Chapter 04

The Potential use of Probiotics as Medicine

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ABSTRACT

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit to the host. Currently, seven different bacterial genera are used as probiotics. The extensive investigation of probiotic microbes is mostly because of their promising health benefits. They have a broad spectrum of health benefits that range from gut restoration to disease treatment and from the eradication of pathogens to increasing the shelf life of food. The production of antimicrobial substances like bacteriocins can also enhance their usage potential. Probiotics are used in medical practices, clinical settings, agriculture, aquaculture, disease treatment, enhancing host functionality, improving mental health, the food industry, healthcare industries, and beautification. Due to the overwhelming effects, the medicinal aspects of probiotics are also explored, and surprisingly, they were found to be astounding. Strains from different sources, both in single and multiple forms, with different formulations and a vast route of administration, are used for the treatment of digestive, respiratory, and other diseases. Unlike medicine, there are no strict criteria, but different guidelines are proposed that must be followed while administering probiotic products. The most commonly used probiotics for medicinal purposes are from *Lactobacillus*, while strains from other sources are also used. Some often, i.e., blotting, mild gas production, and headaches, and others, like sepsis and infections, are the rare, documented shortcomings in the medicinal potential of probiotics. The medicinal potential of probiotics can be advanced by using state-of-the-art technologies that focus on accurate strain identification, deep genomic analysis, and the design of new probiotic strains with the desired properties. The application of artificial intelligence can also help in their advancement. This chapter will explain the potential of probiotics as medicine, shed light on their therapeutic potential, the advantages and disadvantages of using probiotics as therapeutic agents, and explain the guidelines that help consumers while taking probiotics as medicine. Moreover, the Islamic perspective of probiotics as medicine is also elucidated.

KEYWORDS
Bacterial therapy, Disease, *Lactobacillus,* Medicine

Received: 27-Jun-2024
Revised: 12-Jul-2024
Accepted: 19-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Hussain A, Al-Arifa N, Qureshi SR, Parveen S, Um-E-Habiba-U-Nisa and Ali SA, 2024. The potential use of probiotics as medicine. In: Liu P (ed), Gut Heath, Microbiota and Animal Diseases. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 30-43. https://doi.org/10.47278/book.CAM/2024.058

INTRODUCTION

The overwhelming and potential spectrum of probiotics confirms a stronghold in almost all aspects of life and the scientific field. The field is growing exponentially, and currently, thousands of scientific publications are dedicated to exploring new areas and potential applications. For instance, in the first decade of the 21st century, over 5000 publications were dedicated to their medical aspects (Rijkers et al., 2011; Verna and Lucak, 2010). It is anticipated that the commercial market for probiotics will touch 77 billion USD in 2025, indicating their huge application in a vast area, including pharmaceuticals (Baral et al., 2021). The concept, which was developed a century ago, now has roots in biotechnology, medicine, pharmaceuticals, and industries. Different potential applications have been identified and are still ongoing. Nobel laureate Elie Metchnikoff in 1907 proposed the idea of enhancing lifespan by changing gut-healthy bacteria. He proposed that if the gut microbiota is changed with healthy bacteria (now called probiotics), it will help to increase the life of an individual. The idea became more prompting when, in the 1950s, it was described by Vergin that these are active substances that help in healthy development. In 1965, Lilly and Stillwell coined the term probiotics and described them as an immune-modulatory substance that has the potential to alter host immunity and enhance intestinal functions (Hussain, 2023a; Butel, 2014). In the 21st century, the World Health Organization in 2002, and the International Scientific Association for Probiotics and Prebiotics (ISAPP) in 2013 defined probiotics as "live microorganisms that, when administered in adequate amounts, confer a benefit to the host" (Hussain et al., 2023; Maftei et al., 2024; Hill et al., 2014; Nueno-Palop and Narbad, 2011; Damodharan et al., 2020). Thus, new, and emerging applications are identified in many areas and have become one of the most researched topics.

The human and other animal intestine is a complex and dynamic population of 1000 species, constituting approximately 10^{14} microorganisms (Piqué et al., 2019; George Kerry et al., 2018; Heshmati, 2021; Sharma et al., 2013). The bulk of these bacteria in the human body are thought to reside in the gastrointestinal tract (GIT), with an estimated ten times more bacteria than body cells (Fijan, 2014). Normally, there is an eubiosis status of all gut microbiota (the presence of all types of microorganisms in the gut), which can lead to dysbiosis once the balance is changed. Different systems, i.e., quorum sensing, are involved in inter- and intra-bacterial communication, which is facilitated by small peptides called auto-inducers (Khoso et al., 2024). Likewise, the gut microbiota can also affect the physiology, endocrinology, and psychological aspects of the individual, and thus, any dysbiosis in the gut microbes can lead to vast detrimental effects. Collectively, all these microbes create micro-ecological niches in the gut. Similarly, probiotics are also considering the common residents of the gut with potential positive attributes. The word probiotics has its roots in Greek, which means "for life" (Maftei et al., 2024; George Kerry et al., 2018).

The potential positive attributes of probiotics give them unique properties, including strain safety, safe origin, production of antimicrobial substances, etc., and hence limit the number of probiotic microorganisms. Currently, seven genera are proposed to have probiotic strains dominated by the lactic acid bacteria (*Lactobacillus*, *Bifidobacterium*, and *Enterococcus*), followed by some yeast species (Hussain et al., 2023; Maftei et al., 2024). This strain constraint in probiotics is due to its strain-dependent nature and selection criteria. The strain-dependent phenomena explains that we cannot generalize a statement about a genus, and even the presence of one or two virulence traits (negative characters) did not exclude the species from probiotic selections. There are selection criteria that must be followed to propose or claim a strain for its probiotic potential. These criteria comprise non-pathogenic nature, no antibiotic and virulence characteristics, capacity of bacteriocin production, killing of pathogens, immunomodulatory potential, tolerance properties, aggregation formation capacity, long shelf life, short generation time, and viability and survivability during and after processes. Some criteria are proposed for their specific applications (Piqué et al., 2019; Hussain, 2023a).

The clear mechanism of action is not completely understood, but the proposed mechanisms are largely dependent on their viability and effectiveness in the host. Their effectiveness can be affected by the secretion of metabolites and proteins, the expression of surface molecules, and their direct interaction with the host cells, similarly, their survivability is related to their potential to endure harsh gut conditions and their adherence potential to mucosal surfaces (Hussain, 2023a).

Probiotics covered a wide range of health benefits in animals and humans through direct and indirect usage. Particularly, their treatment potential for different diseases has increased very rapidly and is still ongoing, though there is no pure dose-dependent profile like drugs (Tachibana et al., 2020; Naseem et al., 2023). Their health benefits include strengthening of the immune system; improvement in intestinal function (Hill et al., 2014); reduction in allergic reactions (Pandey et al., 2015; Araújo and Ferreira, 2013); and metabolic illnesses; alteration in pain perceptions; and advancement in food consumption (Pandey et al., 2015). Diseases caused by T-cell imbalance (asthma, rhinitis, dermatitis, eczema, etc.) are also treated with probiotics (Fijan, 2014; Benyacoub et al., 2003; Piqué et al., 2019; Islam, 2016; Hussain, 2023b).

However, the development of probiotics, particularly their commercialization, is not an easy task but rather a dangerous, expensive, and complex process in terms of their selection, processing, safety assessment, and authorization. Commercially, probiotics come in many forms, including powder, gel, capsules, tablets, granules, etc., and all have the exact information of their respective genus, species, strains, shelf life, number of colonies per ml, storage conditions, serving size, and associated health claims and consumer information (Sharma et al., 2013; Sanders et al., 2019; Pandey et al., 2015; Anadón et al., 2006). The production of different probiotic metabolites, including short-chain fatty acids, nitrous oxide, hydrogen peroxide, etc., is also used in different applications.

Besides the well-established, validated, and authentic applications, there are still some areas in which ambiguities are found. The scarce area is due to no or fewer clinical trials, small, tested populations, limited efficacy, poor genomic analysis, and post-experiment operational analysis. There is also a controversial debate about whether a probiotic strain can be used as medicine, although there are examples indicating the medicinal properties and therapeutic potential of probiotics. The regulatory authorities have strict guidelines that must be followed by probiotic strains that are proposed to be used as medicine. To the best of our knowledge, the available data on this aspect is not sufficient and well documented. Hence, keeping in mind the literature gap, this article aims to provide recent, updated, and conclusive literature about the medicinal properties, potential, and recommendations of probiotics. We also enlist some basic guidelines and proposed properties that are followed during this probiotic potential.

The Health Profile of Probiotics

Probiotics have an excellent health profile, indicating their intrinsic potential to treat or reduce disease prevalence. These huge benefits are due to their intrinsic potential, and recently, some have been developed due to their genome editing capabilities. The benefits of probiotics are equally applicable to humans and other animals, besides their biotechnological and industrial aspects (Hussain, 2023b). The beneficial spectrum of probiotics imparts some widespread applications, some with frequent benefits, and others are specific, as summarized in Fig 1. Additional benefits include regulation, stimulation, and modulation of immunity; improving intestinal barrier function (Hill et al., 2014); helping in the treatment of necrotizing enterocolitis (George Kerry et al., 2018; Nueno-Palop and Narbad, 2011); being used in the treatment of enteric infection (Shanahan, 2003; Damodharan et al., 2020); and increasing cell survivability by preventing apoptosis (O'Hara and Shanahan, 2007). The metabolites produced by probiotics, commonly called postbiotics, also have potential health effects. For instance, the production of hydrogen peroxide (H_2O_2), organic acids, and short-chain fatty acids (SCFAs) enables them to survive in the gut and is greatly involved in psychological disorders (Hussain et al., 2023). Probiotics also have the potential to restore gut dysbiosis and help in the treatment of nonalcoholic fatty liver disease (NAFLD) (Heshmati, 2021; Plaz-Diaz et al., 2019). Probiotics are also used as an alternative to antibiotics; this area was recently summarized (Rabetafika et al., 2023).

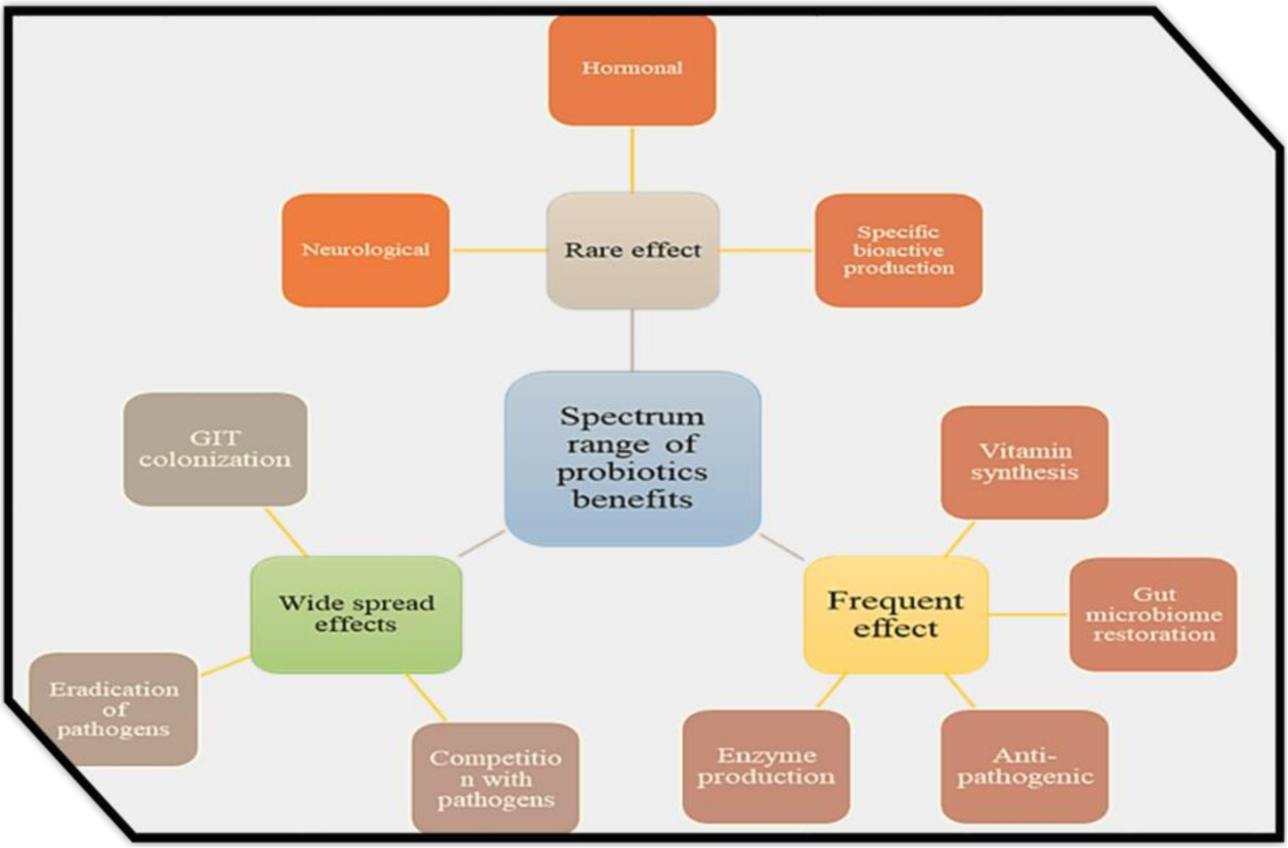

Fig. 1: The different potentials of probiotics in their health profiles—gut restoration and antimicrobial—are the exceptional benefits of probiotics (Hussain ~~A~~. 2023b)

The concept of the gut-brain axis revolutionized the potential use of gut microbiota, particularly probiotics, in the field of psychological disorders. It's now well established that probiotics can greatly affect brain and mental function, helping in the treatment of neurodegenerative disorders. The term psychobiotics (coined in 2013) is dedicated to potentially describing those probiotics that have a role in cognition. Other physiological properties, like sleep, mood, personality, etc., are greatly influenced by probiotics (Fuochi and Furneri, 2023). A pretty well-known body of literature is available describing the association, role, mechanisms, and pathways that are involved in the gut-brain axis. This potential confirmed the probiotic role in clinical settings and medicine (Hussain, 2023a; Hussain, and Ali, 2024a).

Aging, which is considered the natural and progressive loss of physical and physiological aspects of body cells, is creating a new horizon in the area of probiotics research. The advancement in geroscience entails the process of reducing cell age and enhancing life span. The concept of gerobiotics (probiotics with anti-aging potential) attracts researchers to determine the exact role and mechanisms of how probiotics help in this regard. Although this area is of limited research, different strains have been identified that show promising anti-aging properties in animal models ~~(Abrar and Arisha, 2023~~). Some of the currently available probiotics products include Florastor (*Saccharomyces boulardii)*, Florajen, RisaQuad, Bacid (LAC), Risa-Bid, Novaflor, Dofus, Flora-Q, (*L. acidophilus*) Intestinex (*L. acidophilus),* Florajen3, Zelac, Prodigen, Provella (*Bifidobacterium* and *Lactobacillus*), Floranex (*L. acidophilus* and *bulgaricus*), etc. (Drug.com). The currently used probiotics in human applications are summarized in Table 1.

Table 1: The currently used probiotic strains in humans for medicinal purposes (B; *Bifidobacterium*, L; *Lactobacillus*, S; *Streptococcus*, E; *Enterococcus*, AAD; antibiotic associated diarrhea (AAD), IBS; Irritable bowel syndrome)

Probiotics	Description	References
*E. faecium SF68 (*NCIMB 10415*)*	It is used in the treatment of enteritis and diarrhea, to prevent cell death, and to enhance immune responses.	(Holzapfel et al., 2018; Fu et al., 2022; Lodemann et al., 2015).
E. faecalis (Symbioflor 1)	Regulate immune diseases like chronic sinusitis or bronchitis.	(Cebrián et al., 2012)
E. faecium EK 13	It causes a reduction in fecal *E. coli* counts.	(Franz et al., 2011; Suvorov et al., 2019).
L. rhamnosus GG	It affects IBS.	(Chapman et al., 2011)
E. faecium L3	It shows antimicrobial, antiviral, anti-pathogenic, and anti-fungal activities.	(Aziz et al., 2019)
B. breve M-16-V	It suppresses the pro-inflammatory cytokine production.	(Piqué et al., 2019)
E. faecium CRL 183	It helps with colon tumors and enhances IL-4, IFN-γ, and TNF-α.	(Hanchi et al., 2021)
L. johnsonii	It inhibits the growth of H. pylori.	(Piqué et al., 2019)
*E. faecium (*PR88*)*	Relief symptoms in IBS	(Ferreira et al., 2013)
S. thermophilus CRL1190	It enhanced protection against H. pylori.	(Piqué et al., 2019)
L. reuteri 17938	It is widely studied for the treatment of colic in infants.	(Sanders et al., 2018)
VSL#3 (multi-strain probiotic)	It is used in the treatment of IBS and the prevention of endotoxin passage.	(Chapman et al., 2011; Piqué et al., 2019; Weichselbaum, 2009).
B. breve C50 and *S. thermophilus* 065	Reduce atopy in children	(Piqué et al., 2019)
L. reuteri, L. rhamnosus, and *P. freudenreichii*	This combination was found to enhance IBS symptoms and reduce mucin degradation.	(Chapman et al., 2011)
*B. bifidum (*MG731), *L. reuteri (*MG5346), and *L. rhamnosus (*MG5200)	The mixture significantly induces apoptosis in human gastric cancer	(Fuochi and Furneri, 2023)
L. rhamnosus 19070-2 and *L. reuteri* DSM 122460	It was found to improve the symptoms of atopic dermatitis (AD).	(Chapman et al., 2011)
B. lactis and *L. rhamnosus GG*	These can reduce the severity of eczema.	(Kechagia et al., 2013)
E. coli Nissle 1917	It can relapse in Crohn's disease patients.	(Santosa et al., 2006)
L. fermentum CECT5716	It can decrease the incidence of GIT and respiratory infections in infants.	(Butel, 2014)
L. reuteri and *B. breve*	It regulates the intestinal microbiota and improves the metabolism of tryptophan. Also used in the treatment of diarrhea.	(Fuochi and Furneri, 2023; Piqué et al., 2019).
Saccharomyces cerevisiae	Help in the regulation of antibiotic-associated pseudomembranous colitis	(Piqué et al., 2019)
L. acidophilus HA122	It is commercialized for the treatment of infantile colic.	(Piqué et al., 2019)
S. thermophilus	Help in the production of IgA	(Piqué et al., 2019; Maftei et al., 2024)
Saccharomyces boulardii	Have the potential to treat AAD	(Santosa et al., 2006)
L. paracasei subsp. paracasei CNCM I-1518	It has preventive effects on upper respiratory tract infections.	(Maftei et al., 2024)

Safety and Guidelines for Human Consumption of Probiotics

The safety of probiotics in animals' usage can be determined at different levels. Probiotics are widely used in husbandry science and pet foods, while their administration in humans is limited. (Sanders et al., 2018). The quality, amount, storage, reliability, accuracy, and proper labeling of probiotic products for animal use must be clearly stated. To ensure the safe use of probiotics in animals, certain autonomous regulatory bodies provide an unbiased opinion on probiotic products Likewise, before a probiotic product is commercialized, its excellent safety profile must be maintained and properly stated to the target consumers (Sanders et al., 2018). Data suggests that before taking a probiotic product, it is important to study its mode of action, preventive or treatment properties, and clinical trials (Maftei et al., 2024). These properties can be studied from the available literature, consumers' information, the country's guidelines, etc., for probiotic products. For instance, the American Gastroenterological Association (AGA) documented the use of probiotic products for the treatment of gastrointestinal disorders (Maftei et al., 2024). According to the literature, the widely available data about probiotic's potentials are based on skepticism. Earlier, Reid (2005) analyzed 25 probiotic products and reported that less than 1% of the claimed viability is present instead of the billions of bacteria mentioned (Reid, 2005). Thus, it is suggested that many probiotic products have been mislabeled and don't have the labeled cfu/mL in the products (Reid, 2005). The use of probiotics in humans has some criteria and guidelines proposed for safe usage and precautions that are followed. These guidelines and precautions are represented in Fig. 2. (data collected from (Sanders et al., 2018; Tegegne and Kebede, 2022; Rijkers et al., 2011; Maftei et al., 2024; Reid et al., 2003; Gupta and Garg, 2009; Quijano, 2011)).

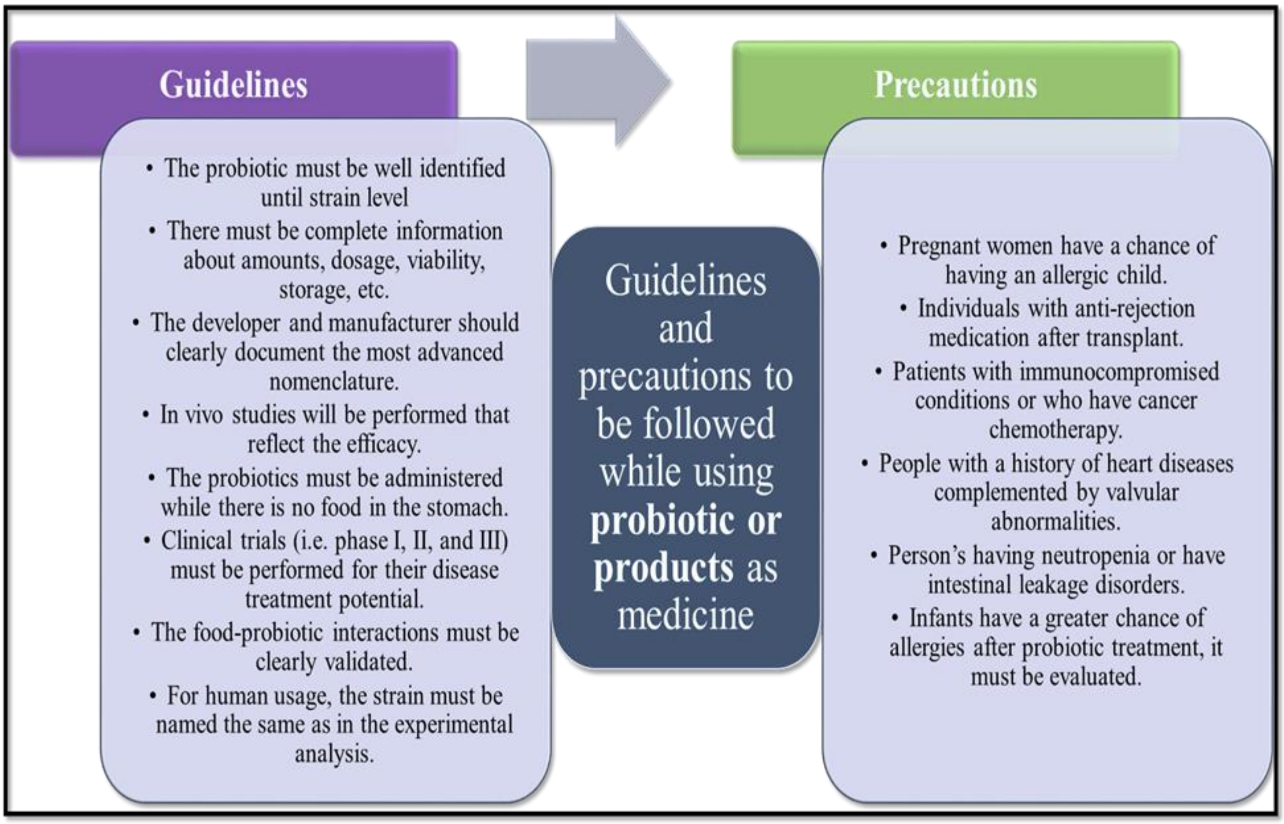

Fig. 2: The schematic illustration shows the guidelines and precautionary measurements while taking probiotics or their products for animal and human usage, particularly as medicine.

Routes of Administration of Probiotics in Humans

Probiotics are developed in different forms, each with their pros and cons. These forms include capsules, sprays, granules, powders, etc. The administration of probiotics in humans depends on the type of formulation, purpose of usage, and strains of probiotics. Probiotics may be administered via mouth, vagina, injection, or in spray form, depending on the objectives. The route of intake of probiotics also has its advantages and disadvantages (Verna and Lucak, 2010). Recently, Baral et al. (2021) summarized the formulation, dosage, and route of administration of probiotics (Baral et al., 2021).

Oral administration of probiotics is considered an easy and potential route of intake as different formulations are taken via mouth. More versatile probiotic species are taken via rectal therapy, but they fail if the probiotics don't have strong pH resistance (Mombelli and Gismondo, 2000). Vaginal intake of probiotics is good for lactobacilli repopulation and is used during bacterial vaginosis (Mombelli and Gismondo, 2000). Besides the routes of intake and form of probiotics, how they will be taken is also important. Food additives and the yogurt vs. milk delivery system have their properties (Verna and Lucak, 2010). Besides the administration, probiotic therapy also has the advantages of low cost and fewer negative reactions (Sarkar, 2013). A new combinatorial approach of probiotics with other substances (for instance, plant oils) is used to achieve maximum benefits (Hussain, 2023c). The medicinal aspects of probiotics, their pros and cons, challenges, advancements, future perspectives, etc. are summarized in Fig 3.

Medicinal Applications of Probiotics and their Safety Concerns

The health profile of probiotics is vast and has proven usage in animals and humans. Nasreen et al. (2024) documented that 76% of physicians are confident that probiotics could help in patient management (Nasreen et al., 2024). Their potential in these subjects enhanced the value of probiotics, particularly their medicinal aspects. As described, commercialization of probiotic strains is not an easy task, and it has become more tedious and requires more investigation when it is used in animal settings. The use of probiotics in humans even required more clarification, investigations, experimental validations, animal studies, and clinical trials (Sanders et al., 2018). However, the application of probiotics in humans is much less than that which is claimed and submitted for approval. These regulations become more severe when the selected strains are from doubtful sources; for instance, the genus *Enterococcus* has a doubtful nature but is still used as a probiotic and hence requires more careful evaluation when used in humans (Hussain et al., 2023; Butel, 2014). The bacterial therapy or probiotic medicinal domains are illustrated in Fig 4.

The dependency on probiotics for medicinal value also depends on the age and gender of an individual and also on the probiotic's formula, amounts, forms, and duration (Sarkar, 2013; Santosa et al., 2006). Recently, Poindexter et al. (2021) documented the role of probiotics in preterm infants and concluded that a good number of clinical trials were dedicated to this aspect (Poindexter et al., 2021). Different studies were conducted which show that single and multiple-strain probiotic combinations have a role in the treatment of necrotizing enterocolitis (NEC) in preterm infants (Poindexter et al., 2021). Likewise, it is more important to carefully select a probiotic for elderly people, as they have weak immunity and multiple disease statuses (Baker et al., 2009). *Lactobacillus rhamnosus* GG (LGG) and *B. lactis* BB-12 are the most studied probiotics for disease prevention, and *L. reuteri* SD2222 is the most investigated probiotic for disease treatment (Gupta and Garg, 2009; Reid et al., 2003). The different human diseases that are treated with single or multiple probiotics are compiled in Table 2.

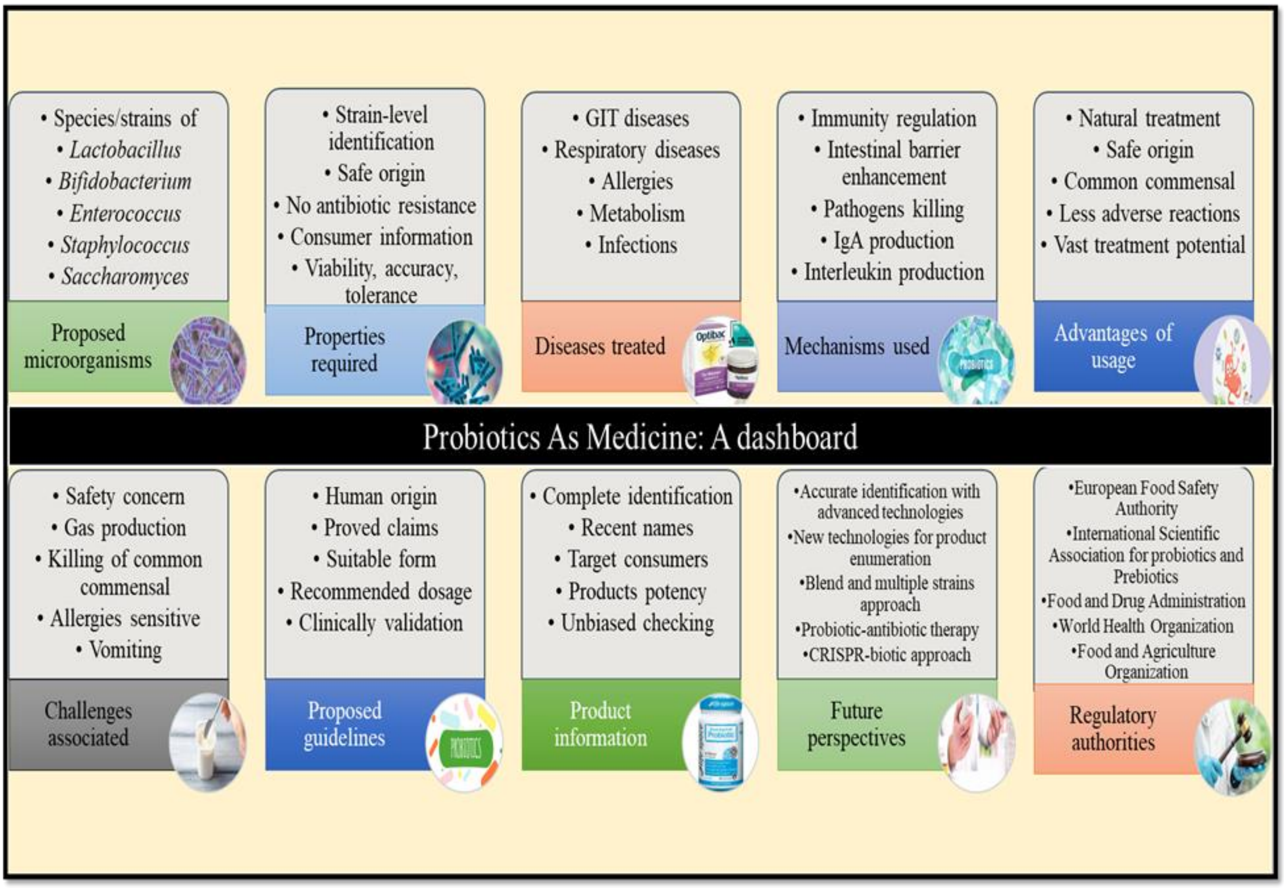

Fig. 3: A dashboard exploring the medicinal aspects of probiotics, reflecting the potential usage of probiotics as medicine and their allies.

The Harmful Nature of Probiotics in Human Usage

Probiotics, although having a broad spectrum of health benefits, also have negative aspects. The harmful nature of probiotics may be due to the strain's intrinsic properties, the potential of acquired traits, or whether they are developed after usage. Blotting, mild gas production, vomiting, headaches, etc. are the well-known negative consequences of probiotics (Islam, 2016; Maftei et al., 2024). Allergy to probiotic usage is also one of the key harmful aspects. The production of postbiotics with toxic effects in animals can enhance their harmful aspects. For instance, postbiotic D-lactate in children with short bowel syndrome may create an acidosis condition that leads to hyperventilation or encephalopathy (Butel, 2014). Some probiotics produce thirst in the body when taken for the first time. Some probiotics have less capacity to colonize in the host, thus creating problems. Likewise, poor viability during storage, single and multiple strain effects, and some strain's intrinsic drawbacks makes them of less use in humans (Sarkar, 2013).

Different studies were conducted to evaluate the various aspects of probiotics in animals and humans. It is also known that not only the probiotic microbes but also their products (metabolites/ postbiotics) have disease treatment potential and have good health benefits (Fuochi and Furneri, 2023; Piqué et al., 2019). The safety concerns with probiotics in animal and human usage are timely compiled by the European Food Safety Authority (EFSA) (Piqué et al., 2019). It was also established that single strains and multiple strains have different effects on the health profile (Poindexter et al., 2021). Chapman et al. (2011) documented the health benefits of probiotics in terms of single and multiple-strain approaches, both in animals and humans (Chapman et al., 2011).

The acquisition of foreign genetic materials creates a great risk of probiotic usage in humans. For example, the transfer of antibiotic resistance genes from the host to the probiotic strains and then to the common commensal of gut produce creates antibiotic resistance, and thus, the potential of antibiotics vanishes (Butel, 2014). Sepsis, endocarditis, liver abscess, etc. are the rare side effects of probiotics (Islam, 2016; Snydman, 2008).

Table 2: The different types of human diseases that are prevented or treated with probiotics (L; *Lactobacillus*, B; *Bifidobacterium*)

Diseases	Probiotics	References
Gastrointestinal tract		
Inflammatory bowel disease (IBD)	*S. boulardii* and *L. rhamnosus GG*	(Weichselbaum, 2009; Santosa et al., 2006; Maftei et al., 2024).
Irritable bowel syndrome (IBS)	*L. plantarum* 299v, *L. plantarum,* and *B. breve*	(Santosa et al., 2006; Islam, 2016).
Ulcerative colitis (UC)	*Escherichia coli Nissle (EcN)*, VSL#3	(Weichselbaum, 2009; Sanders et al., 2018; Islam, 2016).
Crohn's disease (CD)	L. *rhamnosus GG (LGG), B. breve, B. longum,* and *L. casei*	(Weichselbaum, 2009; Santosa et al., 2006; George Kerry et al., 2018; Verna and Lucak, 2010).
Pouchitis	*L. paracasei subsp. paracasei, L. plantarum, L. acidophilus, L. delbrueckii. bulgaricus, B. longum, B. breve,, and S. salivarius*	(Maftei et al., 2024; Verna and Lucak, 2010).
Constipation	*L. casei Shirota (LcS)*	(Weichselbaum, 2009).
Infantile colic	*L. reuteri* 17938	(Sanders et al., 2018).
Necrotizing enterocolitis (NEC)	*B. breve* BBG-001*, L. acidophilus, B. infantis*	(Sanders et al., 2018; Poindexter et al., 2021; Gupta and Garg, 2009).
Gastroenteritis	*L. rhamnosus GG, L. rhamnosus* GR-1, and *L. fermentum* RC-14	(Brown and Valiere, 2004; Reid et al., 2003).
Antibiotic-associated diarrhea (AAD)	*L. casei* DN-114 001*, L. bulgaricus, S. thermophilus, L. acidophilus, L. rhamnosus, L. reuteri, L. bulgaricus, L. rhamnosus GG,* and *S. boulardii*	(Weichselbaum, 2009; Santosa et al., 2006; Sanders et al., 2018; Maftei et al., 2024; Brown and Valiere, 2004).
Acute diarrhea	*S. boulardii, LGG, B. lactis* BB-12, and *L. reuteri* SD 2222	(Weichselbaum, 2009; Islam, 2016; Brown and Valiere, 2004; Gupta and Garg, 2009).
Traveler's diarrhea	*S. boulardii, LGG, L. acidophilus, L. bulgaricus, B. bifidum,* and *S. thermophilus*	(Weichselbaum, 2009; Santosa et al., 2006; Islam, 2016; Brown and Valiere, 2004).
Immune system diseases		
Common cold	*L. gasseri* PA 16/8, *B. longum* SP 07/3, and *B. bifidum* MF 20/5	(Weichselbaum, 2009).
Type 1 diabetes	*B. (longum, infantis, breve); L. (acidophilus, delbrueckii. Bulgaricus, plantarum*	(Tegegne and Kebede, 2022).
Japanese cedar pollen (JCP)	*L. casei Shirota (LcS), L. rhamnosus* ATCC 53103, and *L. acidophilus* L-92	(Weichselbaum, 2009).
Eczema/dermatitis	*L. rhamnosus* HN001, *B. animalis subsp. lactis* HN019	(Weichselbaum, 2009; Islam, 2016).
Infections		
Helicobacter pylori infections	*L. gasseri OLL 2716(LG21), L. casei, L. gasseri, L. johnsonii, and L. reuteri* DSM 17648	(Brown and Valiere, 2004; Gupta and Garg, 2009; Kimura, 2004; Sarkar, 2013; Reid et al., 2003; Rabetafika et al., 2023).
Chronic kidney disease (CKD)	*L. casei HY2743* and *L. casei HY7201*	(Ranjha et al., 2021).
Urinary tract infections (UTI)	*L. (fermentum, brevis, casei, vaginalis, delbrueckii, salivarius, reuteri,* and *rhamnosus).*	(Mombelli and Gismondo, 2000; George Kerry et al., 2018).
Surgical Infections	*L. fermentum* RC-14, *L. plantarum* 299, *L. acidophilus, L. lactis, L. casei. B. longum, B. bifidum, and B. infantis*	(Gupta and Garg, 2009; Rabetafika et al., 2023).
Vaginosis	*L. johnsonii, L. acidophilus, L. rhamnosus* GR-1, *L. fermentum* RC-14, and *L. crispatus* CTV-05	(Mombelli and Gismondo, 2000; Cheng et al., 2019; Reid et al., 2003; Rabetafika et al., 2023).
Uro-genital infections	*L. rhamnosus* GR-1 *and L. fermentum* RC-14	(Gupta and Garg, 2009).
Clostridium difficile colitis (CDC)	*L. rhamnosus GG, S. boulardii,* and *L. casei*	(Reid et al., 2003; Verna and Lucak, 2010; Rabetafika et al., 2023).
Genitourinary tract infections	*L. GR-1 and B-54* or *RC-14*	(Brown and Valiere, 2004).
Dermatological diseases	*L. salivarius* LS03*; Lactococcus and Streptococcus salivary; B. adolescentis* SPM0308	(Maftei et al., 2024).
Virus related disorders		
SARS-CoV-2	*Bacillus (coagulans, subtilis, clausii), L. plantarum,* KABP022, KABP023, and KAPB033	(Maftei et al., 2024).

Respiratory tract infections	*L. paracasei subsp. paracasei* CNCM I-1518*; L. plantarum* HEAL9*; L. paracasei* 8700	(Maftei et al., 2024; Rabetafika et al., 2023).
Influenza	*L. paracasei* CNCM I-1518	(Maftei et al., 2024).
HIV	*L. plantarum, Pediococcus acidilactici, Lactobacilli*	(Maftei et al., 2024; Gupta and Garg, 2009).
HPV	*L. rhamnosus* GR-1, *Limosilactobacillus reuteri* RC-14	(Maftei et al., 2024).
Cancer		
Breast cancer	*B. infantis* and *L. acidophilus*	(Brown and Valiere, 2004; Gupta and Garg, 2009).
Bladder cancer	*L. casei, B. longum*	(Mombelli and Gismondo, 2000).
Colon cancer	*L. johnsonii, L. reuteri, L. bulgaricus, B. longum, L. rhamnosus GG, B. lactis* Bb12*, and L. fermentum* NCIMB-5221 and -8829	(Santosa et al., 2006; Tegegne and Kebede, 2022; George Kerry et al., 2018).
Metabolic disorders		
Hypercholesterolemia	*L. johnsonii and L. reuteri*	(Mombelli and Gismondo, 2000; Quijano, 2011).
Bloating	*L. reuteri and B. breve*	(Piqué et al., 2019).
Hepatic diseases	VSL#3	(Brown and Valiere, 2004).
Lactose digestion	*Streptococcus salivarius subsp. thermophilus and Lactobacillus delbrueckii subsp. bulgaricus*	(Brown and Valiere, 2004).
Hyperlipidemia	*L. reuteri, L. gasseri*	(Brown and Valiere, 2004).
Lactose intolerance	*Lactobacilli, L. bulgaricus B. animalis, L. paracasei, B. animalis. lactis* BB12, *L. acidophilus* NFCM, *S. thermophilus,* and *L. johnsonii* La1	(Mombelli and Gismondo, 2000; Singh et al., 2011; Quijano, 2011; Sarkar, 2013).
Anti-obesity	*L. gasseri* BNR17, *L. casei, L. acidophilus,* and *B. longum*	(George Kerry et al., 2018).
non-alcoholic fatty liver disease	*B. infantis, L. acidopilus,* and *Bacillus cereus*	(Cheng et al., 2019).
Others		
Oral candidiasis	*B. animalis, Lactococcus lactis, L. helveticus, L. rhamnosus GG* ATCC53103, *L. rhamnosus* LC705	(Gupta and Garg, 2009; Singh et al., 2011; Allaker and Stephen, 2017).
Halitosis	*Streptococcus salivarius* K12, *L. salivarus* WB21	(Ranjha et al., 2021; Allaker and Stephen, 2017).
Mental health	*L. rhamnosus, L. helveticus, L. brevis* DPC6108, *L. plantarum, L. fermentum, B. longum spp. Infantis, L. acidophilus,* and *L. casei*	(Cheng et al., 2019; Roobab et al., 2020; George Kerry et al., 2018).
Anti-sclerosis	*B. subtilis* and *B. coagulans*	(Roobab et al., 2020).
Osteoporosis	*L. reuteri* and *B. longum.*	(Ranjha et al., 2021).
Antiparasitic	*L. acidophilus* NCFM	(Nasreen et al., 2024).
Obesity	*B. pseudocatenulatum* SPM 1204, *B. longum* SPM 1205, *and B. longum* SPM 1207	(Ranjha et al., 2021).

Probiotics as Medicine: The Islamic Perspective

Probiotics, as described, have a crucial role in the prevention and treatment of different diseases. Humans are facing plenty of diseases that need to be treated with different substances. Disease occurring is natural, and it was created by ALLAH Almighty. Islam, which is a comprehensive religion that covers all aspects of someone's life, is hence called the complete code of life. Islam is the second-largest religion in the world, with approximately 1.8 billion followers, and this number is increasing rapidly (Hussain, 2024). Islam has a complete set of rules, commands, and guidelines that compel Muslims to follow them in every situation except in emergencies. Emergency, from an Islamic perspective, has its criteria and is known as Durrha (Badiuzzamani and Gunardi, 2021). Halal and haram are the two opposite terms in Islam, in which the former is allowed or permissible for use or doing, while the latter is non-permissible or not allowed to do or use. The effect of halal and haram is not only because of religious commands but in a real sense, these have a bad effect on humans if the harm is used. As the ALLAH almighty, create the human, and ALLAH knows what is good for us and what is not good to use, even if it seems the other way around, i.e., the haram seems good or beneficial for usage. Currently, the halal food industry is growing fast and has become the leading industry, particularly among the Muslim population (Yap and Al-Mutairi, 2023) (Hussain A, & Ali, S.A, 2024b).

The concept of halal and haram is vast and similarly applicable to food substances. Halal food means that is free from any haram or najas source, does not contain haram ingredients, and is not processed in haram or najas instruments. In the Quran, it is mentioned that “eat halal and tayybha,” which means the item must be halal and should be clean for usage (Mohd et al., 2018). Haram is the opposite of halal and is not allowed to be used except in Durrah situations. Almost all things must be halal until they are not declared haram in Islam. Halal pharmaceutical substances must be taken using the described halal criteria (Mohd et al., 2018). The Islamic approach to medicine and its aspects are shown in Fig 5.

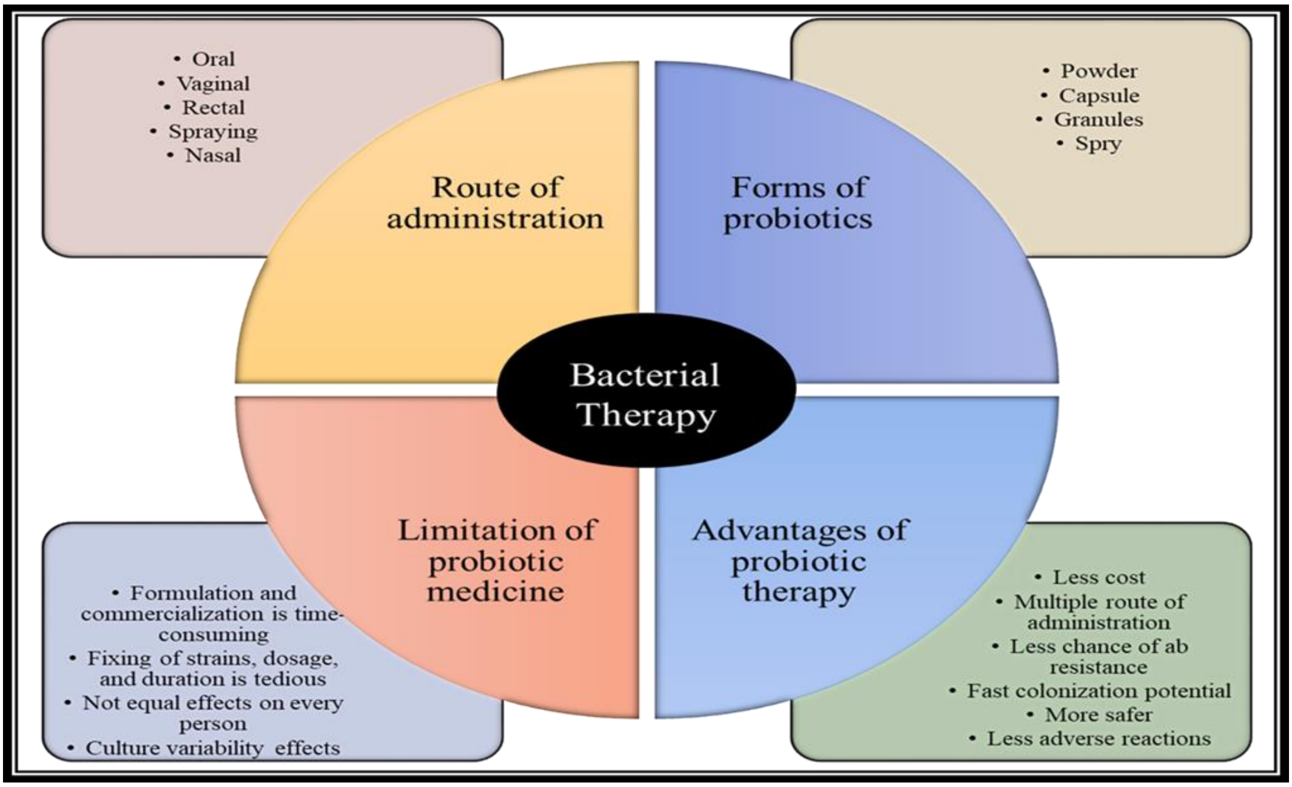

Fig. 4: The potential domains of bacterial therapy (probiotic as medicine)

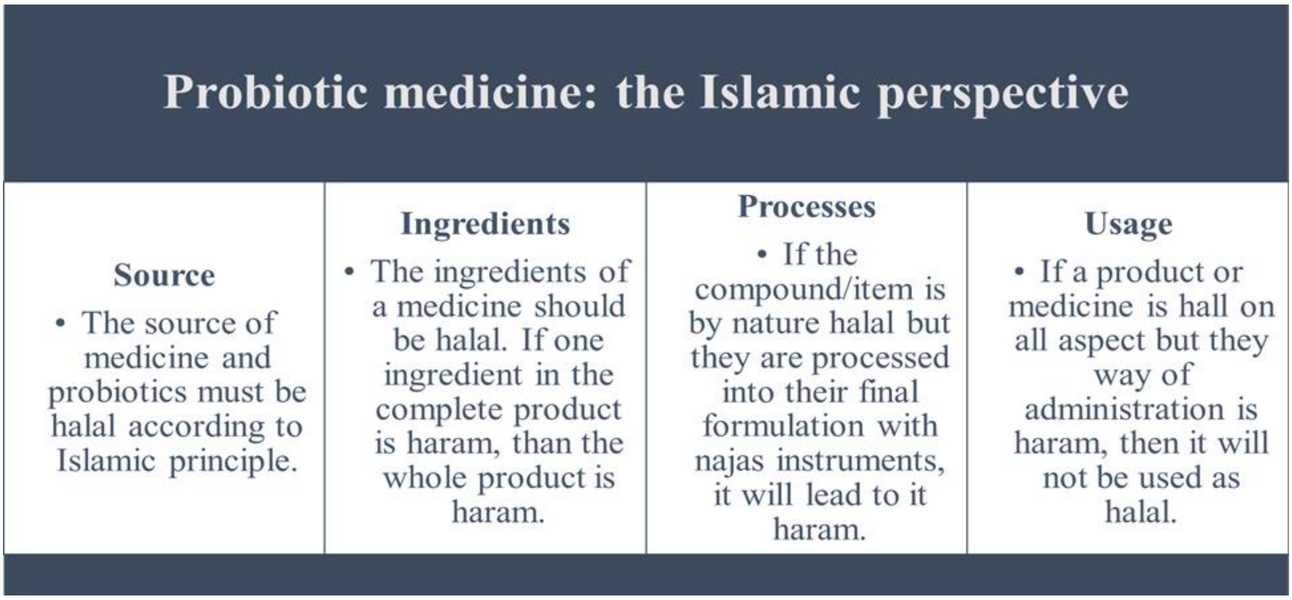

Fig. 5: The Islamic perspective of probiotic medicine

In medicine, the same halal and haram concepts are applied, as medicine is something that is ingested or taken inside the body. The source, process, ingredients, usage, etc. must be halal for any medicine to be taken. In the case of probiotics, most strains are isolated from human organs, and according to Islamic guidelines, the use of any human organ is not allowed, thus creating doubt about the use of probiotics. With the exception of two-year-old babies, which are fed with breastfeeding, they have advantages as their derived strains are used for human consumption, as the urine of a two-year-old baby is considered clean, as described in a hadith (Badiuzzamani and Gunardi, 2021; Yap and Al-Mutairi, 2023). The pivotal points that determine the halal perception of microbial products are the source, nature of microbes, growth media compositions, metabolites, production process, and the additives that help them be used for specific functions (Kurniati and Hafsan, 2022). Hence, it is important to check the halal and haram nature of probiotic medicine before administration.

Challenges

The literature showed the potential of probiotics or their products to be used as medicine or as a therapeutic agent to reduce and treat animals' diseases. The key mechanisms for this are their gut restoration and immunity modulation abilities, which help to repopulate the normal flora and, thus, aid in disease treatment. Currently, there is strong evidence that shows their medicinal potential, but it still needs to be complemented with more experimental data and animal studies (Stavropoulou and Bezirtzoglou, 2020). The antibiotic resistance potential is considered a positive attribute for probiotics but it creates problems when the person is infected so the antibiotic will not be working, thus creating a greater risk in disease treatment. The potential challenges associated include (i) the authorization and regulation of probiotic strains; (ii) the safety profile in terms of genetic stability, i.e., no acquisition of foreign substances; (iii) the creation of a dose-dependent profile; (iv) due to the strain-dependent nature, one strain may show different effects; and (v) the individual genetic profile, which showed different reactions against probiotics (Mejía-Caballer et al., 2021; Wolfe et al., 2023; Nami et al., 2015).

Recent Advancement and Future Perspectives

Modern technologies enable researchers to play with the genetics of microorganisms. New methods, procedures, and protocols are constantly developed for the better usage of microorganisms. Biotechnology, in this regard, contributes significantly. Genetic tools like the CRISPR-Cas system and genomic analysis deeply reflect the potential of microorganisms for any possible application. In the same area, the field of probiotics has advanced with different technologies. The development of CRISPR-biotics, next-generation probiotics, psychobiotics, gerobiotics, immunobiotics, and engineered probiotics are a few glimpses of using advanced technologies (Tegegne and Kebede, 2022).

Likewise, the competitions are still ongoing and are anticipated to be more precise, advanced, and accurate in the future. These advancements are supposed to help in strain identification, enhance reliability, and improve reproducibility (Maftei et al., 2024).

The future perspectives in the field of probiotic medicine include, but are not limited to, the following developments:

- The development of designer probiotics with the required properties is currently getting attention. These probiotics have advanced properties and have greater potential.
- Synthetic biology and probiotics are a new approach that has the potential to aid more probiotic products and elucidate new applications.
- The recent trend of fecal bacteriotherapy or fecal microbiota transplantation (FMT) (the transferring of good or healthy bacteria to the patient for gut restoration) can be more productive when probiotic strains are used (Tegegne and Kebede, 2022).
- The role of probiotics in gnotobiotics can be experimentally validated.
- The development of emerging technologies like 3D bioprinting can also be applied to enhance the field with more potential and accuracy (Hussain et al., 2024).
- Next-generation probiotics development is increasing, identifying different novel strains with probiotic potential using genetic analysis methods.
- The development of CRISPR-biotics (using the CRISPR-Cas system for probiotic development) is also a new trend in the probiotic field, which enhances the properties of probiotics (Hussain, A. & Ali, SA. 2023d).
- Gerobiotics, which are anti-aging probiotics, also received greater attention and showed their potential in combating aging processes.
- Psychobiotics, which are probiotics with the potential to treat cognitive function impairments, are currently under consideration.
- The potential role of artificial intelligence (AI) and allied technologies can be used to identify more advanced applications.

Conclusion

The spectrum of different applications of probiotics confirms their roots in multiple domains of life. Ranging from food and biotechnological applications to human disease treatment, this is just a glimpse of their strength. Due to the overwhelming effects, the medicinal aspects of probiotics are also explored, and surprisingly, they were found to be astounding. Strains from different sources, both in single and multiple forms, were screened for different diseases, and they showed promising results. Although, unlike medicine, there are no strict criteria, different guidelines are proposed that must be followed while administering probiotics. The formulation of probiotics, route of administration, delivery system, etc. are the contributing factors to the therapeutic potential of probiotics. Some often, i.e., blotting, mild gas, and allergies, and others, like sepsis and infections, are the documented shortcomings in the medicinal potential of probiotics. This study is limited to providing the theory and guidelines about probiotics medicine, although there is no case study or particular population studied, were added. Advancement in the field can be elaborated by fast and accurate methods of identification, genetic manipulation for profound properties, and the development of new aspects of applications using advanced technologies of artificial intelligence, machine learning, and deep learning.

Acknowledgment

This research project is financially supported by the Higher Education Commission of Pakistan (NRPU-20–1339/R&D/09) and Seed Fund from ICCBS to Syed Abid Ali.

Ethical Declaration
Not applicable

Conflict of Interest
The authors have no conflict of interest

Data Access Statement
Not analyzed new data

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