations in delivery mechanisms, such as encapsulation technologies and smart delivery systems, can improve the survival and efficacy of probiotics as they pass through the digestive system, ensuring they reach their target site in the gut. Advances in genetic engineering could enable the creation of genetically modified probiotics with enhanced functionality, such as targeted delivery of therapeutic compounds or improved survival and colonization in the gut. Further research into the precise mechanisms of action of different probiotic strains can provide deeper insights into their role in health and disease, facilitating more targeted and effective applications.

5. Conclusion

Probiotics are an exciting and rapidly developing field of study with significant effects on human health. These good bacteria play a major role in preserving and improving the balance of the gut microbiota. They are primarily obtained via fermented foods and nutritional supplements. Their potential for therapeutic use is highlighted by their advantageous activities, which include enhancing the intestinal barrier, regulating the immunological response, and generating vital metabolites. Probiotics have been shown to help treat a variety of illnesses, including mental health problems, systemic diseases like diabetes, and gastrointestinal ailments. Although the efficacy of probiotics varies greatly depending on the strain and the health status of the individual, the isolation and characterization of particular probiotic strains have permitted focused therapeutic uses. The growing understanding of the gut microbiome's critical role in general health is fueling the field's expansion. To completely comprehend and maximize the use of probiotics in clinical settings, more study is necessary.

Data Availability

Data is available on request.

References

[1] K. I. Mohr, "History of antibiotics research," *Curr. Top. Microbiol. Immunol.*, vol. 398, no. January, pp. 237–272, 2016, doi: 10.1007/82_2016_499.

[2] L. D. Blondeau and J. M. Blondeau, "Antimicrobial Resistance," *Diagnostics Ther. Vet. Dermatology*, pp. 163–174, 2021, doi: 10.1002/9781119680642.ch16.

[3] A. Salahi and W. A. Abd El-Ghany, "Beyond probiotics, uses of their next-generation for poultry and humans: A review," *J. Anim. Physiol. Anim. Nutr. (Berl).*, no. October 2023, pp. 1–12, 2024, doi: 10.1111/jpn.13972.

[4] C. Wiegers, E. H. T. van Beek, and O. F. A. Larsen, "Clinical research with probiotics as an indicator of global valorization since the year 2000," *Front. Microbiol.*, vol. 14, no. December, pp. 1–9, 2023, doi: 10.3389/fmicb.2023.1323920.

[5] P. A. Mackowiak, "Recycling Metchnikoff: Probiotics, the intestinal microbiome and the quest for long life," *Front. Public Heal.*, vol. 1, no. NOV, pp. 1–3, 2013, doi:

10.3389/fpubh.2013.00052.

[6] L. Morelli and L. Capurso, “FAO/WHO Guidelines on Probiotics: 10 Years Later,” *J. Clin. Gastroenterol.*, vol. 46, 2012.

[7] C. Hill *et al.*, “Expert consensus document: The international scientific association for probiotics and prebiotics consensus statement on the scope and appropriate use of the term probiotic,” *Nat. Rev. Gastroenterol. Hepatol.*, vol. 11, no. 8, pp. 506–514, 2014, doi: 10.1038/nrgastro.2014.66.

[8] M. Adel, A.-F. M. El-Sayed, S. Yeganeh, M. Dadar, and S. S. Giri, “Effect of Potential Probiotic Lactococcus lactis Subsp. lactis on Growth Performance, Intestinal Microbiota, Digestive Enzyme Activities, and Disease Resistance of Litopenaeus vannamei,” *Probiotics Antimicrob. Proteins*, vol. 9, no. 2, pp. 150–156, 2017, doi: 10.1007/s12602-016-9235-9.

[9] M. A. Azcárate-Peril, M. Sikes, and J. M. Bruno-Bárcena, “The intestinal microbiota, gastrointestinal environment and colorectal cancer: A putative role for probiotics in prevention of colorectal cancer?,” *Am. J. Physiol. - Gastrointest. Liver Physiol.*, vol. 301, no. 3, 2011, doi: 10.1152/ajpgi.00110.2011.

[10] C. Maldonado Galdeano, S. I. Cazorla, J. M. Lemme Dumit, E. Vélez, and G. Perdigón, “Beneficial effects of probiotic consumption on the immune system,” *Ann. Nutr. Metab.*, vol. 74, no. 2, pp. 115–124, 2019, doi: 10.1159/000496426.

[11] G. V. de Melo Pereira, B. de Oliveira Coelho, A. I. Magalhães Júnior, V. Thomaz-Soccol, and C. R. Soccol, “How to select a probiotic? A review and update of methods and criteria,” *Biotechnol. Adv.*, vol. 36, no. 8, pp. 2060–2076, 2018, doi: https://doi.org/10.1016/j.biotechadv.2018.09.003.

[12] J. Plaza-Díaz *et al.*, “Gene expression profiling in the intestinal mucosa of obese rats administered probiotic bacteria,” *Sci. Data*, vol. 4, no. 1, p. 170186, 2017, doi:

10.1038/sdata.2017.186.

[13] M. C. Collado, M. Gueimonde, and S. Salminen, “Chapter 23 - Probiotics in Adhesion of Pathogens: Mechanisms of Action,” R. R. Watson and V. R. B. T.-B. F. in P. H. Preedy, Eds., Boston: Academic Press, 2010, pp. 353–370. doi: https://doi.org/10.1016/B978-0-12-374938-3.00023-2.

[14] S. Hemaiswarya, R. Raja, R. Ravikumar, and I. S. Carvalho, “Mechanism of action of probiotics,” *Brazilian Arch. Biol. Technol.*, vol. 56, no. 1, pp. 113–119, 2013, doi: 10.1590/S1516-89132013000100015.

[15] E. A. Trush, E. A. Poluektova, A. G. Beniashvilli, O. S. Shifrin, Y. M. Poluektov, and V. T. Ivashkin, “The Evolution of Human Probiotics: Challenges and Prospects,” *Probiotics Antimicrob. Proteins*, vol. 12, no. 4, pp. 1291–1299, 2020, doi: 10.1007/s12602-019-09628-4.

[16] “Gram-positive bacteria with probiotic potential for the Apis mellifera L. honey bee: the experience in the northwest of Argentina. Probiotics and antimicrobial proteins”.

[17] G. Reid and J. Burton, “Use of Lactobacillus to prevent infection by pathogenic bacteria,” *Microbes Infect.*, vol. 4, no. 3, pp. 319–324, 2002, doi: 10.1016/S1286-4579(02)01544-7.

[18] R. A. Yunes *et al.*, “A Multi-strain Potential Probiotic Formulation of GABA-Producing Lactobacillus plantarum 90sk and Bifidobacterium adolescentis 150 with Antidepressant Effects,” *Probiotics Antimicrob. Proteins*, vol. 12, no. 3, pp. 973–979, 2020, doi: 10.1007/s12602-019-09601-1.

[19] S. Fijan, J. A. ter Haar, and L. Varga, “Probiotic Microorganisms and Their Benefit to Human Health,” *Adv. Probiotics*, pp. 3–22, 2021, doi: 10.1016/b978-0-12-822909-5.00001-0.

[20] S. Karimi, F. Azizi, M. Nayeb-Aghaee, and L. Mahmoodnia, “The antimicrobial activity of probiotic bacteria Escherichia coli isolated from different natural sources against

hemorrhagic E. coli O157:H7," *Electron. Physician*, vol. 10, no. 3, pp. 6548–6553, 2018, doi: 10.19082/6548.

[21] S. Karimi, E. Rashidian, M. Birjandi, and L. Mahmoodnia, "Antagonistic effect of isolated probiotic bacteria from natural sources against intestinal Escherichia coli pathotypes," *Electron. Physician*, vol. 10, no. 3, pp. 6534–6539, 2018, doi: 10.19082/6534.

[22] R. Article, "Pakistan Veterinary Journal," vol. 8318, pp. 303–308, 2012.

[23] A. Latif *et al.*, "Probiotics: mechanism of action, health benefits and their application in food industries," *Front. Microbiol.*, vol. 14, no. August, 2023, doi: 10.3389/fmicb.2023.1216674.

[24] C. L. Ohland and W. K. MacNaughton, "Probiotic bacteria and intestinal epithelial barrier function," *Am. J. Physiol. - Gastrointest. Liver Physiol.*, vol. 298, no. 6, 2010, doi: 10.1152/ajpgi.00243.2009.

[25] M. Bermudez-Brito, J. Plaza-Díaz, S. Muñoz-Quezada, C. Gómez-Llorente, and A. Gil, "Probiotic mechanisms of action," *Ann. Nutr. Metab.*, vol. 61, no. 2, pp. 160–174, 2012, doi: 10.1159/000342079.

[26] M. L. van Tassell and M. J. Miller, "Lactobacillus adhesion to mucus," *Nutrients*, vol. 3, no. 5, pp. 613–636, 2011, doi: 10.3390/nu3050613.

[27] C. Petruzziello, A. Saviano, and V. Ojetti, "Probiotics, the Immune Response and Acute Appendicitis: A Review," *Vaccines*, vol. 11, no. 7, 2023, doi: 10.3390/vaccines11071170.

[28] D. Sajedi, R. Shabani, and A. Elmieh, "Changes in leptin, serotonin, and cortisol after eight weeks of aerobic exercise with probiotic intake in a cuprizone-induced demyelination mouse model of multiple sclerosis," *Cytokine*, vol. 144, p. 155590, 2021, doi: https://doi.org/10.1016/j.cyto.2021.155590.

[29] D. Gangaraju, A. V. Raghu, and P. Siddalingaiya Gurudutt, " Green synthesis of γ□aminobutyric acid using permeabilized probiotic Enterococcus faecium for biocatalytic

application ," *Nano Sel.*, vol. 3, no. 10, pp. 1436–1447, 2022, doi: 10.1002/nano.202200059.

[30] S. Srivastav *et al.*, "Probiotics mixture increases butyrate, and subsequently rescues the nigral dopaminergic neurons from MPTP and rotenone-induced neurotoxicity," *J. Nutr. Biochem.*, vol. 69, pp. 73–86, 2019, doi: https://doi.org/10.1016/j.jnutbio.2019.03.021.

[31] L. Quintieri, F. Fanelli, L. Monaci, and V. Fusco, "Milk and Its Derivatives as Sources of Components and Microorganisms with Health-Promoting Properties: Probiotics and Bioactive Peptides," *Foods*, vol. 13, no. 4, 2024, doi: 10.3390/foods13040601.

[32] T. Li, D. Teng, R. Mao, Y. Hao, X. Wang, and J. Wang, "A critical review of antibiotic resistance in probiotic bacteria," *Food Res. Int.*, vol. 136, p. 109571, 2020, doi: https://doi.org/10.1016/j.foodres.2020.109571.

[33] M. Zommiti, M. G. J. Feuilloley, and N. Connil, "Update of probiotics in human world: A nonstop source of benefactions till the end of time," *Microorganisms*, vol. 8, no. 12, pp. 1–33, 2020, doi: 10.3390/microorganisms8121907.

[34] V. Fusco and G. M. Quero, "Culture-Dependent and Culture-Independent Nucleic-Acid-Based Methods Used in the Microbial Safety Assessment of Milk and Dairy Products.," *Compr. Rev. food Sci. food Saf.*, vol. 13, no. 4, pp. 493–537, Jul. 2014, doi: 10.1111/1541-4337.12074.

[35] L. Fontana, M. Bermudez-Brito, J. Plaza-Diaz, S. Muñoz-Quezada, and A. Gil, "Sources, isolation, characterisation and evaluation of probiotics," *Br. J. Nutr.*, vol. 109, no. S2, pp. S35–S50, 2013, doi: DOI: 10.1017/S0007114512004011.

[36] M. Cunningham *et al.*, "Shaping the Future of Probiotics and Prebiotics," *Trends Microbiol.*, vol. 29, no. 8, pp. 667–685, 2021, doi: 10.1016/j.tim.2021.01.003.

[37] H. Bodke and S. Jogdand, "Role of Probiotics in Human Health.," *Cureus*, vol. 14, no. 11, p. e31313, Nov. 2022, doi: 10.7759/cureus.31313.

[38] A. Ricci *et al.*, "Scientific Opinion on the update of the list of QPS-recommended biological agents intentionally added to food or feed as notified to EFSA," *EFSA J.*, vol. 15, no. 3, 2017, doi: 10.2903/J.EFSA.2017.4664.

[39] "The European Union summary report on trends and sources of zoonoses, zoonotic agents and food-borne outbreaks in 2016.," *EFSA journal. Eur. Food Saf. Auth.*, vol. 15, no. 12, p. e05077, Dec. 2017, doi: 10.2903/j.efsa.2017.5077.

[40] K. Singh and A. Rao, "Probiotics: A potential immunomodulator in COVID-19 infection management," *Nutr. Res.*, vol. 87, pp. 1–12, 2021, doi: https://doi.org/10.1016/j.nutres.2020.12.014.

[41] V. Bunešová *et al.*, "Bifidobacterium animalis subsp. lactis strains isolated from dog faeces," *Vet. Microbiol.*, vol. 160, no. 3, pp. 501–505, 2012, doi: https://doi.org/10.1016/j.vetmic.2012.06.005.

[42] Z. Abbasi, S. M. Ghasemi, Y. Ahmadi, and D. Shokri, "Isolation and Identification of Effective Probiotics on Drug-Resistant Acinetobacter baumannii Strains and Their Biofilms," *Can. J. Infect. Dis. Med. Microbiol.*, vol. 2024, 2024, doi: 10.1155/2024/8570521.

[43] S. E. A. *et al.*, "Isolation of Lactobacillus salivarius 1077 (NRRL B-50053) and Characterization of Its Bacteriocin, Including the Antimicrobial Activity Spectrum," *Appl. Environ. Microbiol.*, vol. 77, no. 8, pp. 2749–2754, Apr. 2011, doi: 10.1128/AEM.02481-10.

[44] A. Ghiaei, S. M. Ghasemi, and D. Shokri, "Investigating the Antagonistic Effect of Indigenous Probiotics on Carbapenem-Resistant Pseudomonas aeruginosa Strains," *Biomed Res. Int.*, vol. 2023, 2023, doi: 10.1155/2023/6645657.

[45] B. R. Goldin, "Health benefits of probiotics," *Br. J. Nutr.*, vol. 80, no. SUPPL. 2, 1998, doi: 10.1017/s0007114500006036.

[46] H. Naeem *et al.*, “Role of Probiotics against Human Cancers, Inflammatory Diseases, and Other Complex Malignancies,” *J. Food Biochem.*, vol. 2024, 2024, doi: 10.1155/2024/6632209.

[47] Y. K. Lee and S. K. Mazmanian, “Has the Microbiota Played a Critical Role in the Evolution of the Adaptive Immune System?,” *Science (80-.).*, vol. 330, no. 6012, pp. 1768–1773, Dec. 2010, doi: 10.1126/science.1195568.

[48] I. Spacova, J. L. Ceuppens, S. F. Seys, M. I. Petrova, and S. Lebeer, “Probiotics against airway allergy: host factors to consider,” *DMM Dis. Model. Mech.*, vol. 11, no. 7, 2018, doi: 10.1242/DMM.034314.

[49] H. Knipe, B. Temperton, A. Lange, D. Bass, and C. R. Tyler, “Probiotics and competitive exclusion of pathogens in shrimp aquaculture,” *Rev. Aquac.*, vol. 13, no. 1, pp. 324–352, 2021, doi: 10.1111/raq.12477.

[50] D. R. Silva, J. de C. O. Sardi, N. de S. Pitangui, S. M. Roque, A. C. B. da Silva, and P. L. Rosalen, “Probiotics as an alternative antimicrobial therapy: Current reality and future directions,” *J. Funct. Foods*, vol. 73, p. 104080, 2020, doi: https://doi.org/10.1016/j.jff.2020.104080.

[51] C. Prabhurajeshwar and K. Chandrakanth, “Evaluation of antimicrobial properties and their substances against pathogenic bacteria in-vitro by probiotic Lactobacilli strains isolated from commercial yoghurt,” *Clin. Nutr. Exp.*, vol. 23, pp. 97–115, 2019, doi: https://doi.org/10.1016/j.yclnex.2018.10.001.

[52] J. Plaza-Díaz, F. J. Ruiz-Ojeda, L. M. Vilchez-Padial, and A. Gil, “Evidence of the anti-inflammatory effects of probiotics and synbiotics in intestinal chronic diseases,” *Nutrients*, vol. 9, no. 6, 2017, doi: 10.3390/nu9060555.

[53] A. La Storia, F. A. Di Giuseppe, S. Volpe, V. Oliviero, F. Villani, and E. Torrieri, “Physical properties and antimicrobial activity of bioactive film based on whey protein

and Lactobacillus curvatus 54M16 producer of bacteriocins," *Food Hydrocoll.*, vol. 108, p. 105959, 2020, doi: https://doi.org/10.1016/j.foodhyd.2020.105959.

[54] A. Pérez-Ramos, D. Madi-Moussa, F. Coucheney, and D. Drider, "Current knowledge of the mode of action and immunity mechanisms of lab-bacteriocins," *Microorganisms*, vol. 9, no. 10, 2021, doi: 10.3390/microorganisms9102107.

[55] F. A. C. Martinez, E. M. Balciunas, A. Converti, P. D. Cotter, and R. P. de Souza Oliveira, "Bacteriocin production by Bifidobacterium spp. A review," *Biotechnol. Adv.*, vol. 31, no. 4, pp. 482–488, 2013, doi: https://doi.org/10.1016/j.biotechadv.2013.01.010.

[56] M. Rejaii and A. M. Sani, "Role of probiotics in health and disease," *Int. J. PharmTech Res.*, vol. 9, no. 7, pp. 351–356, 2016.

[57] M. Daniali, S. Nikfar, and M. Abdollahi, "A brief overview on the use of probiotics to treat overweight and obese patients," *Expert Rev. Endocrinol. Metab.*, vol. 15, no. 1, pp. 1–4, 2020, doi: 10.1080/17446651.2020.1719068.

[58] H.-S. Ejtahed *et al.*, "Probiotics supplementation for the obesity management; A systematic review of animal studies and clinical trials," *J. Funct. Foods*, vol. 52, pp. 228–242, 2019, doi: https://doi.org/10.1016/j.jff.2018.10.039.

[59] L. Chen *et al.*, "Lactobacillus acidophilus suppresses colitis-associated activation of the IL-23/Th17 axis," *J. Immunol. Res.*, vol. 2015, 2015, doi: 10.1155/2015/909514.

[60] E. Barengolts, "Gut Microbiota, Prebiotics, Probiotics, and Synbiotics in Management of Obesity and Prediabetes: Review of Randomized Controlled Trials," *Endocr. Pract.*, vol. 22, no. 10, pp. 1224–1234, 2016, doi: https://doi.org/10.4158/EP151157.RA.

[61] J. Sun and N. J. Buys, "Glucose- and glycaemic factor-lowering effects of probiotics on diabetes: a meta-analysis of randomised placebo-controlled trials," *Br. J. Nutr.*, vol. 115, no. 7, pp. 1167–1177, 2016, doi: DOI: 10.1017/S0007114516000076.

[62] C. P. Rosa, G. A. Brancaglion, T. M. Miyauchi-Tavares, P. P. Corsetti, and L. A. de

Almeida, “Antibiotic-induced dysbiosis effects on the murine gastrointestinal tract and their systemic repercussions,” *Life Sci.*, vol. 207, pp. 480–491, 2018, doi: https://doi.org/10.1016/j.lfs.2018.06.030.

[63] Y. Mishima and R. B. Sartor, “Manipulating resident microbiota to enhance regulatory immune function to treat inflammatory bowel diseases,” *J. Gastroenterol.*, vol. 55, no. 1, pp. 4–14, 2020, doi: 10.1007/s00535-019-01618-1.

[64] A. S. Sandberg, G. Önning, N. Engström, and N. Scheers, “Iron supplements containing Lactobacillus plantarum 299v increase ferric iron and up-regulate the ferric reductase DCYTB in human Caco-2/HT29 MTX co-cultures,” *Nutrients*, vol. 10, no. 12, 2018, doi: 10.3390/nu10121949.

[65] N. Hadadi, V. Berweiler, H. Wang, and M. Trajkovski, “Intestinal microbiota as a route for micronutrient bioavailability,” *Curr. Opin. Endocr. Metab. Res.*, vol. 20, p. 100285, 2021, doi: https://doi.org/10.1016/j.coemr.2021.100285.

[66] N. Ohtani, S. Yoshimoto, and E. Hara, “Obesity and cancer: A gut microbial connection,” *Cancer Res.*, vol. 74, no. 7, pp. 1885–1889, 2014, doi: 10.1158/0008-5472.CAN-13-3501.

[67] “Increases Iron Absorption in Young Females- Double Isotope Sequential Single-Blind Studies in Menstruating Women”.

[68] D. J. Korcok, N. A. Tršic-Milanovic, N. D. Ivanovic, and B. I. Dordevic, “Development of probiotic formulation for the treatment of iron deficiency anemia,” *Chem. Pharm. Bull.*, vol. 66, no. 4, pp. 347–352, 2018, doi: 10.1248/cpb.c17-00634.

[69] G. M. Rosen, S. Morrissette, A. Larson, P. Stading, K. H. Griffin, and T. L. Barnes, “Use of a Probiotic to Enhance Iron Absorption in a Randomized Trial of Pediatric Patients Presenting with Iron Deficiency,” *J. Pediatr.*, vol. 207, pp. 192-197.e1, 2019, doi: 10.1016/j.jpeds.2018.12.026.

[70] A. Ballini *et al.*, “Probiotics Improve Urogenital Health in Women.,” *Open access Maced.*

J. Med. Sci., vol. 6, no. 10, pp. 1845–1850, Oct. 2018, doi: 10.3889/oamjms.2018.406.

[71] M. G. Cagetti, S. Mastroberardino, E. Milia, F. Cocco, P. Lingström, and G. Campus, "The use of probiotic strains in caries prevention: A systematic review," *Nutrients*, vol. 5, no. 7, pp. 2530–2550, 2013, doi: 10.3390/nu5072530.

[72] T. Hedayati-Hajikand, U. Lundberg, C. Eldh, and S. Twetman, "Effect of probiotic chewing tablets on early childhood caries - a randomized controlled trial," *BMC Oral Health*, vol. 15, no. 1, pp. 1–5, 2015, doi: 10.1186/s12903-015-0096-5.

[73] M. R. Jørgensen, G. Castiblanco, S. Twetman, and M. K. Keller, "Prevention of caries with probiotic bacteria during early childhood. Promising but inconsistent findings," *Am. J. Dent.*, vol. 29, no. 3, pp. 127–131, 2016.

[74] A. M. Pujia *et al.*, "The probiotics in dentistry: a narrative review," *Eur. Rev. Med. Pharmacol. Sci.*, vol. 21, no. 6, pp. 1405–1412, 2017.

[75] M. E. Jach *et al.*, "The Role of Probiotics and Their Metabolites in the Treatment of Depression," *Molecules*, vol. 28, no. 7, 2023, doi: 10.3390/molecules28073213.

[76] A. Oniszczuk, T. Oniszczuk, M. Gancarz, and J. Szymańska, "Role of gut microbiota, probiotics and prebiotics in the cardiovascular diseases," *Molecules*, vol. 26, no. 4, pp. 1–15, 2021, doi: 10.3390/molecules26041172.

[77] J. Khongrum *et al.*, "Safety and Effects of Lactobacillus paracasei TISTR 2593 Supplementation on Improving Cholesterol Metabolism and Atherosclerosis-Related Parameters in Subjects with Hypercholesterolemia: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial," *Nutrients*, vol. 15, no. 3, 2023, doi: 10.3390/nu15030661.

[78] B. Arroll, "Common cold.," *BMJ Clin. Evid.*, vol. 2011, Mar. 2011.

[79] T. Vos *et al.*, "Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global

Burden of Disease Study 2015," *Lancet*, vol. 388, no. 10053, pp. 1545–1602, 2016, doi: 10.1016/S0140-6736(16)31678-6.

[80] D. Furushima *et al.*, "Prevention of acute upper respiratory infections by consumption of catechins in healthcare workers: A randomized, placebo-controlled trial," *Nutrients*, vol. 12, no. 1, pp. 1–12, 2020, doi: 10.3390/nu12010004.

[81] Y. Zhao, B. R. Dong, and Q. Hao, "Probiotics for preventing acute upper respiratory tract infections," *Cochrane Database Syst. Rev.*, no. 8, 2022, doi: 10.1002/14651858.CD006895.pub4.

[82] K. Shida *et al.*, "Daily intake of fermented milk with Lactobacillus casei strain Shirota reduces the incidence and duration of upper respiratory tract infections in healthy middle-aged office workers," *Eur. J. Nutr.*, vol. 56, no. 1, pp. 45–53, 2017, doi: 10.1007/s00394-015-1056-1.

[83] A. Singh, A. Agarwal, E. Abhishek, S. Jain, R. Jawarker, and M. Raza, "Probiotics as an adjuvant treatment for recurrent aphthous ulcer," *Int. J. Health Sci. (Qassim).*, no. August, 2022, doi: 10.53730/ijhs.v6ns5.9689.

[84] X. Dou *et al.*, "Probiotic-loaded calcium alginate/fucoidan hydrogels for promoting oral ulcer healing," *Int. J. Biol. Macromol.*, vol. 244, p. 125273, 2023, doi: https://doi.org/10.1016/j.ijbiomac.2023.125273.

[85] M. Nirmala, S. G. Smitha, and G. J. Kamath, "A Study to Assess The Efficacy of Local Application of Oral Probiotic in Treating Recurrent Aphthous Ulcer and Oral Candidiasis," *Indian J. Otolaryngol. Head Neck Surg.*, vol. 71, no. 1, pp. 113–117, 2019, doi: 10.1007/s12070-017-1139-9.

[86] A. Lanas and F. K. L. Chan, "Peptic ulcer disease," *Lancet*, vol. 390, no. 10094, pp. 613–624, 2017, doi: https://doi.org/10.1016/S0140-6736(16)32404-7.

[87] B. Liang, Y. Yuan, X. J. Peng, X. L. Liu, X. K. Hu, and D. M. Xing, "Current and future

perspectives for Helicobacter pylori treatment and management: From antibiotics to probiotics," *Front. Cell. Infect. Microbiol.*, vol. 12, no. November, pp. 1–13, 2022, doi: 10.3389/fcimb.2022.1042070.

[88] R. L. Siegel, K. D. Miller, and A. Jemal, "Cancer statistics, 2018," *CA. Cancer J. Clin.*, vol. 68, no. 1, pp. 7–30, 2018, doi: 10.3322/caac.21442.

[89] A. Jemal, R. Siegel, E. Ward, Y. Hao, J. Xu, and M. J. Thun, "Cancer Statistics , 2009 BOTH SEXES FEMALE BOTH SEXES ESTIMATED DEATHS," *CA Cancer J Clin*, vol. 59, no. 4, pp. 1–25, 2009, doi: 10.1002/caac.20073.Available.

[90] K. N. Anderson, R. B. Schwab, and M. E. Martinez, "Reproductive risk factors and breast cancer subtypes: a review of the literature," *Breast Cancer Res. Treat.*, vol. 144, no. 1, pp. 1–10, 2014, doi: 10.1007/s10549-014-2852-7.

[91] G. Reid *et al.*, "New scientific paradigms for probiotics and prebiotics," *J. Clin. Gastroenterol.*, vol. 37, no. 2, pp. 105–118, 2003, doi: 10.1097/00004836-200308000-00004.

[92] R. Azam *et al.*, "Lactobacillus acidophilus and Lactobacillus crispatus culture supernatants downregulate expression of cancer-testis genes in the MDA-MB-231 cell line," *Asian Pacific J. Cancer Prev.*, vol. 15, no. 10, pp. 4255–4259, 2014, doi: 10.7314/APJCP.2014.15.10.4255.

[93] F. K. Tabung, L. S. Brown, and T. T. Fung, "Dietary Patterns and Colorectal Cancer Risk: a Review of 17 Years of Evidence (2000–2016)," *Curr. Colorectal Cancer Rep.*, vol. 13, no. 6, pp. 440–454, 2017, doi: 10.1007/s11888-017-0390-5.

[94] C. Meng, C. Bai, T. D. Brown, L. E. Hood, and Q. Tian, "Human Gut Microbiota and Gastrointestinal Cancer," *Genomics. Proteomics Bioinformatics*, vol. 16, no. 1, pp. 33–49, Feb. 2018, doi: 10.1016/j.gpb.2017.06.002.

[95] R. Hendler and Y. Zhang, "Probiotics in the Treatment of Colorectal Cancer," *Medicines*,

vol. 5, no. 3, p. 101, 2018, doi: 10.3390/medicines5030101.

[96] S. Selvamani *et al.*, “Efficacy of Probiotics-Based Interventions as Therapy for Inflammatory Bowel Disease: A Recent Update,” *Saudi J. Biol. Sci.*, vol. 29, no. 5, pp. 3546–3567, 2022, doi: https://doi.org/10.1016/j.sjbs.2022.02.044.

[97] B. S. Sivamaruthi, P. Kesika, and C. Chaiyasut, “A mini-review of human studies on cholesterol-lowering properties of probiotics,” *Sci. Pharm.*, vol. 87, no. 4, 2019, doi: 10.3390/scipharm87040026.

[98] J. Bassaganya-Riera, M. Viladomiu, M. Pedragosa, C. De Simone, and R. Hontecillas, “Immunoregulatory Mechanisms Underlying Prevention of Colitis-Associated Colorectal Cancer by Probiotic Bacteria,” *PLoS One*, vol. 7, no. 4, p. e34676, Apr. 2012.

[99] Z. Faghfoori, B. Pourghassem Gargari, A. Saber Gharamaleki, H. Bagherpour, and A. Yari Khosroushahi, “Cellular and molecular mechanisms of probiotics effects on colorectal cancer,” *J. Funct. Foods*, vol. 18, pp. 463–472, 2015, doi: https://doi.org/10.1016/j.jff.2015.08.013.

[100] H. Tjalsma, A. Boleij, J. R. Marchesi, and B. E. Dutilh, “A bacterial driver–passenger model for colorectal cancer: beyond the usual suspects,” *Nat. Rev. Microbiol.*, vol. 10, no. 8, pp. 575–582, 2012, doi: 10.1038/nrmicro2819.

[101] Q. Zhu, R. Gao, W. Wu, and H. Qin, “The role of gut microbiota in the pathogenesis of colorectal cancer,” *Tumor Biol.*, vol. 34, no. 3, pp. 1285–1300, 2013, doi: 10.1007/s13277-013-0684-4.

[102] A. Verma and G. Shukla, “Probiotics Lactobacillus rhamnosus GG, Lactobacillus acidophilus Suppresses DMH-Induced Procarcinogenic Fecal Enzymes and Preneoplastic Aberrant Crypt Foci in Early Colon Carcinogenesis in Sprague Dawley Rats,” *Nutr. Cancer*, vol. 65, no. 1, pp. 84–91, Jan. 2013, doi: 10.1080/01635581.2013.741746.

[103] D. Mohania, V. K. Kansal, P. Kruzliak, and A. Kumari, “Probiotic Dahi Containing

Lactobacillus acidophilus and Bifidobacterium bifidum Modulates the Formation of Aberrant Crypt Foci, Mucin-Depleted Foci, and Cell Proliferation on 1,2-Dimethylhydrazine-Induced Colorectal Carcinogenesis in Wistar Rats," *Rejuvenation Res.*, vol. 17, no. 4, pp. 325–333, Feb. 2014, doi: 10.1089/rej.2013.1537.

[104] A. Nowak, K. Śliżewska, J. Błasiak, and Z. Libudzisz, "The influence of Lactobacillus casei DN 114 001 on the activity of faecal enzymes and genotoxicity of faecal water in the presence of heterocyclic aromatic amines," *Anaerobe*, vol. 30, pp. 129–136, 2014, doi: https://doi.org/10.1016/j.anaerobe.2014.09.014.

[105] S. A. dos Reis, L. L. da Conceição, N. P. Siqueira, D. D. Rosa, L. L. da Silva, and M. do C. G. Peluzio, "Review of the mechanisms of probiotic actions in the prevention of colorectal cancer," *Nutr. Res.*, vol. 37, pp. 1–19, 2017, doi: https://doi.org/10.1016/j.nutres.2016.11.009.

[106] F. Bray, J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre, and A. Jemal, "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries," *CA. Cancer J. Clin.*, vol. 68, no. 6, pp. 394–424, 2018, doi: 10.3322/caac.21492.

[107] D. Sia, A. Villanueva, S. L. Friedman, and J. M. Llovet, "Liver Cancer Cell of Origin, Molecular Class, and Effects on Patient Prognosis," *Gastroenterology*, vol. 152, no. 4, pp. 745–761, 2017, doi: https://doi.org/10.1053/j.gastro.2016.11.048.

[108] C. K. Y. Ng, S. Piscuoglio, and L. M. Terracciano, "Molecular classification of hepatocellular carcinoma: The view from metabolic zonation.," *Hepatology (Baltimore, Md.)*, vol. 66, no. 5. United States, pp. 1377–1380, Nov. 2017. doi: 10.1002/hep.29311.

[109] K.-L. Ko, L.-Y. Mak, K.-S. Cheung, and M.-F. Yuen, "Hepatocellular carcinoma: recent advances and emerging medical therapies.," *F1000Research*, vol. 9, 2020, doi: 10.12688/f1000research.24543.1.

[110] H. Gupta, G. S. Youn, M. J. Shin, and K. T. Suk, "Role of gut microbiota in hepatocarcinogenesis," *Microorganisms*, vol. 7, no. 5, 2019, doi: 10.3390/microorganisms7050121.

[111] M. L. Y. Wan and H. El-Nezami, "Targeting gut microbiota in hepatocellular carcinoma: probiotics as a novel therapy.," *Hepatobiliary Surg. Nutr.*, vol. 7, no. 1, pp. 11–20, Feb. 2018, doi: 10.21037/hbsn.2017.12.07.

[112] Q. Liu *et al.*, "Surface components and metabolites of probiotics for regulation of intestinal epithelial barrier," *Microb. Cell Fact.*, vol. 19, no. 1, p. 23, 2020, doi: 10.1186/s12934-020-1289-4.

[113] N. C. Chávez-Tapia *et al.*, "Current evidence on the use of probiotics in liver diseases," *J. Funct. Foods*, vol. 17, pp. 137–151, 2015, doi: https://doi.org/10.1016/j.jff.2015.05.009.

[114] Y. Zhao *et al.*, "Role of lung and gut microbiota on lung cancer pathogenesis," *J. Cancer Res. Clin. Oncol.*, vol. 147, no. 8, pp. 2177–2186, 2021, doi: 10.1007/s00432-021-03644-0.

[115] R. P. Dickson and G. B. Huffnagle, "The Lung Microbiome: New Principles for Respiratory Bacteriology in Health and Disease," *PLOS Pathog.*, vol. 11, no. 7, p. e1004923, Jul. 2015.

[116] R. P. Dickson, F. J. Martinez, and G. B. Huffnagle, "The role of the microbiome in exacerbations of chronic lung diseases," *Lancet*, vol. 384, no. 9944, pp. 691–702, 2014, doi: https://doi.org/10.1016/S0140-6736(14)61136-3.

[117] R. P. Dickson, J. R. Erb-Downward, and G. B. Huffnagle, "The role of the bacterial microbiome in lung disease," *Expert Rev. Respir. Med.*, vol. 7, no. 3, pp. 245–257, Jun. 2013, doi: 10.1586/ers.13.24.

[118] R. P. Dickson, Y. J. Huang, F. J. Martinez, and G. B. Huffnagle, "The lung microbiome and viral-induced exacerbations of chronic obstructive pulmonary disease: new

observations, novel approaches.," *American journal of respiratory and critical care medicine*, vol. 188, no. 10. United States, pp. 1185–1186, Nov. 2013. doi: 10.1164/rccm.201309-1573ED.

[119] H. Sadrekarimi *et al.*, "Emerging role of human microbiome in cancer development and response to therapy: special focus on intestinal microflora," *J. Transl. Med.*, vol. 20, no. 1, p. 301, 2022, doi: 10.1186/s12967-022-03492-7.