

DOI: 10.14744/ejma.2023.06078 EJMA 2023;3(4):153–159

Review



Exploring the Efficacy of Probiotics: A Comprehensive Review of Current Evidence and Future Directions

🕩 Shivam Mishra

Department of Zoology, S S Khanna Girls' Degree College, Prayagraj, Uttarpradesh, India

Abstract

Probiotics, defined as live microorganisms that confer a health benefit to the host, have gained widespread attention in recent years for their potential to treat and prevent a variety of health conditions. In this comprehensive review, we explore the current evidence on the efficacy of probiotics, including their mechanism of action and clinical applications. We also discuss the challenges and limitations facing the field, including the lack of regulation and standardization of probiotic products, and the difficulty in conducting high-quality clinical trials of probiotic therapies. Finally, we outline future directions for probiotic research, including the identification and characterization of novel probiotic strains, the development of engineered probiotics, and the potential applications of probiotics in the prevention and treatment of mental health disorders. Overall, this review provides a comprehensive overview of the current state of the field of probiotics and highlights the potential for future advancements in probiotic therapies. **Keywords:** Eczema, Irritable Bowel Syndrome, Probiotics, probiotic strains

Cite This Article: Mishra S. Exploring the Efficacy of Probiotics: A Comprehensive Review of Current Evidence and Future Directions. EJMA 2023;3(4):153–159.

Drobiotics are microorganisms that can provide a range of health benefits when consumed. They are often referred to as "good bacteria" because they can help to balance the microbial ecosystem in the gut and support digestive health.^[1] Probiotics are found in a variety of foods and supplements, and their popularity has grown significantly in recent years due to the increasing interest in natural and holistic approaches to health and wellness. The human gut is home to trillions of microorganisms, including bacteria, viruses, and fungi.^[2] While some of these microorganisms are harmful and can cause disease, many of them are beneficial and play important roles in maintaining overall health. ^[3] Probiotics are one type of beneficial microorganism that can help to keep the gut microbiome in balance.[4] Probiotics can be found in a variety of foods, including yogurt, kefir, sauerkraut, kimchi, and other fermented foods.^[5-8] These foods are made by adding live cultures of beneficial bacteria to the ingredients and allowing them to ferment. ^[9] During the fermentation process, the bacteria consume the sugars and other nutrients in the food, producing lactic acid and other compounds that give the food its character-istic tangy flavor.^[10]

In addition to being found in fermented foods, probiotics are also available in supplement form. Probiotic supplements typically contain a combination of different strains of beneficial bacteria, such as Lactobacillus and Bifidobacterium, which are known to have specific health benefits. ^[11,12] There are many potential health benefits associated with probiotics. One of the most well-known benefits is their ability to support digestive health.^[13] Probiotics can help to improve the balance of bacteria in the gut, which can reduce symptoms of digestive issues such as bloating,

Address for correspondence: Shivam Mishra, MD. Department of Zoology, S S Khanna Girls' Degree College, Prayagraj, Uttarpradesh, India Phone: +9450055542 E-mail: svmbioinfo@gmail.com



Submitted Date: April 18, 2023 Revision Date: April 18, 2023 Accepted Date: July 19, 2023 Available Online Date: June 11, 2024

[©]Copyright 2023 by Eurasian Journal of Medical Advances - Available online at www.ejmad.org

OPEN ACCESS This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

constipation, and diarrhea.^[14] Probiotics have also been shown to support immune function. Because the majority of the body's immune system is located in the gut, having a healthy balance of gut bacteria is important for overall immune health.^[15] Studies have shown that probiotics can help to improve the body's immune response and reduce the risk of infections.^[16]

Other potential health benefits of probiotics include improved mental health, reduced inflammation, and better skin health.^[17] Research is ongoing to fully understand the many ways that probiotics can support overall health and wellness.^[18] While probiotics are generally considered safe, it's important to note that not all probiotics are created equal. Different strains of bacteria can have different effects on the body, and some may be more beneficial than others. Additionally, the quality of probiotic supplements can vary widely, and some products may not contain the amount or type of bacteria that they claim to.^[19] It's also important to note that while probiotics can be beneficial for many people, they may not be appropriate for everyone. People with compromised immune systems or other underlying health conditions should talk to their healthcare provider before taking probiotic supplements.^[20]

What Are Probiotics?

Probiotics are living microorganisms that confer health benefits on the host when ingested in adequate amounts. These beneficial bacteria are found in fermented foods, dietary supplements, and in some cases, in prescription drugs.^[21] They are primarily composed of strains of the Lactobacillus and Bifidobacterium genera, but other types of bacteria and yeasts can also function as probiotics.^[22] The health benefits of probiotics are largely attributed to their ability to maintain the balance of the gut microbiota, the complex community of microorganisms residing in the digestive tract.^[23] The gut microbiota plays a crucial role in many physiological processes, including digestion, immune function, and metabolism. When the microbiota is imbalanced, dysbiosis can occur, which is associated with a range of health problems such as inflammatory bowel disease, obesity, and allergies.^[24]

Probiotics work in several ways to restore and maintain gut microbiota balance. They can compete with harmful bacteria for nutrients and adhesion sites in the gut, produce antimicrobial substances that inhibit the growth of pathogens, and modulate the immune response to reduce inflammation.^[25] Probiotics can also help break down dietary fiber and other complex carbohydrates that are otherwise indigestible by the human digestive system, producing shortchain fatty acids that provide energy to the colon cells and promote their growth.^[26] The health benefits of probiotics are supported by a large body of scientific evidence. Studies have shown that probiotics can improve symptoms of irritable bowel syndrome, reduce the risk of antibiotic-associated diarrhea and Clostridioides difficile infection,^[27] and enhance the immune response to vaccines. Probiotics may also have a positive impact on mental health, as they have been shown to reduce anxiety and depression symptoms in some individuals.^[28]

Probiotics can be found in a variety of foods, however, the amount and type of probiotics in these foods can vary greatly, and some products may not contain enough probiotics to confer significant health benefits.^[29] To ensure a consistent and adequate intake of probiotics, dietary supplements are also available in various forms, such as capsules, powders, and gummies.^[30] These supplements can contain a single probiotic strain or a combination of strains, and the dosage and duration of use should be determined by a healthcare provider.^[31] While probiotics are generally considered safe, individuals with weakened immune systems or underlying health conditions should exercise caution when using probiotic supplements, as they may be at increased risk of infection.^[32] In rare cases, probiotic use has been associated with adverse effects such as gastrointestinal symptoms, infections, and allergic reactions.^[33] Therefore, it is important to consult with a healthcare provider before starting probiotic supplementation, especially if you have any underlying health conditions or are taking medications that could interact with probiotics.[34]

Potential Health Benefits of Probiotics

Probiotics are living microorganisms that can confer a wide range of health benefits to the host when ingested in adequate amounts (Table 1).

The primary function of probiotics is to restore and maintain the balance of the gut microbiota, which plays a crucial role in many physiological processes, including digestion, immune function, and metabolism.^[56]

Here are some potential health benefits of probiotics.

Improved Digestive Health

Probiotics can improve digestive health by reducing symptoms of digestive disorders such as irritable bowel syndrome, inflammatory bowel disease, and diarrhea. For example, a review several randomized controlled trials found that probiotics significantly reduced the severity and frequency of symptoms in people with irritable bowel syndrome.^[57] Similarly, a meta-analysis of 20 randomized controlled trials found that probiotics reduced the risk of antibiotic-associated diarrhea by 42%.^[58] Probiotics can also help break down dietary fiber and other complex

Table 1.			
Probiotic Strain	Health Condition	Potential Benefits	Refferences
Bifidobacterium bifidum	Irritable Bowel Syndrome	Reduced abdominal pain and bloating	[35]
Lactobacillus acidophilus	Antibiotic-Associated Diarrhea	Reduced risk of diarrhea	[36]
Lactobacillus rhamnosus GG	Eczema	Reduced risk of eczema in infants and young children	[37]
Saccharomyces boulardii	Clostridium difficile Infection	Reduced risk of infection	[38]
Bifidobacterium lactis BB-12	Immune System Function	Reduced incidence of respiratory tract infections in people with weakened immune systems	[39]
Streptococcus thermophilus	Inflammatory Bowel Disease	Reduced inflammation and improved gut health	[40]
Lactobacillus reuteri	Infant Colic	Reduced crying time in infants with colic	[41]
Escherichia coli Nissle 1917	Ulcerative Colitis	Improved remission rates in people with ulcerative colit	is ^[42]
Bifidobacterium longum	Anxiety and Depression	Reduced symptoms of anxiety and depression	[43]
Bifidobacterium bifidum	Irritable Bowel Syndrome	Reduced abdominal pain and bloating	[44]
Bifidobacterium animalis subsp. lactis	Immune System Function	Reduced incidence of respiratory tract infections in older adults	[45]
Lactobacillus acidophilus	Antibiotic-Associated Diarrhea	Reduced risk of diarrhea	[46]
Lactobacillus fermentum	Cardiovascular Health	Reduced cholesterol levels and blood pressure	[47]
Lactobacillus plantarum	Irritable Bowel Syndrome	Reduced symptoms of IBS and improved gut health	[48]
Lactobacillus helveticus	Stress and Anxiety	Reduced symptoms of stress and anxiety	[49]
Bacillus coagulans	Digestive Disorders	Improved symptoms of IBS and IBD	[50]
Lactococcus lactis	Immune System Function	Increased production of immune cells	[51]
Enterococcus faecium	Gut Health	Improved gut barrier function and reduced inflammatic	on ^[52]
Pediococcus acidilactici	Digestive Health	Improved symptoms of IBS and IBD	[53]
Propionibacterium freudenreichii	Gut Health	Improved gut barrier function and reduced inflammatic	on ^[54]
Streptococcus thermophilus TH-4	Digestive Disorders	Improved symptoms of lactose intolerance and digestive discomfort	[55]

This table includes a range of probiotic strains and their potential benefits based on studies and research.

carbohydrates that are otherwise indigestible by the human digestive system, producing short-chain fatty acids that provide energy to the colon cells and promote their growth. This can improve the overall health of the digestive tract and reduce the risk of colon cancer.^[59]

Enhanced Immune Function

Probiotics can enhance immune function by modulating the immune response and reducing inflammation. Studies have shown that probiotics can increase the production of natural killer cells, which are a type of white blood cell that plays a key role in immune defense against infections and cancer.^[60] Probiotics can also stimulate the production of antibodies, which are proteins that recognize and neutralize pathogens such as viruses and bacteria.^[61] Probiotics can also reduce the production of pro-inflammatory cytokines, which are signaling molecules that contribute to the development of inflammation.^[62] Chronic inflammation is associated with a wide range of health problems, including autoimmune diseases, cardiovascular disease, and cancer. By reducing inflammation, probiotics may help prevent and treat these conditions.^[63,64]

Improved Mental Health

Probiotics may improve mental health by reducing symptoms of anxiety and depression. The gut-brain axis is a bidirectional communication system that links the gut microbiota with the central nervous system.^[65] Probiotics can modulate this communication system by producing neurotransmitters such as serotonin and gamma-aminobutyric acid (GABA),^[66] which are involved in regulating mood and behavior. Several studies have shown that probiotics can reduce symptoms of anxiety and depression in both healthy individuals and those with clinical disorders. ^[67] For example, a randomized controlled trial found that a combination of *Lactobacillus helveticus* and *Bifidobacterium longum* reduced symptoms of depression and anxiety in individuals with major depression.^[68]

Lowered Cholesterol Levels

Probiotics may help lower cholesterol levels by breaking down bile in the gut. Bile is a substance produced by the liver that helps digest fats.^[69] When bile is broken down by probiotics, the liver needs to produce more bile acids, which in turn requires more cholesterol to be used as a precursor.^[70] This reduces the amount of cholesterol in the blood. Several studies have shown that probiotics can reduce total cholesterol levels by up to 11% and LDL (bad) cholesterol levels by up to 9%.^[71] These effects are modest, but they may be beneficial for people with high cholesterol levels or a high risk of cardiovascular disease.^[72]

Improved Skin Health

Probiotics may improve skin health by reducing inflammation and enhancing the skin's barrier function. Inflammation is a key contributor to many skin disorders,^[73,74] including acne,^[75] eczema,^[76] and psoriasis.^[77] Probiotics can reduce inflammation by modulating the immune response and promoting the growth of beneficial bacteria on the skin.^[78]

Probiotics can also enhance the skin's barrier function by increasing the production of ceramides, which are lipids that help keep the skin hydrated and prevent the entry of harmful substances.^[79]

Safety and Efficacy of Probiotics

Probiotics are generally considered safe for most people, although there are some potential risks associated with their use. For example, some people may experience digestive symptoms such as gas, bloating, and diarrhea when they first start taking probiotics. These symptoms are usually mild and temporary, and they usually subside within a few days to a week.^[80] In rare cases, probiotics can cause more serious health problems. For example, people with weakened immune systems, such as those with HIV/AIDS, may be at increased risk of developing infections when they take probiotics.^[81] Additionally, some strains of bacteria used in probiotics have been associated with infections in certain populations, such as premature infants and people with heart valve problems. Despite these potential risks, probiotics are generally considered safe for most people. However, it is important to note that the safety and efficacy of probiotics can vary depending on the specific strain and dose used, as well as individual factors such as age and health status.^[82]

Conclusion

In conclusion, probiotics have gained widespread popularity due to their potential health benefits, particularly for digestive disorders, allergies, and immune system function. However, the safety and efficacy of probiotics remain a topic of debate. While most studies report few adverse effects associated with the use of probiotics, rare cases of infections and other adverse effects have been reported, particularly in people with weakened immune systems or serious underlying medical conditions. Moreover, the efficacy of probiotics varies depending on the strain and dosage used. Therefore, it is important for healthcare providers to carefully evaluate the potential benefits and risks of probiotic use in individual patients. Further research is needed to determine the optimal strains, dosages, and duration of probiotic therapy for various health conditions. Overall, probiotics have the potential to be a valuable addition to traditional medical treatments, but their safety and efficacy must be carefully evaluated in each individual case.

Future Direction

While the future of probiotics is promising, there are still significant challenges that need to be addressed. One of the biggest challenges is the lack of regulation and standardization of probiotic products. This makes it difficult for consumers and healthcare professionals to determine which probiotics are safe and effective. Additionally, conducting high-quality clinical trials of probiotics is challenging due to the complexity of the microbiome and the individual variation in gut bacteria. Nevertheless, with continued research and development, probiotics have the potential to become a powerful therapeutic option for a range of health conditions.

Disclosures

Peer-review: Externally peer-reviewed. **Conflict of Interest:** None declared.

References

- Wallace, Chris, et al. "Probiotics for management of functional abdominal pain disorders in children." Cochrane Database of Systematic Reviews 2 (2023).
- Hajela N, Nair GB, Ganguly NK. Are probiotics a feasible intervention for prevention of diarrhoea in the developing world? Gut Pathog. 2010 Aug 29;2(1):10.
- Pickard JM, Zeng MY, Caruso R, Núñez G. Gut microbiota: Role in pathogen colonization, immune responses, and inflammatory disease. Immunol Rev. 2017 Sep;279(1):70-89.
- 4. Williams NT. Probiotics. Am J Health Syst Pharm. 2010 Mar 15;67(6):449-58. doi: 10.2146/ajhp090168. PMID: 20208051.
- 5. Kok CR, Hutkins R. Yogurt and other fermented foods as sources of health-promoting bacteria. Nutr Rev. 2018 Dec 1;76(Suppl 1):4-15.
- Azizi NF, Kumar MR, Yeap SK, Abdullah JO, Khalid M, Omar AR, Osman MA, Mortadza SAS, Alitheen NB. Kefir and Its Biological Activities. Foods. 2021 May 27;10(6):1210.
- Touret T, Oliveira M, Semedo-Lemsaddek T. Putative probiotic lactic acid bacteria isolated from sauerkraut fermentations. PLoS One. 2018 Sep 7;13(9):e0203501.
- 8. Park KY, Jeong JK, Lee YE, Daily JW 3rd. Health benefits of kimchi (Korean fermented vegetables) as a probiotic food. J Med

- Aslam H, Green J, Jacka FN, Collier F, Berk M, Pasco J, Dawson SL. Fermented foods, the gut and mental health: a mechanistic overview with implications for depression and anxiety. Nutr Neurosci. 2020 Sep;23(9):659-671.
- Dimidi E, Cox SR, Rossi M, Whelan K. Fermented Foods: Definitions and Characteristics, Impact on the Gut Microbiota and Effects on Gastrointestinal Health and Disease. Nutrients. 2019 Aug 5;11(8):1806.
- Karimi O, Pena AS. Probiotics: Isolated bacteria strain or mixtures of different strains? Two different approaches in the use of probiotics as therapeutics. Drugs Today (Barc). 2003 Aug;39(8):565-97.
- Luo J, Li Y, Xie J, Gao L, Liu L, Ou S, Chen L, Peng X. The primary biological network of Bifidobacterium in the gut. FEMS Microbiol Lett. 2018 Apr 1;365(8).
- Wu H, Chiou J. Potential Benefits of Probiotics and Prebiotics for Coronary Heart Disease and Stroke. Nutrients. 2021 Aug 21;13(8):2878.
- Rao SSC, Brenner DM. Efficacy and Safety of Over-the-Counter Therapies for Chronic Constipation: An Updated Systematic Review. Am J Gastroenterol. 2021 Jun 1;116(6):1156-1181.
- 15. de Vos WM, Tilg H, Van Hul M, Cani PD. Gut microbiome and health: mechanistic insights. Gut. 2022 May;71(5):1020-1032.
- Tanaka Y, Shimizu S, Shirotani M, Yorozu K, Kitamura K, Oehorumu M, Kawai Y, Fukuzawa Y. Nutrition and Cancer Risk from the Viewpoint of the Intestinal Microbiome. Nutrients. 2021 Sep 23;13(10):3326.
- 17. Matejuk A. Skin Immunity. Arch Immunol Ther Exp (Warsz). 2018 Feb;66(1):45-54.
- Suez J, Zmora N, Segal E, Elinav E. The pros, cons, and many unknowns of probiotics. Nat Med. 2019 May;25(5):716-729. doi: 10.1038/s41591-019-0439-x. Epub 2019 May 6. PMID: 31061539.
- 19. Lehtinen S, Blanquart F, Lipsitch M, Fraser C; with the Maela Pneumococcal Collaboration. On the evolutionary ecology of multidrug resistance in bacteria. PLoS Pathog. 2019 May 13;15(5):e1007763.
- Vallvé-Juanico J, Houshdaran S, Giudice LC. The endometrial immune environment of women with endometriosis. Hum Reprod Update. 2019 Sep 11;25(5):564-591.
- Parvez S, Malik KA, Ah Kang S, Kim HY. Probiotics and their fermented food products are beneficial for health. J Appl Microbiol. 2006 Jun;100(6):1171-85.
- 22. Vitellio P, Celano G, Bonfrate L, Gobbetti M, Portincasa P, De Angelis M. Effects of Bifidobacterium longum and Lactobacillus rhamnosus on Gut Microbiota in Patients with Lactose Intolerance and Persisting Functional Gastrointestinal Symptoms: A Randomised, Double-Blind, Cross-Over Study. Nutrients. 2019 Apr 19;11(4):886.
- 23. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button

JE, Wolfe BE, Ling AV, Devlin AS, Varma Y, Fischbach MA, Biddinger SB, Dutton RJ, Turnbaugh PJ. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014 Jan 23;505(7484):559-63.

- 24. Weiss GA, Hennet T. Mechanisms and consequences of intestinal dysbiosis. Cell Mol Life Sci. 2017 Aug;74(16):2959-2977.
- 25. Pellerito A, Ameen SM, Micali M, Caruso G. Antimicrobial Substances for Food Packaging Products: The Current Situation. J AOAC Int. 2018 Jul 1;101(4):942-947.
- 26. Sun M, Wu W, Liu Z, Cong Y. Microbiota metabolite short chain fatty acids, GPCR, and inflammatory bowel diseases. J Gastroenterol. 2017 Jan;52(1):1-8.
- 27. Abad CLR, Safdar N. A Review of Clostridioides difficile Infection and Antibiotic-Associated Diarrhea. Gastroenterol Clin North Am. 2021 Jun;50(2):323-340.
- 28. Firth J, Teasdale SB, Allott K, Siskind D, Marx W, Cotter J, Veronese N, Schuch F, Smith L, Solmi M, Carvalho AF, Vancampfort D, Berk M, Stubbs B, Sarris J. The efficacy and safety of nutrient supplements in the treatment of mental disorders: a meta-review of meta-analyses of randomized controlled trials. World Psychiatry. 2019 Oct;18(3):308-324.
- 29. Webb L. Probiotics for preventing recurrent bacterial vaginosis. JAAPA. 2021 Feb 1;34(2):19-22.
- Sivamaruthi BS, Suganthy N, Kesika P, Chaiyasut C. The Role of Microbiome, Dietary Supplements, and Probiotics in Autism Spectrum Disorder. Int J Environ Res Public Health. 2020 Apr 12;17(8):2647.
- Kobyliak N, Abenavoli L, Falalyeyeva T, Mykhalchyshyn G, Boccuto L, Kononenko L, Kyriienko D, Komisarenko I, Dynnyk O. Beneficial effects of probiotic combination with omega-3 fatty acids in NAFLD: a randomized clinical study. Minerva Med. 2018 Dec;109(6):418-428.
- 32. Kothari D, Patel S, Kim SK. Probiotic supplements might not be universally-effective and safe: A review. Biomed Pharmacother. 2019 Mar;111:537-547.
- 33. Martínez Vázquez SE, Nogueira de Rojas JR, Remes Troche JM, Coss Adame E, Rivas Ruíz R, Uscanga Domínguez LF. The importance of lactose intolerance in individuals with gastrointestinal symptoms. Rev Gastroenterol Mex (Engl Ed). 2020 Jul-Sep;85(3):321-331. English, Spanish.
- 34. Kim CS, Cha L, Sim M, Jung S, Chun WY, Baik HW, Shin DM. Probiotic Supplementation Improves Cognitive Function and Mood with Changes in Gut Microbiota in Community-Dwelling Older Adults: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial. J Gerontol A Biol Sci Med Sci. 2021 Jan 1;76(1):32-40.
- 35. Ku S, Park MS, Ji GE, You HJ. Review on Bifidobacterium bifidum BGN4: Functionality and Nutraceutical Applications as a Probiotic Microorganism. Int J Mol Sci. 2016 Sep 14;17(9):1544.
- 36. Cheng H, Ma Y, Liu X, Tian C, Zhong X, Zhao L. A Systematic Review and Meta-Analysis: Lactobacillus acidophilus for

Treating Acute Gastroenteritis in Children. Nutrients. 2022 Feb 6;14(3):682.

- Szajewska H, Hojsak I. Health benefits of Lactobacillus rhamnosus GG and Bifidobacterium animalis subspecies lactis BB-12 in children. Postgrad Med. 2020 Jun;132(5):441-451.
- 38. Bohbot JM, Zhioua F. Intérêt de Saccharomyces boulardii CNCM I-745 dans la prise en charge des infections vulvo-vaginales [The benefit of Saccharomyces boulardii CNCM I-745 in the management of vulvovaginal infections]. Gynecol Obstet Fertil Senol. 2021 Sep;49(9):716-723. French.
- 39. Merenstein DJ, Tan TP, Molokin A, Smith KH, Roberts RF, Shara NM, Mete M, Sanders ME, Solano-Aguilar G. Safety of Bifidobacterium animalis subsp. lactis (B. lactis) strain BB-12-supplemented yogurt in healthy adults on antibiotics: a phase I safety study. Gut Microbes. 2015;6(1):66-77.
- 40. Guandalini S. Probiotics for prevention and treatment of diarrhea. J Clin Gastroenterol. 2011 Nov;45 Suppl:S149-53.
- 41. Mu Q, Tavella VJ, Luo XM. Role of Lactobacillus reuteri in Human Health and Diseases. Front Microbiol. 2018 Apr 19;9:757.
- 42. de Vrese M, Schrezenmeir J. Probiotics, prebiotics, and synbiotics. Adv Biochem Eng Biotechnol. 2008;111:1-66.
- 43. Chichlowski M, Shah N, Wampler JL, Wu SS, Vanderhoof JA. Bifidobacterium longum Subspecies infantis (B. infantis) in Pediatric Nutrition: Current State of Knowledge. Nutrients. 2020 May 28;12(6):1581.
- 44. Skrzydło-Radomańska B, Prozorow-Król B, Cichoż-Lach H, Majsiak E, Bierła JB, Kosikowski W, Szczerbiński M, Gantzel J, Cukrowska B. The Effectiveness of Synbiotic Preparation Containing Lactobacillus and Bifidobacterium Probiotic Strains and Short Chain Fructooligosaccharides in Patients with Diarrhea Predominant Irritable Bowel Syndrome-A Randomized Double-Blind, Placebo-Controlled Study. Nutrients. 2020 Jul 5;12(7):1999.
- 45. Uusitupa HM, Rasinkangas P, Lehtinen MJ, Mäkelä SM, Airaksinen K, Anglenius H, Ouwehand AC, Maukonen J. Bifidobacterium animalis subsp. lactis 420 for Metabolic Health: Review of the Research. Nutrients. 2020 Mar 25;12(4):892.
- 46. Bungau SG, Behl T, Singh A, Sehgal A, Singh S, Chigurupati S, Vijayabalan S, Das S, Palanimuthu VR. Targeting Probiotics in Rheumatoid Arthritis. Nutrients. 2021 Sep 26;13(10):3376.
- 47. Han HS, Kim JG, Choi YH, Lee KM, Kwon TH, Kim SH. Effect of Lactobacillus Fermentum as a Probiotic Agent on Bone Health in Postmenopausal Women. J Bone Metab. 2022 Nov;29(4):225-233.
- 48. Huang WC, Lee MC, Lee CC, Ng KS, Hsu YJ, Tsai TY, Young SL, Lin JS, Huang CC. Effect of Lactobacillus plantarum TWK10 on Exercise Physiological Adaptation, Performance, and Body Composition in Healthy Humans. Nutrients. 2019 Nov 19;11(11):2836.
- 49. Taverniti V, Guglielmetti S. Health-Promoting Properties of Lactobacillus helveticus. Front Microbiol. 2012 Nov 19;3:392.

- 50. Jäger R, Purpura M, Farmer S, Cash HA, Keller D. Probiotic Bacillus coagulans GBI-30, 6086 Improves Protein Absorption and Utilization. Probiotics Antimicrob Proteins. 2018 Dec;10(4):611-615.
- 51. Lee DH, Park HK, Lee HR, Sohn H, Sim S, Park HJ, Shin YS, Kim YK, Choi Y, Park HS. Immunoregulatory effects of Lactococcus lactis-derived extracellular vesicles in allergic asthma. Clin Transl Allergy. 2022 Mar;12(3):e12138.
- 52. Reuben RC, Roy PC, Sarkar SL, Alam RU, Jahid IK. Isolation, characterization, and assessment of lactic acid bacteria toward their selection as poultry probiotics. BMC Microbiol. 2019 Nov 12;19(1):253.
- 53. Dyshlyuk LS, Milentyeva IS, Asyakina LK, Ostroumov LA, Osintsev AM, Pozdnyakova AV. Using bifidobacterium and propionibacterium strains in probiotic consortia to normalize the gastrointestinal tract. Braz J Biol. 2022 May 4;84:e256945.
- 54. Gaucher F, Bonnassie S, Rabah H, Leverrier P, Pottier S, Jardin J, Briard-Bion V, Marchand P, Jeantet R, Blanc P, Jan G. Benefits and drawbacks of osmotic adjustment in Propionibacterium freudenreichii. J Proteomics. 2019 Jul 30;204:103400.
- 55. Wang H, Brook CL, Whittaker AL, Lawrence A, Yazbeck R, Howarth GS. Effects of Streptococcus thermophilus TH-4 in a rat model of doxorubicin-induced mucositis. Scand J Gastroenterol. 2013 Aug;48(8):959-68.
- 56. Milani C, Duranti S, Bottacini F, Casey E, Turroni F, Mahony J, Belzer C, Delgado Palacio S, Arboleya Montes S, Mancabelli L, Lugli GA, Rodriguez JM, Bode L, de Vos W, Gueimonde M, Margolles A, van Sinderen D, Ventura M. The First Microbial Colonizers of the Human Gut: Composition, Activities, and Health Implications of the Infant Gut Microbiota. Microbiol Mol Biol Rev. 2017 Nov 8;81(4):e00036-17.
- 57. Seminario-Amez M, López-López J, Estrugo-Devesa A, Ayuso-Montero R, Jané-Salas E. Probiotics and oral health: A systematic review. Med Oral Patol Oral Cir Bucal. 2017 May 1;22(3):e282-e288.
- Su Guo Q, Goldenberg JZ, Humphrey C, El Dib R, Johnston BC. Probiotics for the prevention of pediatric antibioticassociated diarrhea. Cochrane Database Syst Rev. 2019 Apr 30;4(4):CD004827.
- 59. Blaak EE, Canfora EE, Theis S, Frost G, Groen AK, Mithieux G, Nauta A, Scott K, Stahl B, van Harsselaar J, van Tol R, Vaughan EE, Verbeke K. Short chain fatty acids in human gut and metabolic health. Benef Microbes. 2020 Sep 1;11(5):411-455.
- 60. Kim JH, Kim DH, Jo S, Cho MJ, Cho YR, Lee YJ, Byun S. Immunomodulatory functional foods and their molecular mechanisms. Exp Mol Med. 2022 Jan;54(1):1-11.
- 61. Moradi-Kalbolandi S, Majidzadeh-A K, Abdolvahab MH, Jalili N, Farahmand L. The Role of Mucosal Immunity and Recombinant Probiotics in SARS-CoV2 Vaccine Development. Probiotics Antimicrob Proteins. 2021 Oct;13(5):1239-1253.
- 62. Sun S, Xu X, Liang L, Wang X, Bai X, Zhu L, He Q, Liang H, Xin

X, Wang L, Lou C, Cao X, Chen X, Li B, Wang B, Zhao J. Lactic Acid-Producing Probiotic Saccharomyces cerevisiae Attenuates Ulcerative Colitis via Suppressing Macrophage Pyroptosis and Modulating Gut Microbiota. Front Immunol. 2021 Nov 24;12:777665.

- Haase S, Haghikia A, Wilck N, Müller DN, Linker RA. Impacts of microbiome metabolites on immune regulation and autoimmunity. Immunology. 2018 Jun;154(2):230-238.
- Makrgeorgou A, Leonardi-Bee J, Bath-Hextall FJ, Murrell DF, Tang ML, Roberts A, Boyle RJ. Probiotics for treating eczema. Cochrane Database Syst Rev. 2018 Nov 21;11(11):CD006135.
- 65. Ansari F, Pourjafar H, Tabrizi A, Homayouni A. The Effects of Probiotics and Prebiotics on Mental Disorders: A Review on Depression, Anxiety, Alzheimer, and Autism Spectrum Disorders. Curr Pharm Biotechnol. 2020;21(7):555-565.
- 66. Chen G, Chen ZM, Fan XY, Jin YL, Li X, Wu SR, Ge WW, Lv CH, Wang YK, Chen JG. Gut-Brain-Skin Axis in Psoriasis: A Review. Dermatol Ther (Heidelb). 2021 Feb;11(1):25-38.
- Taylor AM, Holscher HD. A review of dietary and microbial connections to depression, anxiety, and stress. Nutr Neurosci. 2020 Mar;23(3):237-250.
- 68. Messaoudi M, Lalonde R, Violle N, Javelot H, Desor D, Nejdi A, Bisson JF, Rougeot C, Pichelin M, Cazaubiel M, Cazaubiel JM. Assessment of psychotropic-like properties of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in rats and human subjects. Br J Nutr. 2011 Mar;105(5):755-64.
- 69. Jia B, Zou Y, Han X, Bae JW, Jeon CO. Gut microbiome-mediated mechanisms for reducing cholesterol levels: implications for ameliorating cardiovascular disease. Trends Microbiol. 2023 Jan;31(1):76-91.
- Wong JM, de Souza R, Kendall CW, Emam A, Jenkins DJ. Colonic health: fermentation and short chain fatty acids. J Clin Gastroenterol. 2006 Mar;40(3):235-43.
- 71. Oak SJ, Jha R. The effects of probiotics in lactose intolerance: A systematic review. Crit Rev Food Sci Nutr. 2019;59(11):1675-1683.
- 72. Román GC, Jackson RE, Gadhia R, Román AN, Reis J. Mediterranean diet: The role of long-chain ω -3 fatty acids in fish; poly-

phenols in fruits, vegetables, cereals, coffee, tea, cacao and wine; probiotics and vitamins in prevention of stroke, age-related cognitive decline, and Alzheimer disease. Rev Neurol (Paris). 2019 Dec;175(10):724-741.

- 73. Fang Z, Li L, Zhang H, Zhao J, Lu W, Chen W. Gut Microbiota, Probiotics, and Their Interactions in Prevention and Treatment of Atopic Dermatitis: A Review. Front Immunol. 2021 Jul 14;12:720393.
- 74. Kim SH, Seong GS, Choung SY. Fermented Morinda citrifolia (Noni) Alleviates DNCB-Induced Atopic Dermatitis in NC/Nga Mice through Modulating Immune Balance and Skin Barrier Function. Nutrients. 2020 Jan 18;12(1):249.
- 75. Goodarzi A, Mozafarpoor S, Bodaghabadi M, Mohamadi M. The potential of probiotics for treating acne vulgaris: A review of literature on acne and microbiota. Dermatol Ther. 2020 May;33(3):e13279.
- 76. Sun S, Chang G, Zhang L. The prevention effect of probiotics against eczema in children: an update systematic review and meta-analysis. J Dermatolog Treat. 2022 Jun;33(4):1844-1854.
- 77. Yu Y, Dunaway S, Champer J, Kim J, Alikhan A. Changing our microbiome: probiotics in dermatology. Br J Dermatol. 2020 Jan;182(1):39-46.
- 78. Mottin VHM, Suyenaga ES. An approach on the potential use of probiotics in the treatment of skin conditions: acne and atopic dermatitis. Int J Dermatol. 2018 Dec;57(12):1425-1432.
- 79. Lu D, Wang L, Wang L, An L, Huo M, Xu H, Shi J. Probiotic Engineering and Targeted Sonoimmuno-Therapy Augmented by STING Agonist. Adv Sci (Weinh). 2022 Aug;9(22):e2201711.
- Shen NT, Maw A, Tmanova LL, Pino A, Ancy K, Crawford CV, Simon MS, Evans AT. Timely Use of Probiotics in Hospitalized Adults Prevents Clostridium difficile Infection: A Systematic Review With Meta-Regression Analysis. Gastroenterology. 2017 Jun;152(8):1889-1900.e9.
- 81. Miller H, Ferris R, Phelps BR. The effect of probiotics on CD4 counts among people living with HIV: a systematic review. Benef Microbes. 2016 Jun;7(3):345-51.
- Gupta V, Garg R. Probiotics. Indian J Med Microbiol. 2009 Jul-Sep;27(3):202-9.