Section A-Review paper

AN UPDATED REVIEW ON PROBIOTICS AND RELATED PRODUCTS IN TREATMENT OF VARIOUS AILMENTS

Alimuddin Saifi[1], Gazala Noor[2],Vaishali[3],Arvind Kumar[3], Nazia Siddiqui[1],Bhuwanendra Singh[4*]

1.Department of Pharmaceutical Technology, M.I.E.T. Meerut, U.P India.

2.Faculty of Pharmacy, Integral University, Lucknow U.P India.

3.Department of Pharmaceutical Chemistry, SD College of Pharmacy & Vocational Studies, Muzaffarnagar, U.P India.

4.Department of Pharmacognosy, SD College of Pharmacy & Vocational Studies, Muzaffarnagar, U.P India.

***Corresponding Author's Email Id:**bhuwanendrasingh14@gmaiil.com

Abstract

Probiotics are live bacteria that provide the human body with health advantages when consumed. The oral consumption of probiotics has been suggested as a potential preventive measure for the common side effect of diarrhoea that may arise from antibiotic use. Probiotics function through the restoration of an imbalanced gastrointestinal microbiota. Probiotics are present in various fermented foods, yogurt, dietary supplements, and cosmetic products. Several bacterial strains aid in the process of food digestion, eliminate pathogenic cells, and synthesize essential vitamins. Several microorganisms found in probiotic products exhibit similarity to the microorganisms that naturally occur in the human body. The health benefits of probiotic strains belonging to genera such as Bifidobacterium, Lactobacillus, Enterococcus, Saccharomyces, Streptococcus, Escherichia coli, Pedococcus, and Leuconostochave been well established.

The present review article offers an outline of the current research status on probiotics and probiotic products in the management of diverse medical conditions. The article describes the probiotics' methods of action, including how they affect the immune system and the gut flora. The authors investigate the information that is currently available about probiotics' efficacy in treating a range of medical disorders, such as gastrointestinal ailments, allergies, respiratory infections, and metabolic disorders. The literature review underscores the potential of probiotics as a secure and efficacious therapeutic modality for a spectrum of health conditions, while underscoring the necessity for additional research to fully actualize their potential.

Key Words: Probiotics, ailments, health benefits, microbiome.

1. INTRODUCTION

The etymology of the term "probiotic" can be traced back to its Greek roots, where "pro" denotes "for" and "biotic" pertains to "life." Hence, the term "probiotic" implies a substance or agent that is beneficial for life. In 1965, Lilly & Stillwell established the initial definition of probiotics as "substances that are released" by one microbe that encourages the development of another. Probiotics are unquestionably the opposite of antibiotics, according to the definition. Probiotics were first identified by Parker in 1974 as the organisms and chemicals that support the balance of gut microbes[1].

According to Fuller, who concurs with Parker's definition [2], [3], probiotics are live microbial feed supplements that benefit the host (animal or human) by balancing the gut microbial flora. According to the Food and Agriculture Organisation of the United Nations and theFAO-WHO, probiotics are live bacteria that, when given in the right amounts, dramatically enhance the host's health. The ISAPP, an international scientific association for probiotics and prebiotics, has endorsed this definition as the one that most accurately characterises probiotics. Consuming advantageous microorganisms that are later added to the gut microbiota is a component of probiotic therapies. Numerous helpful bacteria starve off dangerous bacteria by competing with them for nutrients [4]. Probiotics have a vital role in a number of physiological processes that benefit human health [5]. Numerous probiotic bacteria from the genera Lactobacillus, Bifidobacterium, Saccharomyces, Enterococcus, Streptococcus, Pedococcus, Leuconostoc, and Escherichia coli have been shown to provide health benefits [6]. Because of the close ties between the gut microbiota, health, and disease, there is a lot of interest in using probiotics (live microorganisms) or prebiotics (non-digestible substrates) to change the gut microbiota in a way that would prevent or treat certain disorders. [7] Synbiotics are dietary supplements that combine probiotics and prebiotics. To extend the probiotics' intestinal persistence, prebiotics are added to the mix. It has been demonstrated that consuming probiotics, prebiotics, and synbiotics can change the composition of the GI microbiota and restore the delicate microbial balance, potentially enhancing general health. Live bacteria known as probiotics have been shown to provide a multitude of health benefits when eaten in adequate doses. They could benefit digestion, immunity, reduce inflammation, and women's health, as well as boost mental health. Probiotics may be found in fermented foods and nutritional supplements[8].

2. PROBIOTICS: Their role in clinical practice and advantages

The Greek phrase for "for life" that gave rise to the term "probiotic" is "for life." Lilly and Stillwell in 1965 "Substances secreted by one microorganism that promote the growth of another" is how probiotics are defined. This definition's main objective was to distinguish them from antibiotics by emphasising their opposing effects. In 1974, Parker used the phrase "organisms and materials which contribute to gut microbial equilibrium" to define probiotics [9], [10] Probiotics are "live microbial feed supplements, which beneficially affect the host (animal or human) by improving its intestinal microbial balance," according to Fuller's 1989 proposal[11].

Probiotics are officially describe as "live microorganisms that, when supplied in sufficient proportions, impart a considerable health benefit on the host" by the F. and A. Organisation of the United Nations and theWHO [12].

Today, experts from all across the globe agree most onprobiotics. The ISAPP later approved it. During probiotic treatment, these beneficial microbes are intentionally eaten and introduced to the gut microbiota. As a consequence, a lot of beneficial bacteria compete with harmful bacteria for nutrients, starving them to death [13]. Probiotics provide an effective natural biological barrier that keeps away many harmful germs by adhering to the inner lining of the intestines. As a result, adhesion is thought to be the starting point of colonisation. Physicochemical factors determineeither specifically or randomly, bacteria and receptor molecules on epithelial cells cling to the epithelium[14].

2.1 Typical Probiotic Microorganisms

Many different microorganisms are used nowadays as probiotics. However, bacteria from the genus Lactobacillus are the most often used. Probiotics are the first and most common class of microorganisms [15]. Numerous bacteria reside in the human GIT. In contradistinction to other intestinal microorganisms, they are acknowledged to be devoid of deleterious impacts [16].

It is worth noting that there are a variety of other Lactobacilli species, such as L. acidophilus, L. rhamnosus, L. casei, L. delbrueckii ssp. bulgaricus, L. johnsonii, L. reuteri, L. brevis, L. cellobiosus, L. curvatus, L. fermentum, L. gasseri, and L. plantarum [17]. Some commonly utilized species include Bifidobacterium breve, B. animalis subsp. lactis, and B. longum biotypes infantis and longum[18].

In recent times, probiotics have undergone a significant transformation with the inclusion of a more diverse range of lactic acid bacteria (LAB) from various genera such as Streptococcus, Lactococcus, Enterococcus, Leuconostoc, Propionibacterium, and Pediococcus. This development has expanded the scope of probiotics, making them more effective in promoting gut health and overall well-being. However, a number of countries are worried that certain Enterococcus species may spread genes for antibiotic resistance. Aspergillus oryzae, yeasts (Saccharomyces cereviciae, Saccharomyces boulardii), non-pathogenic E. coli Nissle 1917, and several spore-forming bacteria are some other unrelated microorganisms that have been used [19],[20].

2.2 Mechanism of action of probiotics

The study of probiotics has revealed numerous mechanisms of action. This article explores the various processes involved in the functioning of intestinal microbial communities. These processes include immune system modulation, interaction with the brain-gut axis, colonization and normalization of disturbed microbial communities, competitive exclusion of pathogens, bacteriocin production, enzymatic activity, production of volatile fatty acids, cell adhesion, cell antagonism, and mucin production. Understanding these processes is crucial for maintaining a healthy gut microbiome in both children and adults. The gut microbiota has been found to play a crucial role in regulating the immune system. This is due to its ability to produce substances that possess immunomodulatory and anti-inflammatory properties, which can activate immune cells. Probiotic bacteria have been found to have immunomodulatory effects through their interactions with various cells in the body, including lymphocytes, dendritic cells, monocytes/macrophages, and epithelial cells. These interactions have been shown to play a significant role in regulating the immune system and promoting overall health. Probiotics have been found to regulate the host immune response, which is one of their key mechanisms of action. The division of the immune system into innate and adaptive components is a well-established concept in immunology. The adaptive immune response is heavily reliant on B and T cells due to their strong attraction to specific antigens. These cells play a critical role in identifying and responding to foreign substances in the body. The innate immune system is a crucial component of the body's defense mechanism against various pathogens. It is activated by specific elements called pathogen-associated molecular patterns (PAMPs), which are commonly found in many diseases. Unlike the adaptive immune system, the innate immune system provides immediate protection against invading pathogens without the need for prior exposure or recognition. This system plays a vital role in the early stages of infection

and helps to prevent the spread of pathogens throughout the body. In the realm of immunology, it is widely accepted that pattern recognition receptors (PRRs) play a crucial role in mediating immune responses to infections. These receptors are known to bind to pathogen-associated molecular patterns (PAMPs), which in turn trigger a cascade of immune responses. TLRs, or Toll-like receptors, are a crucial component of the innate immune system. These transmembrane proteins are a type of pattern recognition receptor (PRR), which play a vital role in recognizing and responding to various pathogens. By detecting specific molecular patterns associated with pathogens, TLRs initiate a cascade of immune responses that help to protect the body from infection. Overall, TLRs are an essential component of the immune system's ability to detect and respond to potential threats. The expression of these molecules is observed on a diverse set of cells, encompassing both immune and non-immune cell types. These include B-cells, natural killer cells, dendritic cells, macrophages, fibroblast cells, epithelial cells, and endothelial cells. In addition to the aforementioned components of PRRs, lectins, adhesion molecules, and nucleotide-binding oligomerization domains also play a crucial role in the recognition of pathogens. These molecules are involved in the detection of specific pathogen-associated molecular patterns (PAMPs) and trigger downstream signaling pathways that lead to the activation of the immune response. Lectins, for instance, are carbohydrate-binding proteins that recognize and bind to specific sugar moieties on the surface of pathogens. Adhesion molecules, on the other hand, facilitate the attachment of immune cells to the site of infection, while nucleotide-binding oligomerization domains detect intracellular pathogens and initiate an immune response. Together, these components of PRRs form a complex network of molecular sensors that enable the immune system to detect and respond to a wide range of pathogens. As per recent studies, it has been found that Pattern Recognition Receptors (PRRs) are composed of NOD-like intracellular receptors (NODLRs). These receptors, along with Toll-like receptors (TLRs), are responsible for safeguarding the cytoplasm. This discovery has opened up new avenues for research in the field of immunology and has provided a better understanding of the immune system's defense mechanisms. In addition to the well-known PRRs, recent studies have identified several other types of PRRs. These include C-type lectin receptors, formylated peptide receptors, retinoic acid inducible-like helicases, and intracellular IL-1-converting enzyme protease-activating factor [21]. These newly discovered PRRs have expanded our understanding of the innate immune system and its ability to detect and respond to a wide range of pathogens and danger signals.

3. Advantages of probiotics

3.1 Probiotic as Functional Food

Probiotics have become increasingly popular in recent years, with many people incorporating them into their diets either through food or non-food products. As a food component, probiotics can be found in a variety of products such as yogurt, kefir, and fermented vegetables. Non-food preparations, such as supplements, are also available for those who prefer a more concentrated form of probiotics. Regardless of the form in which they are consumed, probiotics are believed to provide numerous health benefits, including improved digestion and immune function. Probiotics have gained widespread attention in recent years due to their potential health benefits. Foods that contain these beneficial microorganisms are often referred to as "functional foods." This term is used to describe foods that offer additional health benefits beyond basic nutrition. Probiotic-containing foods such as yogurt, kefir, and sauerkraut are examples of functional foods that have become increasingly popular in the health and wellness industry. By incorporating these foods into your diet, you may be able to support your digestive health and boost your immune system. Functional foods have gained popularity in recent years due to their ability to impact certain biological functions and enhance overall health. These foods contain nutrient- or non-nutrient-rich components that provide various health benefits. [22]. To provide a health benefit, a probiotic product's daily dose and number of live bacteria must be enough. Because they have a high upper permissible level and are not known to be pathogenic, probiotics might be promoted as a beneficial dietary supplement. Currently, using probiotics to cure or prevent any illness is prohibited[23].

The two greatest methods to boost the quantity of good bacteria in the stomach are via fermented meals and nutritional supplements. Fermented foods are the most organic sources. During the process of lactofermentation, natural bacteria eat the sugar and starch in the food, which leads to the creation of lactic acid. This process creates an environment that safeguards the food and promotes the development of several beneficial bacterial species, beneficial enzymes, vitamin B, and omega-3 fatty acid molecules. The specific kinds and quantities of fermented foods that are helpful cannot be determined since there is no recommended daily consumption for probiotics [24].

This article focuses on the viability and resistance of various lactic acid bacteria strains, including lactobacillus, bifidobacteria, and Bacillus strains, as well as isolated probiotic strains such as L. rhamnosus and L. plantarum. These strains are obtained from specific vegetables and citrus fruits. The article explores the strains' ability to withstand different

food environments, including orange juice, cheese, homemade bread, leaves of yams, papayas, casseroles, sugarcane, and taro. Orange juice proved to be a stable medium for L. casei despite the use of probiotic addition strategies. Soybeans have been found to be an excellent support for L. casei cells due to their ability to maintain the vitality of the cells. This characteristic is highly advantageous for their potential use in fermentation processes and as a food ingredient. The preservation of cell vitality is crucial for ensuring the effectiveness of the cells in these applications. Therefore, soybeans can be considered a stable and reliable support for L. casei cells. In a recent study, L. casei was found to exhibit probiotic properties in vitro, indicating its potential as a beneficial dietary supplement [25]. Furthermore, research has demonstrated that L. casei is safe for consumption, making it a promising candidate for use in food products [25].

3.2 Therapeutic benefits of probiotics in various diseases

As soon as probiotic strains are delivered or ingested, the colonization process begins. A small number of studies have focused on this phase, whereas the bulk have just examined the key findings and drawn conclusions about how the use of bacteria affected them. In healthy individuals, probiotic treatment increases the production of short-chain fatty acids (SCFAs), fecal moisture, bowel frequency, and volume of stools [26].

The number of defecations, frequency, or consistency of the stool were unaffected by L. rhamnosus PRSF-L477. It implies that the bacteria were accepted well. The discovery of L. rhamnosus on the faces of individuals in the probiotic-treated group [27]. was of significant concern.

L. salivarius CECT5713 was tested for tolerance in healthy people; the strain was tolerated with no adverse effects noted, but no effort was made to look into intestinal colonization by this strain [28]. People who are overweight or obese may get probiotic strains as individual therapies or as multistrain mixes, and these treatments have consequences beyond just enhancing health. On overweight individuals, a multistrain probiotic mixture known as De Simone formulation has been tested. The De Simone formulation increased insulin sensitivity, altered the makeup of the gut flora, and reduced lipid levels and inflammatory markers such high-sensitivity C-reactive protein [29].

In individuals with obesity and high blood pressure, L. plantarum TENSIA decreased blood pressure and BMI[30].

IBD is the term used to describe a group of systemic diseases that affect the digestive system. In these conditions, the epithelium barrier's capacity to function is impaired, which significantly contributes to the onset of the illness and other issues. IBD may start and

progress because of changes in the gut microbiota [31]. Patients with ulcerative colitis who use probiotics seem to have a higher chance of experiencing a complete remission, particularly when using the De Simone formulation with a mix of Lactobacillus and prebiotics. Trials of probiotic therapy in people with Crohn's disease (CD) did not show a remission effect [32]. C. difficile-related diarrhea may be efficiently treated with probiotics. [33]

The evaluated studies suggest that consuming multistrain probiotics for six to twelve weeks may improve GI index in persons with Type-2 DM. These probiotics need to include between 7 and 100 billion L. Acidophilus, S. thermophilus, L. bulgaricus, and/or Bifidobacterium lactis colony forming units [34]. By managing the microbiota in the gut and lowering oxidative and inflammatory stress, probiotics may increase insulin sensitivity and reduce autoimmune responses. According to recent studies, probiotics affect the host by reducing intestinal permeability and mucosal immune response, using hormones that regulate hunger to regulate eating patterns, and modifying the endocannabinoid (eCB) system, which is connected to inflammation and diabetes. Probiotic supplementation may be used to prevent and treat gestational diabetes, type-1 and type-2 diabetes, and both [35]. A variety of microorganisms, including bacteria, yeasts, and molds, contribute to spontaneous fermentation. Probiotics are found naturally or eaten in fermented foods, namely lactic acid bacteria like Lactobacillus, Bifidobacteria, and Streptococcus species. Fermented foods may provide enzymes, peptides, antimicrobials, antioxidants, and other probiotic properties. These products have been shown to be essential for both treating and preventing cancer [36].

The mental health of humans is benefited by a distinct class of probiotics called psychobiotics. Probiotics have been a popular topic in recent years, but have you heard of psychobiotics? These specialized probiotics have been found to have unique benefits that set them apart from ordinary probiotics. One of the key differences is their ability to produce or promote the production of neurotransmitters, short-chain fatty acids, enteroendocrine hormones, and anti-inflammatory cytokines. These compounds have been linked to improved mood, cognitive function, and overall gut health. So, if you're looking to take your probiotic game to the next level, consider giving psychobiotics a try. Psychobiotics are a class of probiotics that have been shown to have a positive impact on mental health. The most commonly studied psychobiotic bacteria belong to the families Lactobacilli, Streptococci, Bifidobacteria, Escherichia, and Enterococci. These bacteria have been found to improve mood, reduce anxiety and depression, and even enhance

cognitive function. Research in this field is ongoing, but the potential benefits of psychobiotics are promising for those seeking natural ways to support their mental health. The impact of bacteria on the two-way connection between the brain and the gastrointestinal system has been observed. The impact of gut bacteria on the delivery of signals to the central nervous system is a topic of growing interest in the scientific community. Recent studies have shown that the neurons of the enteric nervous system interact directly with neurochemicals produced by gut bacteria, which can have a significant effect on the transmission of signals to the brain. This interaction has important implications for a range of physiological processes, including digestion, metabolism, and immune function. As research in this area continues to advance, it is likely that we will gain a deeper understanding of the complex relationship between gut bacteria and the central nervous system [37], [38].

Probiotics, which are live microorganisms, may reduce diarrhea by balancing the gut flora, a side effect of antibiotic usage. This study evaluated the advantages and disadvantages of probiotic use in outpatients to avoid antibiotic-associated diarrhea. The PubMed database search turned up 17 randomized controlled studies with 3631 subjects. The main finding was the incidence of AAD, and the meta-analysis revealed that 8.0% of the probiotic group and 17.7% of the control group had AAD. Both L. rhamnosus GG and S. boulardii, two distinct probiotic strains, were equally effective. The studies' level of quality was nonetheless average. There were no discernible differences between the intervention and control groups in the meta-analysis of adverse events. As a result, probiotics seem to be safe to use and may be helpful in preventing AAD in outpatients [39].

Table no 1.Probiotic products and their clinical benefits:

A table no 1, summarizing some commonly used probiotic microorganisms, brands, companies, and clinical uses is given as follows:

S.N.	**Probiotic Microorganism**	**Brand Name**	**Company**	**Clinical Uses**	**References**
1.	Lactobacillus acidophilus	Culturelle, Florastor, Bio-K+, Bifilac, Vizylac, Lactobac, Enterogermina	Culturelle, Biocodex, Bio-K+, Tablets India, Sanofi,	Improve digestive health, manage allergies, support immune system, manage diarrhea and constipation,	[40] [41] [42]

			Alkem Labs, Abbott Healthcare	boost immunity	
2.	Bifidobacterium lactis	Align, Probiotic Pearls	Procter & Gamble, Integrative Therapeutics	Improve digestive health, reduce inflammation, support immune system	[43] [44] [45]
3.	Lactobacillus rhamnosus	Culturelle, Florastor, Econorm, Sporlac, Bifilac HP,Enterogermina,	Culturelle, Biocodex, Sanofi, Zuventus, Tablets India, Abbott Healthcare	Reduce risk of antibiotic-associated diarrhea, improve gut health, boost immunity	[46] [47] [48]
4.	Streptococcus thermophilus	Threelac, Florastor, Dabur Probiotic	Global Health Trax, Biocodex, Dabur India	Improve digestive health, manage lactose intolerance	[49] [50]
5.	Saccharomyces boulardii	Florastor, Darolac, Bifilac Sachet	Biocodex, Aristo Pharma, Tablets India	Reduce risk of antibiotic-associated diarrhea, manage inflammatory bowel disease, improve gut health	[51], [52]
6.	Bifidobacterium bifidum	Garden of Life, BioGaia	Garden of Life, BioGaia	Improve gut health, support immune system	[53] [54]
7.	Lactobacillus plantarum	Kyo-Dophilus	Wakunaga of America	Reduce inflammation,	[55], [56]

				support immune, may be effective in controlling COVID-19, system, improve gut health	
8.	Lactobacillus reuteri	BioGaia	BioGaia	Improve gut health, manage colic in infants, positive benefits of *L. reuteri* in a murine acquired immunodeficiency syndrome (AIDS)	[57] [58]

Conclusion:

The utilization of probiotics and related products has exhibited potential in the management of diverse maladies. Probiotics are living microorganisms which, upon being administered in sufficient quantities, bestow advantageous effects upon the host's health. The advantageous outcomes are facilitated by diverse mechanisms, encompassing the regulation of the gut microbiota, fortification of the intestinal barrier function, and regulation of the immune system.A plethora of research endeavours have delved into the prospective utilization of probiotics for the purpose of mitigating diverse afflictions, encompassing gastrointestinal maladies, respiratory infections, allergic ailments, and even psychiatric disorders. Whilst certain scholarly investigations have yielded favourable consequences, others have generated inconclusive findings.It is imperative to acknowledge that the quality of probiotics varies significantly, and distinct strains may elicit diverse outcomes. Henceforth, prudent contemplation ought to be bestowed upon the strain, dosage, and span of probiotic intervention whilst electing a therapeutic course of action. Furthermore, it is imperative to note that probiotics cannot serve as a replacement for conventional medical intervention, and it is incumbent upon patients to seek counsel from their healthcare practitioner prior to commencing probiotic therapy.On the whole, probiotics and their corresponding products exhibit potential as a secure and efficacious supplementary treatment for an array of

maladies. Nevertheless, additional investigation is imperative to enhance our comprehension of their modalities of operation and to pinpoint the optimal strains and quantities for particular ailments.

REFERENCES

[1] J. Schrezenmeir and M. de Vrese, ‑Probiotics, prebiotics, and synbiotics--approaching a definition.,‖ *Am J Clin Nutr*, vol. 73, no. 2 Suppl, pp. 361S-364S, Feb. 2001, doi: 10.1093/AJCN/73.2.361S.

[2] M. Kechagia*et al.*, ‑Health Benefits of Probiotics: A Review,‖ *ISRN Nutr*, vol. 2013, pp. 1–7, Jan. 2013, doi: 10.5402/2013/481651.

[3] T. Vasiljevic and N. P. Shah, ‑Probiotics-From Metchnikoff to bioactives,‖ *Int Dairy J*, vol. 18, no. 7, pp. 714–728, Jul. 2008, doi: 10.1016/J.IDAIRYJ.2008.03.004.

[4] B. Mombelli and M. R. Gismondo, ‑The use of probiotics in medical practice,‖ *Int J Antimicrob Agents*, vol. 16, no. 4, pp. 531–536, Dec. 2000, doi: 10.1016/S0924-8579(00)00322-8.

[5] ‑A beneficial microbe composition,new protective materials for the microbes,the method to prepare the same and uses thereof,‖ Jan. 1999.

[6] S. Fijan, ‑Microorganisms with Claimed Probiotic Properties: An Overview of Recent Literature,‖ *International Journal of Environmental Research and Public Health 2014, Vol. 11, Pages 4745-4767*, vol. 11, no. 5, pp. 4745–4767, May 2014, doi: 10.3390/IJERPH110504745.

[7] M. J. Butel, ‑Probiotics, gut microbiota and health,‖ *Med Mal Infect*, vol. 44, no. 1, pp. 1–8, Jan. 2014, doi: 10.1016/J.MEDMAL.2013.10.002.

[8] ‑(PDF) Probiotics in human—evidence based review.‖ https://www.researchgate.net/publication/26496850_Probiotics_in_human-evidence_based_review (accessed Feb. 08, 2023).

[9] G. Macfarlane and J. Cummings, ‑Probiotics and prebiotics: can regulating the activities of intestinal bacteria benefit health?,‖ *BMJ*, vol. 318, no. 7189, pp. 999–1003, Apr. 1999, doi: 10.1136/BMJ.318.7189.999.

[10] J. Schrezenmeir and M. de Vrese, ‑Probiotics, prebiotics, and synbiotics - Approaching a definition,‖ *American Journal of Clinical Nutrition*, vol. 73, no. 2 SUPPL., 2001, doi: 10.1093/AJCN/73.2.361S.

[11] T. Vasiljevic and N. P. Shah, ‑Probiotics—From Metchnikoff to bioactives,‖ *Int Dairy J*, vol. 18, no. 7, pp. 714–728, Jul. 2008, doi: 10.1016/J.IDAIRYJ.2008.03.004.

[12] ‑Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria – Joint FAO/WHO Expert Consultation.‖ https://www.researchgate.net/publication/237102730_Health_and_Nutritional_Properties_of_

Probiotics_in_Food_Including_Powder_Milk_with_Live_Lactic_Acid_Bacteria_-_Joint_FAOWHO_Expert_Consultation (accessed Feb. 08, 2023).

[13] G. Reid, ‒Safe and efficacious probiotics: what are they?,‖ *Trends Microbiol*, vol. 14, no. 8, pp. 348–352, Aug. 2006, doi: 10.1016/J.TIM.2006.06.006.

[14] ‒A beneficial microbe composition,new protective materials for the microbes,the method to prepare the same and uses thereof,‖ Jan. 1999.

[15] B. Mombelli and M. R. Gismondo, ‒The use of probiotics in medical practice,‖ *Int J Antimicrob Agents*, vol. 16, no. 4, pp. 531–536, Dec. 2000, doi: 10.1016/S0924-8579(00)00322-8.

[16] H. Kimoto-Nira, ‒82 JARQ 41 (3) 2007‖.

[17] J. H. Meurman and I. Stamatova, ‒Probiotics: contributions to oral health,‖ *Oral Dis*, vol. 13, no. 5, pp. 443–451, Sep. 2007, doi: 10.1111/J.1601-0825.2007.01386.X.

[18] L. Masco, G. Huys, E. de Brandt, R. Temmerman, and J. Swings, ‒Culture-dependent and culture-independent qualitative analysis of probiotic products claimed to contain bifidobacteria,‖ *Int J Food Microbiol*, vol. 102, no. 2, pp. 221–230, Jul. 2005, doi: 10.1016/J.IJFOODMICRO.2004.11.018.

[19] W. Krasaekoopt, B. Bhandari, and H. Deeth, ‒Evaluation of encapsulation techniques of probiotics for yoghurt,‖ *Int Dairy J*, vol. 13, no. 1, pp. 3–13, Jan. 2003, doi: 10.1016/S0958-6946(02)00155-3.

[20] D. A. Power, J. P. Burton, C. N. Chilcott, P. J. Dawes, and J. R. Tagg, ‒Preliminary investigations of the colonisation of upper respiratory tract tissues of infants using a paediatric formulation of the oral probiotic Streptococcus salivarius K12,‖ *Eur J Clin Microbiol Infect Dis*, vol. 27, no. 12, pp. 1261–1263, Dec. 2008, doi: 10.1007/S10096-008-0569-4.

[21] J. Plaza-Diaz, F. J. Ruiz-Ojeda, M. Gil-Campos, and A. Gil, ‒Mechanisms of Action of Probiotics,‖ *Advances in Nutrition*, vol. 10, pp. S49–S66, Jan. 2019, doi: 10.1093/ADVANCES/NMY063.

[22] M. A. E. Auty*et al.*, ‒Direct in situ viability assessment of bacteria in probiotic dairy products using viability staining in conjunction with confocal scanning laser microscopy,‖ *Appl Environ Microbiol*, vol. 67, no. 1, pp. 420–425, 2001, doi: 10.1128/AEM.67.1.420-425.2001.

[23] D. C. Lin, ‒Probiotics As Functional Foods,‖ *Nutrition in Clinical Practice*, vol. 18, no. 6, pp. 497–506, Dec. 2003, doi: 10.1177/0115426503018006497.

[24] ‒How to get more probiotics - Harvard Health.‖ https://www.health.harvard.edu/staying-healthy/how-to-get-more-probiotics (accessed Feb. 11, 2023).

[25] U. Roobab, Z. Batool, M. F. Manzoor, M. A. Shabbir, M. R. Khan, and R. M. Aadil, ―Sources, formulations, advanced delivery and health benefits of probiotics,‖ *CurrOpin Food Sci*, vol. 32, pp. 17–28, Apr. 2020, doi: 10.1016/J.COFS.2020.01.003.

[26] M. Olivares *et al.*, ―Oral administration of two probiotic strains, Lactobacillus gasseri CECT5714 and Lactobacillus coryniformis CECT5711, enhances the intestinal function of healthy adults,‖ *Int J Food Microbiol*, vol. 107, no. 2, pp. 104–111, Mar. 2006, doi: 10.1016/J.IJFOODMICRO.2005.08.019.

[27] R. D. Wind, H. Tolboom, I. Klare, G. Huys, and J. Knol, ―Tolerance and safety of the potentially probiotic strain Lactobacillus rhamnosus PRSF-L477: a randomised, double-blind placebo-controlled trial in healthy volunteers,‖ *Br J Nutr*, vol. 104, no. 12, pp. 1806–1816, Dec. 2010, doi: 10.1017/S0007114510002746.

[28] R. D. Wind, H. Tolboom, I. Klare, G. Huys, and J. Knol, ―Tolerance and safety of the potentially probiotic strain Lactobacillus rhamnosus PRSF-L477: a randomised, double-blind placebo-controlled trial in healthy volunteers,‖ *Br J Nutr*, vol. 104, no. 12, pp. 1806–1816, Dec. 2010, doi: 10.1017/S0007114510002746.

[29] H. Rajkumar, N. Mahmood, M. Kumar, S. R. Varikuti, H. R. Challa, and S. P. Myakala, ―Effect of probiotic (VSL#3) and omega-3 on lipid profile, insulin sensitivity, inflammatory markers, and gut colonization in overweight adults: a randomized, controlled trial,‖ *Mediators Inflamm*, vol. 2014, 2014, doi: 10.1155/2014/348959.

[30] K. K. Sharafedtinov*et al.*, ―Hypocaloric diet supplemented with probiotic cheese improves body mass index and blood pressure indices of obese hypertensive patients--a randomized double-blind placebo-controlled pilot study,‖ *Nutr J*, vol. 12, no. 1, 2013, doi: 10.1186/1475-2891-12-138.

[31] F. Xu, J. M. Dahlhamer, E. P. Zammitti, A. G. Wheaton, and J. B. Croft, ―Health-Risk Behaviors and Chronic Conditions Among Adults with Inflammatory Bowel Disease — United States, 2015 and 2016,‖ *MMWR Morb Mortal Wkly Rep*, vol. 67, no. 6, pp. 190–195, Feb. 2018, doi: 10.15585/MMWR.MM6706A4.

[32] M. Ganji-Arjenaki and M. Rafieian-Kopaei, ―Probiotics are a good choice in remission of inflammatory bowel diseases: A meta-analysis and systematic review,‖ *J Cell Physiol*, vol. 233, no. 3, pp. 2091–2103, Mar. 2018, doi: 10.1002/JCP.25911.

[33] J. Z. Goldenberg *et al.*, ―Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children,‖ *Cochrane Database Syst Rev*, vol. 2013, no. 5, May 2013, doi: 10.1002/14651858.CD006095.PUB3.

[34] K. A. Tiderencel, D. A. Hutcheon, and J. Ziegler, ―Probiotics for the treatment of type 2 diabetes: A review of randomized controlled trials,‖ *Diabetes Metab Res Rev*, vol. 36, no. 1, Jan. 2020, doi: 10.1002/DMRR.3213.

[35] A. Ram Yadav, ―Deo N and Yadav AR. Role of Probiotics in Diabetes Mellitus. J Inf Dis Trav Med 2021, 5(2): 000154.,‖ 2021, doi: 10.23880/jidtm-16000154.

[36] T. LegesseBedada, T. K. Feto, K. S. Awoke, A. D. Garedew, F. T. Yifat, and D. J. Birri, ―Probiotics for cancer alternative prevention and treatment,‖ *Biomedicine & Pharmacotherapy*, vol. 129, p. 110409, Sep. 2020, doi: 10.1016/J.BIOPHA.2020.110409.

[37] R. Sharma, D. Gupta, R. Mehrotra, and P. Mago, ―Psychobiotics: The Next-Generation Probiotics for the Brain,‖ *CurrMicrobiol*, vol. 78, no. 2, pp. 449–463, Feb. 2021, doi: 10.1007/S00284-020-02289-5.

[38] A. v. Oleskin and B. A. Shenderov, ―Probiotics and Psychobiotics: the Role of Microbial Neurochemicals,‖ *Probiotics Antimicrob Proteins*, vol. 11, no. 4, pp. 1071–1085, Dec. 2019, doi: 10.1007/s12602-019-09583-0.

[39] S. Blaabjerg, D. M. Artzi, and R. Aabenhus, ―Probiotics for the prevention of antibiotic-associated diarrhea in outpatients—A systematic review and meta-analysis,‖ *Antibiotics*, vol. 6, no. 4. 2017. doi: 10.3390/antibiotics6040021.

[40] A. Jamwal, K. Sharma, R. Chauhan, S. Bansal, and G. Goel, ―Evaluation of commercial probiotic lactic cultures against biofilm formation by Cronobactersakazakii,‖ *Intest Res*, vol. 17, no. 2, p. 192, Apr. 2019, doi: 10.5217/IR.2018.00106.

[41] ―Prebiotics and Probiotics: Know the Difference - Enterogermina.‖ https://www.enterogermina.in/probiotics/myth-vs-fact (accessed May 02, 2023).

[42] ―Bio-K Plus Oral: Uses, Side Effects, Interactions, Pictures, Warnings & Dosing - WebMD.‖ https://www.webmd.com/drugs/2/drug-171884/bio-k-plus-oral/details (accessed May 02, 2023).

[43] D. Mazzantini, M. Calvigioni, F. Celandroni, A. Lupetti, and E. Ghelardi, ―Spotlight on the Compositional Quality of Probiotic Formulations Marketed Worldwide,‖ *Front Microbiol*, vol. 12, p. 2058, Jul. 2021, doi: 10.3389/FMICB.2021.693973/BIBTEX.

[44] K. Arunachalam, H. S. Gill, and R. K. Chandra, ―Enhancement of natural immune function by dietary consumption of Bifidobacterium lactis (HN019),‖ *Eur J Clin Nutr*, vol. 54, no. 3, pp. 263–267, 2000, doi: 10.1038/SJ.EJCN.1600938.

[45] N. B. O. Corrêa, L. A. Péret Filho, F. J. Penna, F. M. L. S. Lima, and J. R. Nicoli, ―A randomized formula controlled trial of Bifidobacterium lactis and Streptococcus thermophilus for prevention of antibiotic-associated diarrhea in infants,‖ *J Clin Gastroenterol*, vol. 39, no. 5, pp. 385–389, May 2005, doi: 10.1097/01.MCG.0000159217.47419.5B.

[46] H. Szajewska and I. Hojsak, ―Health benefits of Lactobacillus rhamnosus GG and Bifidobacterium animalis subspecies lactis BB-12 in children,‖ *https://doi.org/10.1080/00325481.2020.1731214*, vol. 132, no. 5, pp. 441–451, Jul. 2020, doi: 10.1080/00325481.2020.1731214.

[47] ―Read all Latest Updates on and about sporlac powder.‖ https://medicaldialogues.in/topics/sporlac-powder (accessed May 02, 2023).

[48] S. Salva, M. Nuñez, J. Villena, A. Ramón, G. Font, and S. Alvarez, ‒Development of a fermented goats' milk containing Lactobacillus rhamnosus: in vivo study of health benefits,‖ *J Sci Food Agric*, vol. 91, no. 13, pp. 2355–2362, Oct. 2011, doi: 10.1002/JSFA.4467.

[49] O. Uriot, S. Denis, M. Junjua, Y. Roussel, A. Dary-Mourot, and S. Blanquet-Diot, ‒Streptococcus thermophilus: From yogurt starter to a new promising probiotic candidate?,‖ *J Funct Foods*, vol. 37, pp. 74–89, Oct. 2017, doi: 10.1016/J.JFF.2017.07.038.

[50] Y. Luo *et al.*, ‒Influence of high-fat diet on host animal health via bile acid metabolism and benefits of oral-fed Streptococcus thermophilus MN-ZLW-002,‖ *Exp Anim*, vol. 71, no. 4, pp. 468–480, 2022, doi: 10.1538/EXPANIM.21-0182.

[51] G. Zanello, F. Meurens, M. Berri, and H. Salmon, ‒Saccharomyces boulardii Effects on Gastrointestinal Diseases,‖ *Current Issues in Molecular Biology 2009, Vol. 11, Pages 47-58*, vol. 11, no. 1, pp. 47–58, Jun. 2008, doi: 10.21775/CIMB.011.047.

[52] H. Szajewska, A. Skórka, and M. Dylag, ‒Meta-analysis: Saccharomyces boulardii for treating acute diarrhoea in children,‖ *Aliment PharmacolTher*, vol. 25, no. 3, pp. 257–264, Feb. 2007, doi: 10.1111/J.1365-2036.2006.03202.X.

[53] C. Picard, J. Fioramonti, A. Francois, T. Robinson, F. Neant, and C. Matuchansky, ‒Review article: bifidobacteria as probiotic agents – physiological effects and clinical benefits,‖ *Aliment PharmacolTher*, vol. 22, no. 6, pp. 495–512, Sep. 2005, doi: 10.1111/J.1365-2036.2005.02615.X.

[54] S. Ku, M. S. Park, G. E. Ji, and H. J. You, ‒Review on Bifidobacterium bifidum BGN4: Functionality and Nutraceutical Applications as a Probiotic Microorganism,‖ *International Journal of Molecular Sciences 2016, Vol. 17, Page 1544*, vol. 17, no. 9, p. 1544, Sep. 2016, doi: 10.3390/IJMS17091544.

[55] Y. Kageyama*et al.*, ‒Lactobacillus plantarum induces innate cytokine responses that potentially provide a protective benefit against COVID-19: A single-arm, double-blind, prospective trial combined with an in vitro cytokine response assay,‖ *Exp Ther Med*, vol. 23, no. 1, pp. 1–13, Jan. 2022, doi: 10.3892/ETM.2021.10942.

[56] ‒Ebscohost | 33517301 | lactobacillus plantarum -- a literature reviewof therapeutic benefits.‖https://web.p.ebscohost.com/abstract?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=13263390&AN=33517301&h=Yhx9iueAEEVjF%2bvbO3YMh0NAIqIxnmQW4%2bXn1F%2fbOY%2b%2fpRXcTrGImTjN50BZB6ZXRBkolb%2b0Aa7F8yd2%2f4L84Q%3d%3d&crl=c&resultNs=AdminWebAuth&resultLocal=ErrCrlNotAuth&crlhashurl=login.aspx%3fdirect%3dtrue%26profile%3dehost%26scope%3dsite%26authtype%3dcrawler%26jrnl%3d13263390%26AN%3d33517301 (accessed May 02, 2023).

[57] Q. Mu, V. J. Tavella, and X. M. Luo, ‒Role of Lactobacillus reuteri in human health and diseases,‖ *Front Microbiol*, vol. 9, no. APR, p. 757, Apr. 2018, doi: 10.3389/FMICB.2018.00757/BIBTEX.

[58] B. W. Wolf, K. B. Wheeler, D. G. Ataya, and K. A. Garleb, ‐Safety and tolerance of Lactobacillus reuteri supplementation to a population infected with the human immunodeficiency virus,‖ *Food and Chemical Toxicology*, vol. 36, no. 12, pp. 1085–1094, Dec. 1998, doi: 10.1016/S0278-6915(98)00090-8.