### Chapter 28

# Strain-specific Probiotics: Linking Probiotic Strains with Health and Disease

Hira Hameed<sup>1</sup>, Mudassar Mohiuddin<sup>1\*</sup>, Shiza Husnain<sup>2</sup>, Abu Baker Siddique<sup>3</sup>, Shahida Younas<sup>1</sup>, Muhammad Tayyab Sarwar<sup>1</sup>, Riaz Hussain<sup>4</sup> and Muhammad Khalid<sup>1</sup>

<sup>1</sup>Department of Microbiology, FV and AS, Islamia University of Bahawalpur, Pakistan <sup>2</sup>Bahria University Lahore campus, Pakistan <sup>3</sup>Institute of Microbiology. Government College University Faisalabad, Pakistan <sup>4</sup>Department of Pathology, FV and AS, Islamia University of Bahawalpur, Pakistan \*Corresponding author: drmudassar2008@gmail.com

#### ABSTRACT

Probiotics are beneficial live microorganisms present in the food and are not harmful to humans. Several microbial strains act as probiotics, which belong to the genera, *Lactobacillus, Bifidobacteria, Saccharomyces, Bacillus, Streptococcus*, and *Enterococcus*. Probiotics may benefit human health via enhancing intestinal barrier function, generating neurotransmitters, immunomodulating the host's body, and competitively excluding pathogens. In the 1940s, microbiologists were focused on identifying pathogenic microbes and their underlying mechanisms involved in disease pathogenesis. It was later on in 1950s-1980s, when beneficial microbes were point of interest for researchers and they aimed at isolating these strains from the living organisms and the surrounding environment, which later on took attention owing to their potential role in addressing physical health diseases and mental disorders. Probiotics have been found effective in improving physical health during diseases like diabetes, cancer, Alzheimer's disease, and mental health situations by overcoming depression, and anxiety. Researchers have developed the most recent techniques that allow probiotics to tolerate GI stressors and severe processing conditions with relative ease. However, further studies are required for the specification and usage of probiotics as useful strains. This chapter highlights the latest developments about the health advantages of probiotics and their growing uses in the treatment of diseases.

Accepted: 06-Aug-2024 Publishers	<b>KEYWORDS</b> Dysbiosis, Gut health, Gut microbiota, Strain-specific probiotics	Received: 08-Jun-2024 Revised: 01-Jul-2024 Accepted: 06-Aug-2024		A Publication of Unique Scientific Publishers
----------------------------------	--	--	--	---

**Cite this Article as:** Hameed H, Mohiuddin M, Husnain S, Siddique AB, Younas S, Sarwar MT, Hussain R and Khalid M, 2024. Strain-specific probiotics: linking probiotic strains with health and disease. In: Farooqi SH, Aqib AI, Zafar MA, Akhtar T and Ghafoor N (eds), Complementary and Alternative Medicine: Prebiotics and Probiotics. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 234-246. <u>https://doi.org/10.47278/book.CAM/2024.415</u>

#### INTRODUCTION

The probiotic concept is based on the idea that human physiology depends on the commensal microbiota and the advantageous changes to its composition may assist in preserving health and lowering the risk of disease (Latif et al., 2023). The basic concept of probiotics includes all microbial species imparting health benefits as shown in research trials (Zaib et al., 2024). Louis Pasteur revealed the microorganisms responsible for fermentation at the beginning of the 20<sup>th</sup> century (Brogren, 2024), while E. Metchnikoff associated the frequent use of fermented dairy products, such as yogurt, with longer life spans among Bulgarian rural populations. Metchnikoff found lactobacilli fulfilling the criteria to be called probiotic bacteria because they may improve health and prolong the aging process (Renuka et al., 2023).

Probiotic studies typically use single strains, which are sometimes used as yogurt that include *Lactobacillus delbrueckii* subspecies Bulgaricus and Streptococcus thermophilus (Castro et al., 2023). The effectiveness of probiotic strain mixtures is less well understood, particularly if combining strains leads to lower efficiency because of reciprocal inhibition between the component bacteria or to additive or even synergistic benefits in terms of bioactivity (L. V. J. D. d. McFarland & sciences, 2021). Probiotics are recognized to have many health benefits, but it's still important to understand the processes behind how they interact with immune cells to promote immunomodulatory effects (Beterams et al., 2021). Probiotics may benefit to human health by enhancing intestinal barrier function, generating neurotransmitters, immunomodulating the host's body, and competitively excluding pathogens (Mazziotta et al., 2023).

For medicinal and dietary purposes, probiotic microorganisms are essential and helpful (Sharma et al., 2023). Microbial food supplements called probiotics change the Gut microbiota. A few RCTs or randomized controlled studies have examined how probiotic therapies affect T2DM patients' glycemic control (Li et al., 2023). Nutritional factors have been found critical

in the treatment of cancer, as shown by the Association of Modifiable Health's finding that at least 50% of all cancers may have dietary origin (Dasari et al., 2017). Therefore, scientists interested in developing natural medications have been interested in a variety of food elements and natural health products (Noor et al., 2023). Probiotics and their impact on the Gut-Brain axis (GBA) have been found very beneficial and are being used for treating various conditions like Alzheimer's disease. Probiotics have an impact on the immune system and reduce inflammation. It has been discovered that they are important in the area of food-based anti-Alzheimer disease methods (Anand et al., 2023). According to (Azadeh et al., 2023), Probiotics use may help to reduce depression symptoms. Recent researches showed that probiotics can act as antimicrobial agents that can kill or damage the pathogens in the human body along with improving the Gut Microbiota (Fijan, 2023).

#### What are Probiotics?

Probiotics are living non-pathogenic microorganisms found in food that are good for human health (Saarela et al., 2020). The most common element in the age of functional foods is probiotics, whether they are found in food products or medicine. Probiotics have long been seen as an essential element and an attractive target due to their potential health benefits (Fig. 1) (Sanz et al., 2016). Werner Kollath originated the term "probiotic" in 1953. It is derived from the Latin word pro and the Greek word \u03c3 to, which means "for life." Kollath characterized probiotics as living organisms that have vital roles in enhancing health outcomes (Gasbarrini et al., 2016). Lilly and Stillwell originally used this word in 1965 to refer to "substances secreted by one organism which stimulate the growth of another". Probiotics are more precisely described as "a live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance" by Fuller in 1992 (McFarland, 2015). The present history of probiotics begins in the early 1900s with the groundbreaking research of Russian scientist Elie Metchnikoff, who worked at the Pasteur Institute in Paris. While Louis Pasteur discovered the microorganisms that cause fermentation, Metchnikoff initially made an effort to determine whether these microbes could have any negative effect on human health (Diplock et al., 1999). Additionally, according to Metchnikoff, "it is possible to adopt measures to modify the flora in our bodies and to replace the harmful microbes by useful microbes because of the intestinal microbes' dependence on food." This phrase provides a comprehensive explanation of the "probiotic concept" (Gasbarrini et al., 2016). According to the Food and Agriculture Organization (FAO) and the World Health Organization (WHO), these are "live microbes which confer health benefits on host organisms when administered in adequate guantities" (Munir et al., 2022).



**Fig. 1:** Effect of probiotics in the prevention of infectious diseases

#### **General Properties of Probiotics**

The properties that a perfect probiotic preparation needs to possess are enlisted (Table 1) (Harmsen et al., 2000). A dosage of five billion colony-forming units (5x10<sup>9</sup> CFU/day) has been suggested, to be taken for at least five days, to get a sufficient level of health advantages (Gronlund, Lehtonen, & Eerola). The microbes normally recommended in probiotic preparations are generally recognized as safe (GRAS), have decreased intestinal permeability, produce lactic acid, are resistant to bile, pancreatic juice, and hydrochloric acid, are anti-carcinogenic, and should activate the immune system. They should also be able to withstand the acidic and alkaline environment in the stomach and duodenum (Vimala & Kumar, 2006). The viable cell count of a microbe in a probiotic product during the production and shelf-life period is influenced by pH, titratable acidity, molecular oxygen levels, redox potential, hydrogen peroxide, flavoring compounds, and packaging materials (Mortazavian et al., 2015). In probiotic preparations, either single or multistrain cultures of living microbes have

Table 1: Properties for any microorganism to be called a Probiotic.

I hey ought to be able to communicate with or interact with the immune cells connected to the dastro	strointestinal tract.
--	-----------------------

- 2. They ought to be derived from humans.
- 3. It must not be pathogenic.
- 4. Processing resistance.
- 5. Need to be able to affect the local metabolism.

#### **Probiotic Strains**

Probiotic strains are living bacteria added to food to improve health. Several *Lactobacillus* species, *Bifdobacterium sp.*, *Saccharomyces boulardii*, and other microbes have been engaged in imparting health benefits (Ljungh & Wadström, 2006). The majority of probiotic bacteria, including *Lactobacillus sp.*, *Bifdobacterium sp.*, and *Enterococcus sp.*, are members of the Lactic Acid Bacteria (LAB) group (Fig 2) (Klein et al., 1998). In addition other bacterial species including *Bacillus* (Senesi et al., 2001) and *Clostridium butyricum* (Takahashi et al., 2004), the yeast *Saccharomyces boulardii* have also been the focus of many studies (Table 2) (Elmer, Martin, Horner, Mcfarland, & Levy, 1999). Up till now, *Lactobacillus rhamnosus GG* (LGG) was the first probiotic to attract significant clinical attention.[12] Because the *Lactobacillus* strain that the dairy industry had previously used for fermentation could not colonize the gut, *Lactobacillus rhamnosus* strain *GG* was identified in 1985 via the development of a list of optimal probiotic characteristics (Vimala & Kumar, 2006).

T-1-1- 0	N 41 1- 1 - 1		- D 1- 1 - 1	1	2022 0		1
Table 2:	wicrobiai	strains used a	s prodiotics	(Luise et al.	, 2022; Pudgar	' et al., 202 I; S	narma et al., 2021)

Sr.no	Genera	Species reported for probiotic characteristics			
1.	Lactobacillus spp	s spp Lactobacillus rhamnosus Lactobacillus casei			
		Lactobacillus plantarum Lactobacillus reuteri			
		Lactobacillus fermentum Lactobacillus salivarius			
		Lactobacillus paracasei Lactobacillus gasseri			
		Lactobacillus brevis Lactobacillus helveticus			
		Lactobacillus johnsonii			
2.	Bifidobacterium spp	Bifidobacterium bifidum Bifidobacterium longum			
		Bifidobacterium infantis Bifidobacterium breve			
		Bifidobacterium adolescentis Bifidobacterium angulatum			
		Bifidobacterium catenulatum Bifidobacterium dentium			
		Bifidobacterium pseudocatenulatum			
3.	Saccharomyces spp	Saccharomyces chevalieri Saccharomyces dairenensis			
		Saccharomyces ellipsoideus Saccharomyces martiniae			
		Saccharomyces monacensis Saccharomyces norbensis			
		Saccharomyces paradoxus			
4.	Streptococcus spp	Streptococcus thermophiles			
5.	Enterococcus spp	Enterococcus faecium Enterococcus faecalis			
6.	Bacillus spp	Bacillus subtilis Bacillus cereus			
		Bacillus velezensis			

#### **Single-strain vs Multi-strain Probiotics**

Mono-strain probiotics include just one strain of a certain species, while multi-strain use many strains of the same or nearly related species (Timmerman et al., 2004). Since the gut microbiome is complex and comprises more than 400 species, it has been hypothesized that using a variety of probiotic strains may be more effective in restoring the microbiome once dysbiosis has arisen (Ouwehand et al., 2000). However, evidence-based efficacy supports the use of single-strain probiotics. Synergistic effects of several strains in the combination (increased adherence, higher pathogen inhibition) may be one advantage of multi-strain mixes (Timmerman et al., 2004). Different strains may potentially have different pathways of action, resulting in a broader coverage (Medina et al., 2007). For example, *B. longum W11* stimulates the growth of T-helper cells, but *B. longum NCIMB8809* does not (Mileti et al., 2009). A potential drawback of multi-strain mixtures might be reduced effectiveness owing to antagonistic intra-strain suppression by various probiotic strains (Chapman et al., 2012). A multistrain probiotic may have more effectiveness and consistency than a mono-strain probiotic. Colonization of an ecosystem offering a habitat for over 400 species in conjunction with individually selected host factors is expected to be more effective with multiple-strain probiotic preparations (Klaenhammer & Kullen, 1999) (Table 3).

Table 3: Single strain and Multi strain probiotics

	Single Strain Probiotics	Multi Strain Probiotics
1.	Bacillus coagulans	Bacillus coagulans GBI-30
2.	Bacillus subtilis	Bacillus subtilis DE111
З.	Lactobacillus rhamnosus LCR35	Lactobacillus rhamnosus

4.	Lactobacillus pentous/plantarum	Lactobacillus pentous/plantarum complex

#### Mechanism of Action

Several mechanisms (Kumar Bajaj et al., 2015; Walker, 2008) have been proposed for the activity of probiotics (Macfarlane & Cummings, 1999) (Fig. 3). Despite outstanding achievements in the field of probiotics, a fundamental breakthrough is still awaited particularly in documenting their mode of action (Latif et al., 2023). Probiotics may have a good effect on the human host via primary mechanisms which include: their role in removing pathogens by competitive exclusion criteria, betterment in the intestinal barrier functioning, immunomodulating the host's systems, and producing neurotransmitters (Plaza-Diaz et al., 2019). Probiotics contend with infectious agents for food and receptor-binding sites, making it harder for them to survive in the gut (Kumar Bajaj et al., 2015). Probiotics function as antimicrobials by creating short-chain fatty acids (SCFA), organic acids, hydrogen peroxide (Ahire et al., 2021), and bacteriocins (Fantinato et al., 2019), which reduce infective microorganisms in the gut. Furthermore, probiotics lead to more mucin production in the intestine (Chang et al., 2021), maintain the levels of tight junction proteins such as occludin and claudin-1, and modulate the gut immune response (Bu et al., 2022; Ma et al., 2022). Probiotics also influence the innate as well as adaptive immune responses by altering dendritic cells (DC), macrophages, and B and T lymphocytes. Probiotics also stimulate the generation of antiinflammatory cytokines, interact with intestinal epithelial cells, and attract macrophages and mononuclear cells (Petruzziello, Saviano, & Ojetti, 2023). Furthermore, probiotics may generate neurotransmitters in the stomach via the gut-brain axis. Specific probiotic stains may alter serotonin, gamma-aminobutyric acid (GABA), and dopamine levels, influencing mood, behavior, gut motility, and stress-related pathways (Gangaraju et al., 2022; Sajedi et al., 2021; Srivastav et al., 2019). Probiotics have been shown to provide several health benefits, including more effective digestion, suppression of harmful bacteria in the gastrointestinal tract (Sanap et al., 2019), lowering blood pressure and blood sugar (Suez, Zmora, Segal, & Elinav, 2019), enhancing intestinal health (Reid et al., 2019), lowering serum cholesterol, breaking down toxins (Singh & Natraj, 2021), generating cofactors and vitamins (Nasr, 2018), immune system upregulation, anti-inflammatory properties (Abid et al., 2022), and protection against tumors and cancers (Idrees et al., 2022). These mechanisms have been the subject of numerous paradigms (Ferreira et al., 2022; Plaza-Diaz et al., 2019; Reque & Brandelli, 2022).



**Fig. 3.:** Mechanism of Action of Probiotics

#### **Broader Efficacy of Multi-strain Probiotics**

Multi-strain probiotics blend numerous strains, each with its characteristics and effects, their mechanisms of action are complex and multidimensional. Because many bacterial strains interact synergistically, multistrain probiotics may provide a wider variety of advantages than single-strain probiotics (Grumet et al., 2020). These are the main pathways by which probiotics of many strains work. Comparing multi-strain probiotics to single strains, the former may occupy more gastrointestinal tract niches. By more successfully competing for resources and attachment sites on the mucosal surfaces, this varied colonization may stop the proliferation of harmful bacteria (Valdez-Baez et al., 2022). The overall efficacy may be increased by aggregating many strains. As an example, while one strain may increase the functionality of the intestinal barrier,

another strain may change the response of the immune system (Kwoji et al., 2021). The strains are combined to ensure that the gut is kept healthy and that immune responses are stepped up. Different probiotic strains create various bioactive compounds like bacteriocins and short-chain fatty acids (Chugh & Kamal-Eldin, 2020; Maldonado Galdeano et al., 2019). The diverse group of beneficial compounds in a multi-strain composition can potentially promote gut health, heighten the immune system's activity, and impede bacterial growth (Ouwehand et al., 2018). In comparison to single strains, multi-strain probiotic has a greater capacity to alter the overall composition of the gut microbiota (McFarland, 2021). They restore balance to the microbiota after perturbations like antibiotic treatment, dietary changes, or diseases. Different strains interact with different parts of the immune system (Duan et al., 2022). For example, some species of bacteria may increase the production of anti-inflammatory cytokines, while others may stimulate immune cells such as macrophages and natural killer cells. As a result, the immune response becomes both fairer and more effective. (Rizzello et al., 2011; Srivastav et al., 2019). Simultaneously, multi-strain probiotics may impact numerous metabolic pathways or processes, increasing throughput and productivity. They improve digestion and increase nutrient absorption, in addition to enhancing detoxification. They also improve the conversion of lipids and carbohydrates, which means they could potentially help with conditions such as diabetes and obesity (Puvanasundram et al., 2021). Multi-strain probiotics are effective in reducing systemic and local inflammation when several strains exhibit a synergistic effect (Giacchi et al., 2016). This should be pursued, especially for inflammatory conditions within the gastrointestinal system as seen in cases of Crohn's disease and ulcerative colitis (Kumar et al., 2016).

#### **Probiotics in Physical and Mental Health**

#### Diabetes

Diabetes has become a serious health concern across the globe, and it is associated with high blood glucose levels. Diabetes seems to be prevalent, with an estimated 463.0 million persons aged 20 to 79 years old, and the figure is anticipated to rise to 578.4 million by 2030 (Huang et al., 2018). Type 2 diabetes (T2D) is the most common form of diabetes, accounting for around 90% of cases. T2D may lead to a variety of problems, including cardiovascular, eye, renal, nerve, and vascular illnesses (Association, 2014). T2D and its consequences may have an impact on people's quality of life while also increasing treatment costs. As a consequence, diabetes prevention is critical, particularly for high-risk individuals, via screening, lifestyle changes, and nutritional supplements (Wang et al., 2021). Prior research highlighted the impact of gut microbiota in the progression of insulin resistance and diabetes (Gurung et al., 2020; He & Shi, 2017). The total number of bacteria associated with short-chain fatty acids (SCFAs) was shown to be decreased in T2D patients (Qin et al., 2012). Gut microbiota disruption may reduce SCFA synthesis, promote inflammation, impair insulin secretion and sensitivity, and cause insulin resistance (Aw & Fukuda, 2018). It has been proposed that oral probiotic delivery may be a useful strategy for modifying the gut microbiota in those at risk of diabetes (Aw & Fukuda, 2018; Barengolts, 2016). *L acidophilus, L. casei, L. rhamnosus, L. bulgaricus, B. breve, B. longum, B. infantis, B. lactis, Streptococcus thermophilus*, and *Bacillus coagulans* (*L. sporogenes*) are probiotic strains that have been linked to the regulation of blood sugar levels (Yao et al., 2017).

#### Cancer

Numerous *in vitro* research results have demonstrated the positive effects of probiotics in influencing the growth and death of cancer cells (Śliżewska et al., 2020). Probiotics have several anticancer mechanisms, which include lowering intestinal pH, inhibiting enzymes that may produce potentially carcinogenic substances, altering metabolic activity, binding and degrading carcinogens, immunomodulation in reducing chronic inflammation, and positive regulation of intestinal vegetation (Fig. 4) (Reis, da Conceição, and Peluzio, 2019; Molska and Reguła, 2019). Certain microbial strains are utilized to cure cancer, such as subspecies of *Propionibacterium sp.* (*freudenreichii*), *Bifidobacteria, Lactobacilli*, and *Streptococcus sp.* (*salivarius*) (Lu, et al., 2021). These may be used either on their own or in conjunction with antiviral drugs (Zhang et al., 2019). In combination, probiotics and TGF-β receptor blockers may enhance the antitumor immune response, hence inhibiting the development of tumors (Shi et al., 2019). By modifying gut microbiota and reducing carcinogen levels, lactobacilli may reduce the risk of cancer (Ling et al., 1994). Consequences of antitumor medications can include gastrointestinal distress. Radiochemotherapy instantly destroys intestinal cells (Osterlund et al., 2007). Because the stress response it causes destroys the intestinal mucosal barrier (Linn et al., 2019). Probiotics generated from *Lactobacillus* and *Bifidobacterium* can biologically prevent the development of pathogenic bacteria (Zhao et al., 2017).

#### **Alzheimer's Disease**

Alzheimer's disease (AD) is a neurological disorder that progresses over time and is responsible for 80% of dementia cases globally, especially in older adults over 60 years (DeTure & Dickson, 2019). A major global health concern in the future, AD is expected to affect over 131 million people by the year 2050, according to the world AD projection made in 2016 (Prince et al., 2016). The exact pathophysiology of AD is yet unknown. On the other hand, increasing evidence indicates that gut microbiota plays a role in AD neuropathology. Numerous mechanisms exist for the gut microbiota to interact with AD pathogenesis (Rutsch, Kantsjö, & Ronchi, 2020). According to a clinical investigation, the gut microbiota of AD patients has altered in terms of bacterial abundance and microbial diversity, with higher levels of Bacteroidetes and lower levels of Firmicutes and *Bifidobacterium* (Rinninella et al., 2019). Three primary mechanisms by which probiotics affect brain function include immunological modulation, endocrine pathways, and neuronal control (Psichas et al., 2015). The primary metabolites

resulting from gut microbiota fermentation, small chain fatty acids (SCFAs), upregulate anti-inflammatory mediators and decrease pro-inflammatory mediators (Vijay & Morris, 2014). Probiotics work through endocrine pathways to trigger the production of cortisol, a powerful anti-inflammatory hormone, from the adrenal glands by activating the hypothalamic-pituitary-adrenal (HPA) axis. Probiotics also boost the intestine's enteroendocrine L-cells' (EECs) synthesis of peptide YY (PYY) and glucagon-like-peptide-1 (GLP-1) (Yano et al., 2015). Additionally, probiotics emit specific neurotransmitters like GABA (GLU) or regulate the release of neurotransmitters like serotonin (5-HT) through enterochromaffin cells (EC). Together, these neurotransmitters and neuroactive metabolites inhibit neuronal death by exerting neuroprotective effects (Naomi et al., 2022). Most commonly, *Bifidobacterium* and *Lactobacillus* species are used as an effective psychobiotics (Dinan et al., 2013; Zhu et al., 2021).

## **Probiotic Mechanism of Cancer**



## Fig. 5: Probiotics help to restore microbiota in stress and depression **Depression**

Depression and anxiety are intricate and diverse psychiatric disorders, representing significant contributors to global disability (Psychiatry, 2022). Depression is a serious mental issue affecting a significant number of people globally. Symptoms include feelings of hopelessness, grief, loss of interest, poor appetite, and sleep disturbance (Thapar et al., 2022). Pervasive feelings of worry and fear, accompanied by noticeable alteration in behavior are referred to as anxiety (Chorpita & Barlow, 2018). According to the World Health Organization, around 4.4% of the world's population suffers from depression, and anxiety disorder affects more than 260 million (a, 2023). The global burden of disease, injuries, and Risk Factors Study (GBD) underscored the profound impact of mental health issues with depressive and anxiety disorders emerging as the two most disabling conditions. Both were prominently ranked among the 25 leading causes of global burden (Vos et al., 2020).

Common antidepressants and anxiolytics primarily target neurotransmitters in the brain to alleviate symptoms (Radosavljevic et al., 2023). Probiotics have gained growing attention due to their crucial role in mood regulation. Probiotics can affect mood and host health by regulating the microbial-gut-brain axis (Lou, Liu, & Liu, 2023). Scientists have identified the "Gut-brain axis," a communication pathway between the gastrointestinal tract and central nervous system (Chaudhry et al., 2023; Pan et al., 2023). This connection is influenced by various factors like genes, age, sex, diet, and stress. The microbe in our gut, particularly *Bifidobacterium* and *Lactobacillus*, play a crucial role in maintaining gut health and impacting symptoms of depression and anxiety (Kumar et al., 2023; Samiappan & Dhailappan, 2024; Xiong et al., 2023). Probiotics can positively influence the Central nervous system by regulating important neurotransmitters associated with depression and anxiety (Mudaliar et al., 2024). Chronic treatment with specific probiotics, such as *Bifibacterium infantis* and *Lactobacilli* has shown significant improvement in patients with major depressive disorder (Ribera et al., 2024). *Lactobacillus rhamnosus* was identified as a potential analytics (Matin & Dadkhah, 2024) (Fig 5).

#### **Probiotics as an Anti-microbial Agent**

Probiotic antibacterial effects may be determined using a variety of *in vitro* and *in vivo* techniques. Various variations of the spot-on lawn test, the agar well diffusion assay (AWDA), co-culturing techniques, the use of cell lines, and other techniques are examples of *in vitro* procedures (Fijan, 2023). Since the *in vivo* techniques use animal models, research is being done to find alternatives to animal research in accordance with the EU directive 2010/63/EU and its consolidated text EUR-Lex—02010L0063-20190626 from 2019 to preserve animals (Gjerris et al., 2023). As members of the Lactobacillaceae class, lactic acid bacteria, or LAB, are the most significant probiotics that have been shown to benefit the human gastrointestinal system (Santacroce et al., 2019). Probiotics can also generate a wide range of compounds that bear resemblance to antibiotics: Bacteriocins and antibiotics (Fijan, 2023) (Fig. 6).

#### **Challenges of Probiotics as Medicines in Clinical Uses**

Probiotics have made significant progress in therapeutic applications, but it still has several drawbacks and difficulties. To reach its full therapeutic potential and gain broader acceptance, these obstacles must be overcome.

Probiotic strain specificity is important because different bacterial strains can have quite different effects on how effective probiotics are. It takes more investigation and assessment to determine which strain is most suited for a given disease. The absence of uniformity in probiotic strain, dosage, and formulation creates difficulties when comparing research findings and choosing the most effective therapeutic strategy. The success of probiotic products depends on quality control, yet inconsistent production methods and storage environments might degrade product quality and change clinical results. The fact that probiotics are classified differently in different countries as dietary supplements, food additives, or medications, resulting in different regulatory standards and licensing procedures, raises regulatory problems.



**Fig. 6:** Health benefits of Probiotics in physical and mental diseases

#### **Impregnability of Probiotics**

Even though probiotic strains are usually accepted as safe, this isn't always the case because of side effects, substandard probiotic supplements, and antibiotic resistance that can spread. Regarding the side effects of probiotics, it is important to note that while many studies have demonstrated the positive advantages of using probiotics as a health booster, relatively few have addressed the potential risks to the health of patients and healthy consumers that they may offer. Probiotic safety is a crucial factor to consider, particularly for immunocompromised people, critically sick patients, children, and those with central venous catheters, since these individuals may be more susceptible to infections or other problems. Probiotics may interact with other drugs in ways that affect how well a patient responds to therapy, therefore it's critical to recognize and handle these interactions in clinical practice. Taste, cost, and convenience are a few examples of the elements that might make patient compliance difficult. Individual diversity caused by variations in nutrition, genetics, gut flora, and other variables calls for a tailored treatment that will need more time and study to fully comprehend. Some short-term probiotic treatment trials have failed to detect significant changes in the gut microbiota, and specific individuals or diseases might demand an extended period of treatment for effective therapeutic effects. Changes in the gut microbiota may only be temporary with short-term probiotic interventions. Furthermore, the great majority of research on the effects of probiotics on health via the gut-brain axis has been done on animal models, and there remain unanswered questions about how these microorganisms interact with the human body and how to treat certain disorders.

#### **Future Directions and Limitations**

Probiotics have become increasingly well-known and acknowledged for their potential health advantages, but there are still several obstacles that need to be overcome before researchers and business owners can fully realize the benefits of probiotics. Probiotic bacterial strains can affect the human body in many ways. Determining which strains work best for a given set of medical issues and comprehending how they work is essential. Subsequent investigations ought to concentrate on clarifying the impacts of distinct strains and creating customized probiotic therapies. Consequently, it might not be accurate to extrapolate the benefits of probiotics to every strain within a species. Probiotic efficacy can also differ from person to person. What is effective for one person may not be effective for another, and it can be difficult to predict a person's particular reaction to probiotic treatment. Since probiotics are live bacteria, it is crucial to preserve their viability during manufacturing, storage, and ingestion. Putting in place strong quality control procedures and uniform manufacturing standards for probiotics is essential to ensure reliable and efficient products. Even though probiotics have shown several health benefits, further investigation is needed to determine the precise mechanisms and interactions that probiotics and the host have. This information will help with the development of focused probiotic treatments.

#### Conclusions

Probiotics are live and non-pathogenic bacteria that exert beneficial effects on human health even in case of diseases. Different strains of probiotics, either single strains or multi-strains have positive effects on health and disease. Several mechanisms of action have been proposed for probiotics as they are useful in many diseases like diabetes, cancer, Alzheimer's disease, Depression, and anxiety. Probiotics have antimicrobial properties; they can be used in many infectious diseases. For this conventional remedy to show to be a useful tool for medical therapy, it is crucial to carefully choose the probiotic agent, standardize its dose, and have a good understanding of its positive benefits over and above the harmful consequences. In relation to probiotic side effects, it's crucial to remember that although much research has shown the benefits of using probiotics as a health enhancer, only a small number have examined the possible concerns they may pose to patients' and healthy consumers' health. Probiotics have advanced a long way in terms of medicinal uses, but there are still a lot of challenges and disadvantages. More research is required to pinpoint the processes and interactions that

probiotics and the host have.

#### REFERENCES

- W. H. O. J. C. (2023). Depression and other common mental disorders: Global health estimates.[Online].; 2017. 19.
- Abid, S., Farid, A., Abid, R., Rehman, M. U., Alsanie, W. F., Alhomrani, M., and Saqib, S. (2022). Identification, biochemical characterization, and safety attributes of locally isolated Lactobacillus fermentum from Bubalus bubalis (buffalo) milk as a probiotic. *Microorganisms*, 10(5), 954.
- Ahire, J., Jakkamsetty, C., Kashikar, M., Lakshmi, S., and Madempudi, R. (2021). In vitro evaluation of probiotic properties of Lactobacillus plantarum UBLP40 isolated from traditional indigenous fermented food. *Probiotics and Antimicrobial Proteins*, *13*(5), 1413-1424.
- Anand, A., Khurana, N., Kumar, R., and Sharma, N. J. F. B. (2023). Food for the mind: The journey of probiotics from foods to anti-Alzheimer's disease therapeutics. *51*, 102323.
- Association, A. D. (2014). Diagnosis and classification of diabetes mellitus. Diabetes care, 37(Supplement\_1), S81-S90.
- Aw, W., and Fukuda, S. (2018). Understanding the role of the gut ecosystem in diabetes mellitus. *Journal of Diabetes Investigation*, 9(1), 5-12.
- Barengolts, E. (2016). Gut microbiota, prebiotics, probiotics, and synbiotics in management of obesity and prediabetes: review of randomized controlled trials. *Endocrine Practice*, *22*(10), 1224-1234.
- Beterams, A., De Paepe, K., Maes, L., Wise, I. J., De Keersmaecker, H., Rajkovic, A., and Calatayud Arroyo, M. J. F. J. (2021). Versatile human in vitro triple coculture model coincubated with adhered gut microbes reproducibly mimics proinflammatory host-microbe interactions in the colon. 35(12).
- Brogren, C. H. J. A. (2024). Louis Pasteur—The life of a controversial scientist with a prepared mind, driven by curiosity, motivation, and competition. In (Vol. 132, pp. 7-30): Wiley Online Library.
- Bu, Y., Liu, Y., Liu, Y., Wang, S., Liu, Q., Hao, H., and Yi, H. (2022). Screening and probiotic potential evaluation of bacteriocinproducing Lactiplantibacillus plantarum in vitro. *Foods*, *11*(11), 1575.
- Castro, A., Aleman, R. S., Tabora, M., Kazemzadeh, S., Pournaki, L. K., Cedillos, R., and Aryana, K. J. M. (2023). Probiotic Characteristics of Streptococcus thermophilus and Lactobacillus bulgaricus as Influenced by New Food Sources. *11*(9), 2291.
- Chang, Y., Jeong, C., Cheng, W., Choi, Y., Shin, D., Lee, S., and Han, S. (2021). Quality characteristics of yogurts fermented with short-chain fatty acid-producing probiotics and their effects on mucin production and probiotic adhesion onto human colon epithelial cells. *Journal of Dairy Science*, *104*(7), 7415-7425.
- Chapman, C., Gibson, G. R., and Rowland, I. (2012). In vitro evaluation of single-and multi-strain probiotics: Inter-species inhibition between probiotic strains, and inhibition of pathogens. *Anaerobe, 18*(4), 405-413.
- Chaudhry, T. S., Senapati, S. G., Gadam, S., Mannam, H. P. S. S., Voruganti, H. V., Abbasi, Z., and Bheemisetty, N. J. J. o. C. M. (2023). The Impact of Microbiota on the Gut–Brain Axis: Examining the Complex Interplay and Implications. *12*(16), 5231.
- Chorpita, B. F., and Barlow, D. H. J. T. N. P., (2018). The development of anxiety: The role of control in the early environment. 227-264.
- Chugh, B., and Kamal-Eldin, A. (2020). Bioactive compounds produced by probiotics in food products. *Current Opinion in Food Science*, *32*, 76-82.
- D'souza, A. L., Rajkumar, C., Cooke, J., and Bulpitt, C. J. (2002). Probiotics in prevention of antibiotic associated diarrhoea: meta-analysis. *Bmj*, 324(7350), 1361.
- Dasari, S., Kathera, C., Janardhan, A., Kumar, A. P., and Viswanath, B. J. C. N. (2017). Surfacing role of probiotics in cancer prophylaxis and therapy: A systematic review. *36*(6), 1465-1472.
- DeTure, M. A., and Dickson, D. W. (2019). The neuropathological diagnosis of Alzheimer's disease. *Molecular Neurodegeneration*, *14*(1), 1-18.
- Dinan, T. G., Stanton, C., and Cryan, J. F. J. B. P. (2013). Psychobiotics: a novel class of psychotropic. 74(10), 720-726.
- Diplock, A., Aggett, P., Ashwell, M., Bornet, F., Fern, E., and Roberfroid, M. (1999). The European Commission concerted action on functional foods science in Europe (FUFOSE). Scientific concepts of functional foods in Europe. Consensus document. *Br Journal Nutrition*, *81*, 1-27.
- Duan, H., Yu, L., Tian, F., Zhai, Q., Fan, L., and Chen, W. (2022). Antibiotic-induced gut dysbiosis and barrier disruption and the potential protective strategies. *Critical Reviews in Food Science and Nutrition, 62*(6), 1427-1452.
- Elmer, G. W., Martin, S. W., Horner, K. L., Mcfarland, L. V., and Levy, R. H. (1999). Survival of Saccharomyces boulardii in the rat gastrointestinal tract and effects of dietary fiber. *Microbial Ecology in Health and Disease*, *11*(1), 29-34.
- Fantinato, V., Camargo, H. R., and Sousa, A. L. O. P. D. (2019). Probiotics study with Streptococcus salivarius and its ability to produce bacteriocins and adherence to KB cells. *Revista de Odontologia da UNESP, 48*.
- Ferreira, R. d. S., Mendonça, L. A. B. M., Ribeiro, C. F. A., Calças, N. C., Guimarães, R. d. C. A., Nascimento, V. A. d., and Franco, O. L. (2022). Relationship between intestinal microbiota, diet and biological systems: an integrated view. *Critical Reviews* in Food Science and Nutrition, 62(5), 1166-1186.
- Fijan, S. (2023). Probiotics and Their Antimicrobial Effect. 11(2), 528. Retrieved from <a href="https://www.mdpi.com/2076-2607/11/2/528">https://www.mdpi.com/2076-2607/11/2/528</a>

Fijan, S. J. M. (2023). Probiotics and Their Antimicrobial Effect. In (Vol. 11, pp. 528): MDPI.

- Gangaraju, D., Raghu, A. V., and Siddalingaiya Gurudutt, P. (2022). Green synthesis of γ-aminobutyric acid using permeabilized probiotic Enterococcus faecium for biocatalytic application. *Nano Select*, *3*(10), 1436-1447.
- Gasbarrini, G., Bonvicini, F., and Gramenzi, A. (2016). Probiotics history. Journal of clinical gastroenterology, 50, S116-S119.
- Giacchi, V., Sciacca, P., and Betta, P. (2016). Multistrain probiotics: the present forward the future. *Probiotics, Prebiotics, and Synbiotics, 19,* 279-302.
- Gjerris, M., Kornum, A., Röcklinsberg, H., and Sørensen, D. B. (2023). *Biotech Animals in Research: Ethical and Regulatory* Aspects: CRC Press.
- Gronlund, M., Lehtonen, O., and Eerola, E. P. Kero. 1999. Fecal microflora in healthy infants bom by different methods of delivery: permanent changes in intestinal flora aer cesarean delivery. *Journal Pediatr. Gastroenterol. Nutrition, 28*, 9-25.
- Grumet, L., Tromp, Y., and Stiegelbauer, V. (2020). The development of high-quality multispecies probiotic formulations: from bench to market. *Nutrients*, *12*(8), 2453.
- Gurung, M., Li, Z., You, H., Rodrigues, R., Jump, D. B., Morgun, A., and Shulzhenko, N. (2020). Role of gut microbiota in type 2 diabetes pathophysiology. *EBioMedicine*, *51*.
- Harmsen, H. J., Wildeboer–Veloo, A. C., Raangs, G. C., Wagendorp, A. A., Klijn, N., Bindels, J. G., and Welling, G. W. (2000). Analysis of intestinal flora development in breast-fed and formula-fed infants by using molecular identification and detection methods. *Journal of Pediatric Gastroenterology and Nutrition*, 30(1), 61-67.
- He, M., and Shi, B. (2017). Gut microbiota as a potential target of metabolic syndrome: the role of probiotics and prebiotics. *Cell and bioscience*, 7(1), 1-14.
- Huang, Y., Karuranga, S., Malanda, B., and Williams, D. R. R. (2018). Call for data contribution to the IDF Diabetes Atlas 9th Edition 2019. *Diabetes Res Clin Pract*, *140*, 351-352. doi:10.1016/j.diabres.2018.05.033
- Idrees, M., Imran, M., Atiq, N., Zahra, R., Abid, R., Alreshidi, M., and Ghazanfar, S. (2022). Probiotics, their action modality and the use of multi-omics in metamorphosis of commensal microbiota into target-based probiotics. *Frontiers in Nutrition*, 9. doi:10.3389/fnut.2022.959941
- Klaenhammer, T. R., and Kullen, M. J. (1999). Selection and design of probiotics. *International Journal of Food Microbiology*, 50(1-2), 45-57.
- Klein, G., Pack, A., Bonaparte, C., and Reuter, G. (1998). Taxonomy and physiology of probiotic lactic acid bacteria. International Journal of Food Microbiology, 41(2), 103-125.
- Kumar, A., Pramanik, J., Goyal, N., Chauhan, D., Sivamaruthi, B. S., Prajapati, B. G., and Chaiyasut, C. J. P. (2023). Gut Microbiota in Anxiety and Depression: Unveiling the Relationships and Management Options. *16*(4), 565.
- Kumar Bajaj, B., Claes, I. J., and Lebeer, S. (2015). Functional mechanisms of probiotics. Journal of microbiology, biotechnology and food sciences.--, 4(4), 321-327.
- Kumar, M., Hemalatha, R., Nagpal, R., Singh, B., Parasannanavar, D., Verma, V., and Cuffari, B. (2016). Probiotic approaches for targeting inflammatory bowel disease: an update on advances and opportunities in managing the disease. *International Journal of Probiotics and Prebiotics*, 11(3-4), 99.
- Kwoji, I., Aiyegoro, O., Okpeku, M., and Adeleke, M. (2021). Multi-Strain Probiotics: Synergy among Isolates Enhances Biological Activities. Biology 2021, 10, 322. In: s Note: MDPI stays neutral with regard to jurisdictional claims in published ....
- Latif, A., Shehzad, A., Niazi, S., Zahid, A., Ashraf, W., Iqbal, M. W., and Korma, S. A. (2023). Probiotics: mechanism of action, health benefits and their application in food industries. *Frontiers in Microbiology*, 14. doi:10.3389/fmicb.2023.1216674
- Latif, A., Shehzad, A., Niazi, S., Zahid, A., Ashraf, W., Iqbal, M. W., and Khan, I. M. J. F. i. m. (2023). Probiotics: Mechanism of action, health benefits and their application in food industries. *14*.
- Li, G., Feng, H., Mao, X.-L., Deng, Y.-J., Wang, X.-B., Zhang, Q., and Xiao, S.-M. J. J. o. T. M. (2023). The effects of probiotics supplementation on glycaemic control among adults with type 2 diabetes mellitus: a systematic review and meta-analysis of randomised clinical trials. 21(1), 442.
- Ling, W. H., Korpela, R., Mykkänen, H., Salminen, S., and Hänninen, O. (1994). Lactobacillus strain GG supplementation decreases colonic hydrolytic and reductive enzyme activities in healthy female adults. *The Journal of Nutrition, 124*(1), 18-23.
- Linn, Y. H., Thu, K. K., and Win, N. H. H. (2019). Effect of probiotics for the prevention of acute radiation-induced diarrhoea among cervical cancer patients: a randomized double-blind placebo-controlled study. *Probiotics and Antimicrobial proteins*, *11*, 638-647.
- Ljungh, A., and Wadström, T. (2006). Lactic acid bacteria as probiotics. Current issues in Intestinal Microbiology, 7(2), 73-90.
- Lou, H., Liu, X., and Liu, P. J. F. i. P. (2023). Mechanism and implications of pro-nature physical activity in antagonizing psychological stress: the key role of microbial-gut-brain axis. *14*.
- Lu, K., Dong, S., Wu, X., Jin, R., and Chen, H. (2021). Probiotics in cancer. Frontiers in Oncology, 11, 638148.
- Luise, D., Bosi, P., Raff, L., Amatucci, L., Virdis, S., and Trevisi, P. J. F. I. M. (2022). Bacillus spp. probiotic strains as a potential tool for limiting the use of antibiotics, and improving the growth and health of pigs and chickens. *13*, 801827.
- Ma, X.-Y., Son, Y.-H., Yoo, J.-W., Joo, M.-K., and Kim, D.-H. (2022). Tight junction protein expression-inducing probiotics alleviate TNBS-induced cognitive impairment with colitis in mice. *Nutrients*, *14*(14), 2975.
- Macfarlane, G. T., and Cummings, J. H. (1999). Probiotics and prebiotics: can regulating the activities of intestinal bacteria

benefit health? Bmj, 318(7189), 999-1003.

- Maldonado Galdeano, C., Cazorla, S. I., Lemme Dumit, J. M., Vélez, E., and Perdigón, G. (2019). Beneficial effects of probiotic consumption on the immune system. *Annals of Nutrition and Metabolism*, 74(2), 115-124.
- Matin, S., and Dadkhah, M. J. B. R. B. (2024). BDNF/CREB signaling pathway contribution in depression pathogenesis: A survey on the non-pharmacological therapeutic opportunities for gut microbiota dysbiosis. 110882.
- Mazziotta, C., Tognon, M., Martini, F., Torreggiani, E., and Rotondo, J. C. J. C. (2023). Probiotics mechanism of action on immune cells and beneficial effects on human health. *12*(1), 184.
- McFarland, L. V. (2015). From yaks to yogurt: the history, development, and current use of probiotics. *Clinical Infectious Diseases*, 60(suppl\_2), S85-S90.
- McFarland, L. V. (2021). Efficacy of single-strain probiotics versus multi-strain mixtures: systematic review of strain and disease specificity. *Digestive Diseases and Sciences*, 66, 694-704.
- McFarland, L. V. J. D. d., and sciences. (2021). Efficacy of single-strain probiotics versus multi-strain mixtures: systematic review of strain and disease specificity. 66, 694-704.
- Medina, M., Izquierdo, E., Ennahar, S., and Sanz, Y. (2007). Differential immunomodulatory properties of Bifidobacterium logum strains: relevance to probiotic selection and clinical applications. *Clinical and Experimental Immunology, 150*(3), 531-538.
- Mileti, E., Matteoli, G., Iliev, I. D., and Rescigno, M. (2009). Comparison of the immunomodulatory properties of three probiotic strains of Lactobacilli using complex culture systems: prediction for in vivo efficacy. *PloS one*, *4*(9), e7056.
- Molska, M., and Reguła, J. (2019). Potential mechanisms of probiotics action in the prevention and treatment of colorectal cancer. *Nutrients*, *11*(10), 2453.
- Mortazavian, A., Mohammadi, R., and Sohrabvandi, S. (2015). New Advances in the Basic and Clinical Gastroenterology: Delivery of Probiotic Microorganisms into Gastrointestinal Tract by Food Products. Iran: Tehran. *Iran: Tehran. Available from: URL: www. intechopen. com. Cited: January 7th.*
- Mudaliar, S. B., Poojary, S. S., Bharath Prasad, A. S., Mazumder, N. J. P., and Proteins, A. (2024). Probiotics and Paraprobiotics: Effects on Microbiota-Gut-Brain Axis and Their Consequent Potential in Neuropsychiatric Therapy. 1-25.
- Munir, A., Javed, G. A., Javed, S., and Arshad, N. (2022). Levilactobacillus brevis from carnivores can ameliorate hypercholesterolemia: In vitro and in vivo mechanistic evidence. *Journal of Applied Microbiology*, *133*(3), 1725-1742.
- Musazadeh, V., Zarezadeh, M., Faghfouri, A. H., Keramati, M., Jamilian, P., Jamilian, P., and Nutrition. (2023). Probiotics as an effective therapeutic approach in alleviating depression symptoms: an umbrella meta-analysis. *63*(26), 8292-8300.
- Naomi, R., Embong, H., Othman, F., Ghazi, H. F., Maruthey, N., and Bahari, H. (2022). Probiotics for Alzheimerandrsquo;s Disease: A Systematic Review. *14*(1), 20. Retrieved from <u>https://www.mdpi.com/2072-6643/14/1/20</u>
- Nasr, N. (2018). Psychological impact of probiotics and fermented foods on mental health of human in integrated healthy lifestyle. *International Journal of Current Microbiology and Applied Sciences*, 7(08), 2815-2822.
- Noor, S., Ali, S., Riaz, S., Sardar, I., Farooq, M. A., and Sajjad, A. J. M. B. R. (2023). Chemopreventive role of probiotics against cancer: a comprehensive mechanistic review. *50*(1), 799-814.
- Osterlund, P., Ruotsalainen, T., Korpela, R., Saxelin, M., Ollus, A., Valta, P., and Elomaa, I. (2007). Joensuu, H1: CAS: 528: DC% 2BD2sXhtFKktb% 2FJ: Lactobacillus supplementation for diarrhoea related to chemotherapy of colorectal cancer: a randomised study. vol. 97. *Br Journal Cancer*, 1028-1034.
- Ouwehand, A. C., Invernici, M. M., Furlaneto, F. A., and Messora, M. R. (2018). Effectiveness of multi-strain versus single-strain probiotics: current status and recommendations for the future. *Journal of Clinical Gastroenterology*, *52*, S35-S40.
- Ouwehand, A. C., Isolauri, E., Kirjavainen, P. V., Ölkkö, S., and Salminen, S. J. (2000). The mucus binding of Bifidobacterium lactis Bb12 is enhanced in the presence of Lactobacillus GG and Lact. delbrueckii subsp. bulgaricus. *Letters in Applied Microbiology*, *30*(1), 10-13.
- Pan, I., Issac, P. K., Rahman, M. M., Guru, A., and Arockiaraj, J. J. M. N. (2023). Gut-brain axis a key player to control gut dysbiosis in neurological Diseases. 1-19.
- Petruzziello, C., Saviano, A., and Ojetti, V. (2023). Probiotics, the immune response and acute appendicitis: a review. *Vaccines*, 11(7), 1170.
- Plaza-Diaz, J., Ruiz-Ojeda, F. J., Gil-Campos, M., and Gil, A. (2019). Mechanisms of action of probiotics. Advances in nutrition, 10(suppl\_1), S49-S66.
- Prince, M., Comas-Herrera, A., Knapp, M., Guerchet, M., and Karagiannidou, M. (2016). World Alzheimer report 2016: improving healthcare for people living with dementia: coverage, quality and costs now and in the future.
- Psichas, A., Sleeth, M., Murphy, K., Brooks, L., Bewick, G., Hanyaloglu, A., and Frost, G. (2015). The short chain fatty acid propionate stimulates GLP-1 and PYY secretion via free fatty acid receptor 2 in rodents. *International Journal of Obesity*, 39(3), 424-429.
- Psychiatry, G. M. D. C. J. T. L. (2022). Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. 9(2), 137-150.
- Pudgar, P., Povšič, K., Čuk, K., Seme, K., Petelin, M., and Gašperšič, R. J. C. o. i. (2021). Probiotic strains of Lactobacillus brevis and Lactobacillus plantarum as adjunct to non-surgical periodontal therapy: 3-month results of a randomized controlled clinical trial. 25, 1411-1422.
- Puvanasundram, P., Chong, C. M., Sabri, S., Yusoff, M. S., and Karim, M. (2021). Multi-strain probiotics: Functions, effectiveness

and formulations for aquaculture applications. Aquaculture Reports, 21, 100905.

- Qin, J., Li, Y., Cai, Z., Li, S., Zhu, J., Zhang, F., and Shen, D. (2012). A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature*, 490(7418), 55-60.
- Radosavljevic, M., Svob Strac, D., Jancic, J., and Samardzic, J. J. G. (2023). The Role of Pharmacogenetics in Personalizing the Antidepressant and Anxiolytic Therapy. 14(5), 1095.
- Reid, G., Gadir, A. A., and Dhir, R. (2019). Probiotics: reiterating what they are and what they are not. *Frontiers in Microbiology*, 10, 424.
- Reis, S. A. d., da Conceição, L. L., and Peluzio, M. d. C. G. (2019). Intestinal microbiota and colorectal cancer: changes in the intestinal microenvironment and their relation to the disease. *Journal of Medical Microbiology*, 68(10), 1391-1407.
- Renuka, S. R., Kumar, N. A., Manoharan, D., Naidu, D. K. J. J. o. P., and Pharmacotherapeutics. (2023). Probiotics: A Review on Microbiome That Helps for Better Health–A Dermatologist's Perspective. 0976500X231175225.
- Reque, P. M., and Brandelli, A. (2022). An introduction to probiotics. In Probiotics (pp. 1-17): Elsevier.
- Ribera, C., Sánchez-Ortí, J. V., Clarke, G., Marx, W., Mörkl, S., Balanzá-Martínez, V. J. N., and Reviews, B. (2024). Probiotic, prebiotic, synbiotic and fermented food supplementation in psychiatric disorders: A systematic review of clinical trials. 105561.
- Rinninella, E., Raoul, P., Cintoni, M., Franceschi, F., Miggiano, G. A. D., Gasbarrini, A., and Mele, M. C. (2019). What is the healthy gut microbiota composition? A changing ecosystem across age, environment, diet, and diseases. *Microorganisms*, 7(1), 14.
- Rizzello, V., Bonaccorsi, I., Dongarra, M. L., Fink, L. N., and Ferlazzo, G. (2011). Role of natural killer and dendritic cell crosstalk in immunomodulation by commensal bacteria probiotics. *BioMed Research International, 2011*.
- Rutsch, A., Kantsjö, J. B., and Ronchi, F. (2020). The gut-brain axis: how microbiota and host inflammasome influence brain physiology and pathology. *Frontiers in Immunology*, *11*, 604179.
- Saarela, M., Mogensen, G., Fonden, R., Mättö, J., and Mattila-Sandholm, T. (2000). Probiotic bacteria: safety, functional and technological properties. *Journal of biotechnology*, *84*(3), 197-215.
- Sajedi, D., Shabani, R., and Elmieh, A. (2021). 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, 144*, 155590.
- Samiappan, S. C., and Dhailappan, A. (2024). Gut Microbiota Associated with OCD and its Impact Mediated by Probiotics. In *Nutrition and Obsessive-Compulsive Disorder* (pp. 55-65): CRC Press.
- Sanap, D. S., Garje, M. A., and Godge, G. R. (2019). Probiotics, their health benefits and applications for development of human health: a review. *Journal of Drug Delivery and Therapeutics*, 9(4-s), 631-640.
- Santacroce, L., Charitos, I. A., and Bottalico, L. J. E. R. o. A.-i. T. (2019). A successful history: Probiotics and their potential as antimicrobials. 17(8), 635-645.
- Sanz, Y., Portune, K., Del Pulgar, E. G., and Benítez-Páez, A. (2016). Targeting the microbiota: considerations for developing probiotics as functional foods. In *The gut-brain Axis* (pp. 17-30): Elsevier.
- Senesi, S., Celandroni, F., Tavanti, A., and Ghelardi, E. (2001). Molecular characterization and identification of Bacillus clausii strains marketed for use in oral bacteriotherapy. *Applied and Environmental Microbiology*, *67*(2), 834-839.
- Sharma, M., Wasan, A., and Sharma, R. K. J. F. B. (2021). Recent developments in probiotics: An emphasis on Bifidobacterium. *41*, 100993.
- Sharma, P., Das, S., Sadhu, P., Pal, S., Mitra, S., Ghoshal, A., and Ghosh, B. J. J. o. S. i. F. S. (2023). Therapeutic Role of Probiotics In Managing Various Diseases. 10(1S), 6378-6380.
- Shi, L., Sheng, J., Wang, M., Luo, H., Zhu, J., Zhang, B., and Yang, X. (2019). Combination therapy of TGF-β blockade and commensal-derived probiotics provides enhanced antitumor immune response and tumor suppression. *Theranostics*, 9(14), 4115.
- Singh, T. P., and Natraj, B. H. (2021). Next-generation probiotics: a promising approach towards designing personalized medicine. *Critical Reviews in Microbiology*, 47(4), 479-498.
- Sionek, B., Szydłowska, A., Zielińska, D., Neffe-Skocińska, K., and Kołożyn-Krajewska, D. J. M. (2023). Beneficial bacteria isolated from food in relation to the next generation of probiotics. *11*(7), 1714.
- Śliżewska, K., Markowiak-Kopeć, P., and Śliżewska, W. (2020). The role of probiotics in cancer prevention. Cancers, 13(1), 20.
- Srivastav, S., Neupane, S., Bhurtel, S., Katila, N., Maharjan, S., Choi, H., and Choi, D.-Y. (2019). Probiotics mixture increases butyrate, and subsequently rescues the nigral dopaminergic neurons from MPTP and rotenone-induced neurotoxicity. *The Journal of Nutritional Biochemistry*, 69, 73-86.
- Stavropoulou, E., and Bezirtzoglou, E. (2020). Probiotics in medicine: a long debate. Frontiers in immunology, 11, 2192.
- Suez, J., Zmora, N., Segal, E., and Elinav, E. (2019). The pros, cons, and many unknowns of probiotics. *Nature Medicine*, 25(5), 716-729.
- Takahashi, M., Taguchi, H., Yamaguchi, H., Osaki, T., Komatsu, A., and Kamiya, S. (2004). The effect of probiotic treatment with Clostridium butyricum on enterohemorrhagic Escherichia coli O157: H7 infection in mice. *FEMS Immunology and Medical Microbiology*, *41*(3), 219-226.
- Thapar, A., Eyre, O., Patel, V., and Brent, D. J. T. L. (2022). Depression in young people. 400(10352), 617-631.
- Timmerman, H. M., Koning, C. J., Mulder, L., Rombouts, F. M., and Beynen, A. C. (2004). Monostrain, multistrain and multispecies probiotics—A comparison of functionality and efficacy. *International Journal of Food Microbiology*, 96(3),

219-233.

- Valdez-Baez, J. L., De Jesus, L. C. L., Marques, P. H., da Silva Prado, L. C., Felice, A. G., Rodrigues, T. C. V., and de Castro Soares, S. (2022). Comparative genomics in probiotic bacteria. In *Lactic Acid Bacteria in Food Biotechnology* (pp. 245-278): Elsevier.
- Vijay, N., and Morris, M. E. (2014). Role of monocarboxylate transporters in drug delivery to the brain. *Current Pharmaceutical Design*, 20(10), 1487-1498.
- Vimala, Y., and Kumar, P. (2006). Some aspects of probiotics. Indian Journal of Microbiology, 46(1), 1.
- Vos, T., Lim, S. S., Abbafati, C., Abbas, K. M., Abbasi, M., Abbasifard, M., and Abdelalim, A. J. T. L. (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. 396(10258), 1204-1222.
- Walker, W. A. (2008). Mechanisms of action of probiotics. *Clinical Infectious Diseases, 46*(Supplement\_2), S87-S91.
- Wang, X., Yang, J., Qiu, X., Wen, Q., Liu, M., Zhou, D., and Chen, Q. (2021). Probiotics, Pre-biotics and Synbiotics in the Treatment of Pre-diabetes: A Systematic Review of Randomized Controlled Trials. *Frontiers in Public Health*, 9. doi:10.3389/fpubh.2021.645035
- Xiong, R.-G., Li, J., Cheng, J., Zhou, D.-D., Wu, S.-X., Huang, S.-Y., and Li, H.-B. J. N. (2023). The role of gut microbiota in anxiety, depression, and other mental disorders as well as the protective effects of dietary components. *15*(14), 3258.
- Yano, J. M., Yu, K., Donaldson, G. P., Shastri, G. G., Ann, P., Ma, L., and Hsiao, E. Y. J. C. (2015). Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *161*(2), 264-276.
- Yao, K., Zeng, L., He, Q., Wang, W., Lei, J., and Zou, X. (2017). Effect of probiotics on glucose and lipid metabolism in type 2 diabetes mellitus: a meta-analysis of 12 randomized controlled trials. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research*, 23, 3044.

Zaib, S., Hayat, A., and Khan, I. J. M. R. i. M. C. (2024). Probiotics and their beneficial health effects. 24(1), 110-125.

- Zhang, Z., Tang, H., Chen, P., Xie, H., and Tao, Y. (2019). Demystifying the manipulation of host immunity, metabolism, and extraintestinal tumors by the gut microbiome. *Signal Transduction and Targeted Therapy*, 4(1), 41.
- Zhao, R., Wang, Y., Huang, Y., Cui, Y., Xia, L., Rao, Z., and Wu, X. (2017). Effects of fiber and probiotics on diarrhea associated with enteral nutrition in gastric cancer patients: A prospective randomized and controlled trial. *Medicine*, *96*(43).
- Zhu, G., Zhao, J., Zhang, H., Chen, W., and Wang, G. (2021). Probiotics for Mild Cognitive Impairment and Alzheimer's Disease: A Systematic Review and Meta-Analysis. *10*(7), 1672. Retrieved from <u>https://www.mdpi.com/2304-8158/10/7/1672</u>