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Probiotics Benefits, Potential Limitations and Risks

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ABSTRACT

Background: Probiotics are different types of friendly types of yeasts or bacteria that improve the health of humans as well as animals. Their formulation can be used to make a wide range of products, including foods, pharmaceuticals, nutritional supplements and animal feed. Numerous scientific studies have examined and demonstrated the benefits of probiotics for health. Since there may be concerns regarding the safety of probiotics, a thorough understanding of their advantages and disadvantages is crucial before they are widely used. The aim of this study is to shed light on the probiotic world, which has a long history of success across many different fields. Main Body: The definition of probiotics and related terminology, their usage, and the kinds of bacterial strains involved as different species of Lactobacillus; Bifidobacterium. etc., their mode of action and their applications for humans and animals were all covered in this study. Numerous advantages for human health were highlighted, including their ability to treat a range of gastrointestinal issues and their role in lowering the prevalence of numerous other illnesses and infections. Moreover, its possible source of antibiotic resistance, adverse metabolic activities, and other associated side effects such as sepsis were explained. Conclusions: Probiotics have non-neglected hazards that endanger human health and safety, despite their potential advantages and use in the treatment or prevention of numerous clinical disorders. More research on the dangers and proper usage of probiotics is advised because they are a double-edged currency that must be dealt with caution.

INTRODUCTION

Probiotics are nonpathogenic bacteria that are present in certain foods like yogurt and other fermented foods. They help to balance the microbial population in the intestines and boost the number of good bacteria there (Hutkins *et al.*, 2016). Fuller (1992) provided a more precise definition of probiotics as "a live microorganisms feed supplement that improves the intestinal flora of the host animal to the animal's benefit" (de Miranda *et al.*, 2023).

The sophisticated ecology of billions of bacteria that inhabit our gastrointestinal tract, known as the gut microbiota, has a significant impact on immune function, nutrition absorption, gut maturation, and energy metabolism (Rusch *et al.*, 2023). The probiotics are made of healthy living bacteria or yeasts that your body naturally lives. Both beneficial and harmful microorganisms are constantly present in your body. When you acquire an infection, dangerous germs proliferate, blowing your body's natural system out of balance. By removing more harmful bacteria, good bacteria assist in restoring the balance.

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Introducing beneficial microorganisms to your body can be done by taking probiotic pills. Additionally, depending on the location, type, and state of the person's body, they can acquire bacteria via food and dietary supplements (Williams, 2010).

Despite the fact that probiotics provide numerous health advantages, there are growing doubts about their long-term safety that haven't been addressed, creating a "double-edged" challenge for their use. The development of illnesses like bacteremia, the production of poisonous substances, or detrimental metabolic consequences are some of the worries that put probiotics' safety concerns (Zheng *et al.*, 2017).

Three general categories of probiotics have been established based on the analysis of the obtainable data: those with no health claims (usually thought to be safe; no efficacy testing is necessary); or those used as a dietary supplement with a particular health claim (defined strain utilized, evidence-based efficacy from clinical trials or meta-analyses, usage for augmenting natural defenses or relieving symptoms); or as a probiotic medication (clinical studies for a particular condition or illness, usage of a specific strain)(Hill et al., 2014).

Many efforts are currently being conducted to identify the mechanisms that support interactions between gut microbes and hosts. Another recent area of study has been the use of probiotics to reduce disease pathology; however, the impacts and mechanisms of probiotics are not always well understood (Sanders al., et 2019). Furthermore, there are a number of safety concerns that need to be addressed. These include the possibility that certain probiotic strains may transfer intrinsic virulence factors and drug resistance genes, the inadequacy of reliable and clear clinical recommendations. rare occurrences of metabolic disturbances and allergic reactions, urological infections, sepsis, opportunistic infections, ischemia, and a lack of rigorous clinical trials (Rad et al., 2021).

Probiotic research should aim to characterize each person's typical, healthy gut microbiota by determining the species composition and levels of different microorganisms in various parts of the intestine. The goal is to gain knowledge of interactions between the host and the microorganism in the gut, microbe and individual relationships in the microbiota, and the cumulative consequences on the health of these relationships (Isolauri *et al.*, 2004).

Main Text:

1. Related terms and definitions 1.1 Probiotics

Greek is the language from which the word probiotic, was originated which means "for life,". They are nonpathogenic microorganisms, or bacteria, found in certain types of food like yogurt and other fermented foods that enhance the intestinal microbial balance and boost populations of good bacteria in the stomach (Hutkins *et al.*, 2016). **1.2 Prebiotics:**

Gibson and Roberfroid (1995) were the first to use the phrase prebiotic, replacing the word "pro" with the prefix "pre," which means "before" or "for." Prebiotics are what they define as a non-digestible dietary component that has a positive impact on the host by selectively promoting the activity of one or more specific bacteria in the colon. With the exception of its property-specific species, this description and the concept of dietary fiber more or less overlap. For Bifidobacteria, this selection was demonstrated (Gibson & Roberfroid, 1995).

According to Hutkins et al. (2016), these are indigestible fiber components that pass undigested through the upper part of the duct system and promote the development and activity of helpful microorganisms like bacteria and fungi. Prebiotics with bifidogenic effects include insulin, oligofructose, fructo-oligosaccharides (FOS) synthesized from sucrose, galactose- and fructo-oligosaccharides (GOS) and oligosaccharides containing xylose (Hutkins et al., 2016).

Natural sources of prebiotics include the vegetables, fruits, and grains that we consume every day. In addition to serving as a supply of energy, prebiotics provide a number of health benefits, including reducing the incidence and duration of diarrhea, relieving inflammation and other digestive issues, and limiting colon cancer (Peña, 2007). Prebiotics can be obtained as supplements or in foods including onions, garlic, and legumes.

1.3 Synbiotics/ conbiotics

Synbiotics, are a blend of probiotic and prebiotic products that aid in boosting the ability of live microbial dietary additives to persist and colonize the gut, have been created as a result of advancements in microbial research (Tufarelli & Laudadio, 2016). The fusion of probiotics and prebiotics has been defined by other certain authors as conbiotics (Kechagia *et al.*, 2013).

1.4 Postbiotics

Postbiotics, often referred to as metabiotics or biogenics, are soluble substances secreted or released by living bacteria that have a positive physiological impact on the host. It can be present in foods like kefir, kimchi, sauerkraut, and other pickles that have been fermented by live bacteria(Aguilar-Toalá et al., 2018). In 2013, the World Gastroenterology Organization released international standards for probiotics dispelled and prebiotics, which the widespread misconception that any yogurt can be regarded as a probiotic by confirming that the effectiveness of probiotics is doseand strain-specific (Guarner et al., 2011).

Probiotics fall into one of three broad categories, according to a consensus statement from 2014: (1) probiotics with no health claims (generally regarded as safe; no evidence of efficacy is required); (2) as a food supplement with a specific health claim (defined strain used; use for bolstering natural defenses or reducing symptoms); or (3) as a medication (specified probiotic strain utilized, clinical trials for a particular disease or indication, evaluation of risks against benefits, and compliance with drug regulatory criteria) (Hill et al., 2014).

Probiotics' potential health advantages have recently been the subject of greater scientific analysis, and there is now substantial support for their use in the avoidance and therapy of certain human diseases. Probiotics are used for purposes that go far beyond these particular indications, and they are now a significant commercial product. Considering that probiotics are being used more and more frequently in both community and hospital settings (Boyle *et al.*, 2006).

The goal of modern probiotics research is to characterize and evaluate the composition of the gut microbiota, which functions as a microbial ecosystem. It is significant to keep in mind that the benefits of probiotics differ depending on the strain (Yang *et al.*, 2022). As a result, every probiotic strain has a different health claim, and even within a species, bacterial strains can differ significantly in their probiotic capacity (Karaseva *et al.*, 2023).

2. Common Microorganisms used as Probiotics:

Even within the same species, there are several bacterial strains that may have probiotic properties; each one is distinct from the others and may have different areas of site-specific adherence. particular immunological outcomes, and activities on a healthy mucosal milieu vs. an inflamed mucosal milieu (Isolauri et al., 2004). A probiotic can be created from a single bacterial strain or it can also be a consortium (it can contain up to eight different strains). Preparations with several strains have the benefit of being effective in a wider variety of diseases and animal types (Senok et al., 2005). According to Khatoon et al. (2023), the most prevalent strains of Lactobacillus and Bifidobacterium have historically been referred to as "probiotics" (Khatoon et al., 2023). Saccharomyces, Bifidobacterium, and Lactobacillus are three widely utilized probiotics that have been well-studied in both people and animals. Numerous positive impacts on the intestinal mucosal defense system of the host have been demonstrated by probiotics (Kiani et al., 2022). Table 1,

provides a list of specific bacterial species that are now being used as probiotics (Nguyen *et al.*, 2016; Shah, 2007) including different

strains of *Saccharomyces*, *Streptococcus*, *Escherichia*, *Bacillus*, *Bifidobacterium*, and *Lactobacillus*.

Table 1: Microorganisms considered as probiotic	cs (Nguyen et al., 2016; Shah, 2007).
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Lactobacillus	Bifidobacterium	Other lactic acid Bacteria	Non-lactic acid Bacteria
Species	Species		
L. acidphilus	B. adolescentis	Enterococcus faecalis	Bacillus cereus var. toyoi
L. amylovorus	B.animalis	Enterococcus faecium	Bacillus coagulans,
L. casei	B. bifidum	Lactococcus lactis	Bacillus subtilis
L. crispatus	B. breve	Leuconstoc mesenteroides	Bacillus laterosporus
L. delbrueckii Subsp.	B. infantis	Pediococcus acidilactici	Esherichia coli strain nissle
L. fermentum	B. lactis	Sporolactobacillus inulinus	Propionibacterium
L. gallinarum	B. longum	Streptococcus thermophilus	Saccharomyces cerevisiae
L. gasseri	B. essencis		Saccharomyces boulardii
L. johnsonii			
L. paracasei			
L. plantarum			
L. reuteri			
L. rhamnosus			
L. helveticus			
L. lactis			
L. salivarius			

2.1 The Genus Bifidobacterium:

Bifidobacterium is precisely distributed in the genitourinary and digestive systems of humans, where they occupy a variety of ecological niches and are mostly influenced by age and food. They become established soon after birth and dominate the infants' native microbiota. The k-casein glycoproteins found in human colostrum, and also to a limited extent, human milk, promote the growth of these cells. Bifidobacteria become less numerous with age and finally rank third in terms of abundance (accounting for around 25% of the total adult gut flora) behind the genera **Bacteroides** and Eubacterium (Soccol et al., 2010).

2.2 The Genus Lactobacillus:

In the gastrointestinal and vaginal tracts, *Lactobacilli* are found in a variety of habitats and play a significant role in the native microflora of humans and other higher animals. Numerous environmental parameters, including pH, oxygen availability, the concentration of particular substrates, the presence of secretions, and

bacterial interactions, have an impact on their dispersion. Additionally, they are infrequently linked to gastrointestinal and extraintestinal infections, and the strains used in technology are thought to be nonpathogenic and harmless bacteria (Gomes & Malcata, 1999).

2.3 Other Probiotic Microorganisms:

Lactobacillus Although and Bifidobacterium have a stronger relationship with the term probiotic, it may additionally be applied to other, less well-known microbes. For instance, an Italian product marketed as Enterogermina® has been using Bacillus species as probiotics for at least 50 years. Bacillus subtilis, Bacillus cereus, Bacillus coagulans, Bacillus clausii, and Bacillus licheniformis are some of the species that have been investigated by this group. The bacterial spores' characteristics include their resistance to heat, capacity for room-temperature storage, and accessibility in dried form. Since probiotic bacterial spores can survive the stomach's gastric pH, their functions go beyond nutritional supplements to include growth boosters and aquaculture. Additionally, these is altered, competitive adhesion to the mucosa bacteria can reach the small intestinal tract and epithelium is increased, and the immune (Soccol et al., 2010).

susceptible to antibiotics, it is advised to 3.1 Improving the Epithelial Barrier: combine probiotic formulations containing some Bacillus species. A number of studies utilized to defend the body from the have been carried out to confirm the safety of environment is the selectively permeable Bacillus species utilizing both in vitro and lining between the intestinal lumen that is animal testing to determine the toxicity or created negative impacts of the strains. According to gastrointestinal Soccol et al. (2010), a bacterium should only immunoglobulins, be given the name "probiotic" if it exhibits the antibacterial peptides, and the epithelial traits common to strains of probiotics (Soccol junction addition complex, also use it (Snoek et al., 2010)

3. Mechanisms of Probiotics Action:

Probiotics can aid in preventing and managing gastrointestinal infections as well as improving performance and productivity because they have multiple mechanisms of action (Casas & Dobrogosz, 2000). However, these processes are still not fully understood. Probiotics can protect the intestines against recognized diseases in four different ways. (a) Pathogens and probiotics compete for vital nutrients. (b) They cling to adhesion sites, decreasing the amount of ground that can be colonized by pathogens. (c) Probiotics trigger immune cells to secrete cytokines, which are then used to target and destroy infections. (d) In the end, probiotics with direct bacterial contact release bacteriocins (Khoder et al., 2016).

Probiotics can produce antagonistic (bacteriocin-like compounds) that discourage pathogen growth, as well as competitive exclusion (competition for essential nutrients adherence changing sites). pathogen enzymatic activity, immunostimulatory functions, and nutritional advantages like enhancing feed ability to digest and utilization (Kesarcodi-Watson et al., 2008). Bacillus subtilis is a probiotic strain that was studied and characterized due to its antagonistic properties against different pathogenic bacterial strains of vibrio. The main probiotic essential mechanisms that underlie the antagonistic effects of probiotics on diverse the gut epithelial barrier is bacteria. strengthened, the digestive system microbiota

system is modulated to give the host an Given that these bacteria are not advantage (Bermudez-Brito et al., 2012).

A significant defense mechanism by epithelial cells in the mucosa. Numerous including lgA, et al., 2010).

Probiotics boost the immune system in the gastrointestinal epithelium, which can stop chronic GIT inflammation. For example, inflammation can be reduced if a high dose of a probiotic formulation containing four strands of Lactobacilli (L. plantarum, L. acidophilus, L. casei and L. delbrueckii subspecies bulgaricus) three strains of bifidobacteria (B. longum, B. infantis and B.breve), and one strain of Streptococcus (S. salivarius subspecies thermophilus) (Snoek et al., 2010).

3.2 Enhanced Intestinal Mucosal Adhesion:

According to Gou et al. (2022), probiotics help intestinal epithelial survival, enhance barrier function, and cause the intestinal epithelium to respond with barrier protection in order to preserve intestinal epithelial homeostasis (Gou et al., 2022). It is important for the host's interaction with the probiotic strains and is regarded as an essential requirement for colonization (Juntunen et al., 2001). The capacity of probiotics to attach to the intestinal mucosa has been associated with a number of positive consequences (Castagliuolo et al., 2005), is critical for immune system modulation (Schiffrin et al., 1997), and inhibits pathogen growth (Hirano et al., 2003). Mucin, a complex glycoprotein combination released by intestinal epithelial cells (IECs), is the main mucous component that inhibits the attachment of harmful bacteria (González-Rodríguez et al., 2012). The mucosal gel

lipids, contains free proteins, immunoglobulins, and salts as well (Khanvilkar et al., 2001). This interaction suggests a potential link between probiotic bacterial surface proteins and the pathogens' competitive exclusion from mucus (Ouwehand et al., 2002).

It has been demonstrated that a number of probiotic proteins, such as Lactobacillus (Tassell & Miller, 2011), as well as surface adhesins exhibited by bacteria, facilitate the adherence of bacteria to the mucous membrane (Buck et al., 2005). The most well-researched example of bacterial adhesins that target mucus is MUP, which is generated by Lactobacillus reuteri (Hynönen et al., 2002). Probiotics like L. plantarum reportedly cause MUC2 and MUC3 mucin induction, which prevent enteropathogenic E. from adhering. Additionally, coli the intestinal epithelium is protected from pathogen invasion by thickened mucous layers and glycocalyx, as well as the presence of Lactobacillus spp. at microbial sites of attachment (Voltan et al., 2007).

Probiotic strains have the ability to trigger the production of defensins, which are tiny proteins and peptides that have antibacterial, antifungal, and antiviral activity in epithelial cells. They support the proper functioning of the intestinal barrier (Furrie *et al.*, 2005).

3.3 Synthesis of Antibacterial Agents:

Various types of thermostable bacteriocins have antibacterial activity against many animals pathogens including Bacillus sp., Listeria sp., Staphylococcus sp., Enterococcus sp., and Salmonella sp. (Gillor et al., 2008), these thermostable bacteriocins can be synthesized by many species, including (LAB) (Nissen-Meyer et al., 2009), bifidobacteria (Cheikhyoussef et al., 2008) and bacillus (Le Marrec et al., 2000). А different variety of probiotic L. salivarius strain, UCC118, is capable of producing Abp118, a wide-spectrum bacteriocin, which protects mice from Listeria monocytogenes infections (Knorr, 1998).

3.4 Gene Expression Alterations in Pathogenic Bacteria:

Bacteria produce chemical signals, known as autoinducers, that let them interact with one another and have an impact on their behavior (Waters & Bassler, 2005). Quorum sensing is a technique that bacteria employ to communicate with their hosts (Hughes & Sperandio, 2008).

The fermentation products from *L*. acidophilus La-5 can block the extracellular generation of a chemical signal (autoinducer 2) by human enterohaemorrhagic *E*. coli serotype O157:H7 because they reduce the expression of the virulence gene (LEE)locus of enterocyte elimination in vitro. This may hinder quorum sensing and prevent *E*. coli from colonizing the GIT (Medellin-Pena, 2007).

3.5 Probiotics and Immune System Regulation:

Probiotic microorganisms have a well-known ability to modulate the immune system. These microorganisms can interact with dendritic cells (DCs), monocytes/macrophages, lymphocytes, and epithelial cells. There are two types of immune systems: innate and adaptive. B and T cells, which are specialized for particular antigens, are necessary for the adaptive immune response. In contrast, the innate immune system responds to similar molecular pathogen-associated patterns called (PAMPs) molecular patterns that are identified by the innate immune system and shared by the majority of infections (Gómez-Llorente et al., 2010).

The main pathogen response starts with the pattern recognition receptors (PPRs), which bind PAMPs. Toll-like receptors (TLRs) have received the most attention among PPRs. External C-type lectin receptors (CLRs) and internal nucleotide-binding oligomerization domain-containing protein (NOD)-like receptors (NLRs) are known to interact with one another and transmit signals in bacteria (Lebeer *et al.*, 2010).

The complicated nature of hostmicrobe interactions will be clarified by the recent characterization of host groups of pattern-recognition molecules, such as TLR and NOD-like receptors, as well as modulating crucial signaling pathways, such as MAPK, with regard to their capacity to strengthen or reduce stimulation and affect downstream routes. Bermudez-Brito *et al.* (2012) claim that commensal bacteria's activation of these receptors is essential for eliciting detectable antimicrobial responses with minimal inflammation-related tissue injury (Bermudez-Brito *et al.*, 2012).

Probiotics have been shown to lower TLR expression, produce substances that may block TNF- α from interacting with blood mononuclear cells, and decrease NF- κ B signaling in intestinal cells, all of which may assist to lessen inflammation in the intestinal tract (Gómez-Llorente et al., 2010). According to Hoarau *et al.* (2006), a *Bifidobacterium breve* C50 fermentation byproduct can stimulate DC maturation, high IL-10 generation, and prolonged life via the TLR2 pathway. TLR2 also plays a significant role in the recognition of bifidobacteria (Hoarau *et al.*, 2006).

A study done by Plantinga *et al.*, (2011) found that the main immune cells of both humans and mice produce varying amounts of cytokines in response to the *Bifidobacterium breve*, *Lactobacillus* *rhamnosus*, and *Lactobacillus casei* strains (Plantinga *et al.*, 2011).

4. Different Applications of Probiotics:

Probiotics are now being used and applied in a huge variety of products, including foods, medications, and food supplements. According to Zucko et al. (2020), probiotic bacteria are mostly obtained fermented dairy products from and vegetables, which have long been utilized historically. Due to their advantageous health effects, especially with regard to digestive problems, they have already been taken (Zucko et al., 2020). Interestingly, the approach to using them has expanded along with their use. Probiotics are still mostly obtained via fermented milk products and beverages, but they are increasingly being used as nutritional supplements in the form of pills or capsules (De Simone, 2019).

The diversity of food choices containing probiotic strains is considerable and continues to increase. Dairy-based products dominate the market and account for the majority of sales among non-dairy food applications that are effective probiotic delivery systems for consumers, as indicated in Table (2).

-		
Dairy	Non-dairy	
Fermented milk	Soy based products	
Cheese	Nutrition bars	
Ice-cream	Cereals and legume based	
Yogurt	Variety of Vegetables and fruit juices	
Infant formulas	Meat and seafood based	

Table 2: Some foods that contain probiotics.

In Fecal microbiota transplantation (FMT) therapy, a healthy gut bacterium can be transferred from one person to another by the transfer of faeces. According to Costello *et al.* (2016), there are several ways to perform a transplant, including oral capsules, retention enema, infection by upper or lower endoscopy, and nasogastric tubes (Costello *et al.*, 2016). Donor screening is crucial in order to lower the danger of the spread of infectious diseases or other health conditions. Although frozen feces are more effective, fresh feces can also be used (Hamilton *et al.*, 2013).

Following this, the stool bank has helped as a source of preparation. By restoring activities to the illness intestine typically supplied by the native microbiota, FMT is an effective therapy for numerous GI diseases such *Clostridium difficile* infection Clostridium difficile infection (CDI) and inflammatory bowel disease (IBD) (Pinn *et al.*, 2015).

There are still certain hazards involved with the process. Following FMT, norovirus infection has been documented in two patients; in neither of these cases was the donor the source of the infection (Schwartz *et* al., 2013). Additionally, FMT may cause immunocompromised people to contract opportunistic infections, while the current data indicate that this is not a frequent issue for this patient population (Di Bella et al., Another instance 2015). of obesity developing after FMT from an overweight donor has been documented (Macfarlane & Macfarlane, 2012). Further research is required in order to comprehend the effects of FMT outside of the GI tract (Paramsothy et al., 2015).

Probiotics are applied in Animals Feed, where scientists are looking for ways will increase food production while reducing production costs, and keeping quality and safety requirements, as the demand for food of both plant and animal origin is growing in direct proportion to the ongoing growth of the human population. To better the meat's safety and quality while respecting animal welfare ecological concerns, new and animal husbandry techniques have been introduced. The growth in the production of premium meat, milk, eggs and fish is the result of the impact of the many feed additives utilized on animal health. Animal intestinal pathogens, Campylobacter, including Yersinia. Salmonella, and Listeria, directly contribute to food contamination and are a contributor to zoonotic illnesses. All animal feed must adhere to strict requirements without boosting the price of animal production (Markowiak & Śliżewska, 2018).

5. Probiotics and Human Health Benefits:

Probiotics are believed to offer several significant health benefits, including enhanced immunological function, and defense against heart disease, avoiding cancer, alleviating IBS-related diarrhea, lowering blood pressure and cholesterol, nutritional absorption. enhanced and increasing lactose metabolism (Dash et al., 2023; Vera-Santander et al., 2023). Probiotics have benefits in regard to gut microbiota regulation, reduction of lactose intolerance, enhancement of micro- and macronutrient bioavailability, and relief of allergic reaction reactions in individuals at risk (Roobab et al., 2020). Probiotics improve the integrity of the intestinal barrier by preventing harmful microorganisms by limiting binding sites on mucosal epithelial cells and modifying the host immune response (Fusco *et al.*, 2023).

5.1 Prevention of Infectious Diseases:

Common side effects of antibiotics include mild to severe episodes of diarrhea. The proliferation of opportunistic or pathogenic strains is encouraged as the typical bacteria tend to be repressed. From diarrhea to mucosal abnormalities to pseudomembranous inflammation, the spectrum may vary. L. rhamnosus and S. boulardii have been given as part of probiotic therapy in clinical settings. Probiotic use is related to a lower risk of antibiotic-associated diarrhea, according to several studies (Smits et al., 2016). The analysis of existing studies on probiotics for the prevention and treatment of diarrhea associated with antibiotics shows that probiotic application is associated with a reduced risk of the condition, particularly L. rhamnosus, L. casei, and the yeast S. boulardii as these are the probiotics mostly provided (Hempel et al., 2012).

According to animal research, probiotic therapy can reduce Helicobacter pylori infection at a reasonable cost. Therefore, long-term consumption of probiotics; has of positive effect on H. pylori infection in humans, by lowering the likelihood of developing diseases related to high degrees of stomach inflammation. Moreover, the nonimmunological associated mechanisms; The gastric mucosal barrier acts as the initial line of defense against harmful germs as well as nonimmunological barriers like the acidity of the stomach. Additionally, probiotic supplementation has been suggested to improve this barrier by promoting the formation of mucin, competing with H. pylori for adhesion receptors, maintaining the gut mucosal barrier, and creating antimicrobial By secreting antibacterials, substances. probiotics may prevent the growth of H. pylori (Lesbros-Pantoflickova et al., 2007).

Most urinary tract infections (UTI) are caused by members of the Enterobacteriaceae family, such as *Escherichia coli*, which are common residents

of human intestines. UTI can occasionally be caused by a virus or fungus. An increasing prevalence of genital and bladder infections is directly correlated with the loss of the natural genital microbiota, mainly Lactobacillus species. Despite the fact that antimicrobial treatments are typically successful in curing these infections, reactivation is common. With the knowledge that Lactobacillus species not only retain low pH of the vaginal area, creates hydrogen peroxide and inhibits the proliferation of E. coli, it is now giving new notion of modern genitourinary vaccination. This procedure lessens inflammatory responses brought on by microorganisms (Amdekar et al., 2011).

Encouraging findings from a few clinical studies verify the administration of lactobacilli in the treatment of bacterial vaginosis (BV). Probiotics are recommended for the treatment of BV, but there is significant variety in the products, trial procedures, and result back metrics that make this difficult to say for certainty. However, to confirm the benefits of probiotics in the treatment of BV, larger, well-designed irregularly controlled trials using standardized procedures are needed (Mastromarino et al., 2013).

Probiotics are effective at preventing many respiratory disorders, including the common cold and flu, especially if you start taking them before the cold and flu season. According to several studies, if people take different strains of *Bifidobacteria* and *Lactobacillus* for 3-6 months, their symptoms will last on average one to two days less, if not more (Pregliasco *et al.*, 2008).

5.2 Effect of Probiotics on the Digestive System and its Anti-Inflammatory Activity:

Action on irritable bowel syndrome (IBS) is a poorly known gastrointestinal (GI) disorder that typically manifests in early adulthood. Since antibiotics have been linked to the etiology of IBS, they may also alter naturally occurring microorganisms. *L. plantarm* solutions were administered to patients with IBS in four different ways: on their own, in combination with trimebutine or

mebeverine (two medications often used to treat IBS), or as a solution in a pasteurized form. They discovered that supplementing with probiotics in active form led to a larger improvement in symptoms than medication treatment did (Madden & Hunter, 2002).

Within the first few weeks of life, premature infants that are affected by necrotizing enterocolitis (NEC) experience major difficulties. Although there isn't a wellknown cause for inflammatory disease, milk feeding and microbial development are factors. Probiotics are used to treat and prevent inflammatory diseases. They are dietary supplements that contain possibly beneficial bacteria or yeast. According to research done by Alfaleh and Anabrees probiotics (2014).using can prevent inflammatory illness and death in premature babies weighing less than 1500 grams (AlFaleh & Anabrees, 2014).

Recurrent abdominal pain (RAP) has an impact on school-aged youngsters all across the world. Despite being a very benign ailment, probiotics have been found as at least one dietary intervention that may be helpful(Korterink et al., 2015). Children with RAP may have short-term pain relief from probiotics. Although most studies employed a strain of lactobacillus, probiotics can contain a variety of bacteria. Children with RAP may have less pain after taking probiotics. Probiotics may be used by doctors as part of their RAP management plan (Newlove-Delgado et al., 2017). The disorders Crohn's disease (CD) and ulcerative colitis (UC), which are characterized by severe GIT (gastrointestinal tract) inflammation, are collectively referred to as inflammatory bowel disease (IBD). In experimental mouse models, it has been found that *lactobacillus* strains are efficient in lowering mucosal inflammation, although Bifidobacteria appear to be more beneficial. The discovery that a strain of Lactobacillus salivarius, lowered the rate of development from inflammation through dysplasia to colon cancer, was more intriguing than the anti-inflammatory activity of probiotics in experimental intestinal colitis in mice (Uguccioni et al., 1999).

5.3 Lactose Malabsorption (intolerance) Treatment:

Probiotics may be used as an adjunctive therapy for those who are lactose intolerant, particularly if they can express B-galactosidase enzymatic activity (Fassio *et al.*, 2018). According to Almeida *et al.* (2012), it can reduce lactose intolerance's clinical symptoms (Almeida *et al.*, 2012).

5.4 Psycho-biotics:

When consumed in sufficient quantities, psycho-biotics are a type of probiotic that have successful results on mental health (Luang-In et al., 2020). To affect the central nervous system (CNS), they change the gut microbiota (GM). Probiotics can affect a variety of CNS functions, including mental illness and memory. Although the exact mechanism by which bacteria exercise their psycho-biotic potential is still unclear, Sarkar et al. (2016) found that bacteria can help humans by stimulating either the gastrointestinal nervous system or the immune defense system (Sarkar et al., 2016). They have a direct impact on the immune system, cause the release of molecules like neurotransmitters, proteins, and short-chain fatty acids (SCFAs), and affect the (Hypo thalamus- pituitaryadrenocortical) HPA axis stress response (Sarkar et al., 2016), which controls mood and emotion by lowering corticosteroid (CORT) levels (Ait-Belgnaoui et al., 2012). These factors have the potential to have a psychbiotic influence since they can change the psychophysiological indicators of depression and anxiety (Sarkar et al., 2016).

According to Bercik *et al.* (2011), the probiotic strain *B.longum* can significantly lower high levels of anxiety. Probiotics like *L.helveticus* and *B.longum* can help lower subjective anxiety levels (Bercik *et al.*, 2011). In addition, formulations of the probiotic strains *L. helveticus* and *B. longum* have been shown to be more effective at treating depression than placebo (LeBlanc *et al.*, 2017).

5.5 Probiotics for Oral and Dental Health and Hygiene:

In an effort to prevent tooth decay and other oral health issues like gingivitis and periodontitis, probiotics are being applied to oral care products and hygiene practices. This application is still relatively new and is being studied for its efficacy and safety (Huang & Tang, 2015). Researchers have demonstrated the ability of probiotic strains including L. casei and L. rhamnosus GG to limit the development of oral Streptococci, a major cause of tooth decay (Ahola et al., 2002). Streptococcus mutans levels in saliva can also be decreased by probiotic L. reuteri in its various forms, such as chewing gum (Çaglar et al., 2006) or as administered in yogurt Additionally, (Petti et al., 2008). Streptococcus mutans levels in saliva can be decreased by the inclusion of L. rhamnosus in milk or processed cheese. Additionally, probiotic organisms have been added to toothpaste to combat the S.mutans bacteria that cause dental cavities and plaque around braces (Krzyściak et al., 2014).

The condition of foul breath can be brought on by consuming specific foods, metabolic diseases, respiratory tract inspections, etc., but it is typically correlated with an imbalance of the oral microbiota (Parahitiyawa *et al.*, 2010). Most typically, healthy people without bad breath have commensal probiotics like *S. salivarius* in their mouths (Kazor *et al.*, 2003).

5.6 Probiotics Dermal Effect and Skin Care Efficiency:

It has been demonstrated that oral Lactobacillus fermentum may lessen the severity of atopic dermatitis (AD) in young children and that these effects continue even after supplementation is stopped (Weston et al., 2005). One of the latest skincare concepts to combat photoaging and skin aging is probiotic skincare. According to a preliminary study, these products can delay both spontaneous and associated aging. Probiotics have been shown to improve skin barrier function, reduce photoaging, reduce oxidative stress, increase hair quality, and restore acidic skin pH (Sharma et al., 2016). Plant extracts fermented with Lactobacillus buchneri (PELB) were tested for their ability

to prevent photoaging. They found that PELB decreased collagenase and elastase activity while increasing moisture factor and antioxidant enzyme expression. Because PELB protects against UVB-induced photoaging, it can be useful in the beauty industry (Kang *et al.*, 2020).

5.7 Probiotics' Influence on Chronic Diseases:

Studies on probiotics and diabetes are still in their early stages. However, one hypothesized that they could improve insulin sensitivity in people with type 2 diabetes (T2D) (Andreasen et al., 2010). According to a different study (Luoto et al., 2010), consuming probiotics while pregnant can lower the risk of gestational diabetes. According to a different proposed study, T2D patients' kidney function can be improved by consuming 200 ml of soy milk per day that contains L. plantarum (Abbasi et al., 2017). Additionally, 300g of yogurt with L. acidophilus and B. lactis can be consumed for six weeks to enhance the lipid profile in T2D (Ejtahed et al., 2011).

It has been found that consuming significant amounts of yoghurt decreased cholesterolemia, which may be related to a yoghurt component that inhibits the formation of cholesterol from acetate and found that certain strains of *Lactobacillus acidophilus* make it possible for cholesterol to be attached to the intestinal lumen and thereby restrict its absorption, suggesting that consuming probiotics can lower blood cholesterol levels (Sadrzadeh-Yeganeh *et al.*, 2010).

According to Moroti et al. (2012), probiotics can increase HDL cholesterol while decreasing total and LDL cholesterol (Moroti et al., 2012). Additionally, according to certain studies done by Mencarelli et al., (2012), taking supplements of good bacteria may help to lower cholesterol absorption and inflammation of fat reserves (Mencarelli et al., 2012). Studies have revealed that probiotics the can reduce risk of cardiovascular disease by lowering blood cholesterol levels and boosting lipoprotein resistance to oxidation (Descheemaeker & Debruyne, 2002).

Probiotic supplementation has been shown in certain research to reduce body weight and fat buildup in both human and animal models (Kadooka *et al.*, 2010). Another study done by Ilmonen *et al.*, (2011) demonstrates that probiotic supplements given to pregnant women for at least one month prior to delivery and maintained for up to six months after delivery can minimize excessive weight gain in both the mothers and their offspring (Ilmonen *et al.*, 2011).

5.8 Anti-Cancer Activity:

The most frequent forms of breast cancer are estrogen-dependent, and both hereditary and environmental variables might raise the likelihood of getting this disease. Breast tumors may not grow as quickly as other cancers due to certain variables, such as diets high in cultured dairy products (Matar et al., 2003). Milk that has undergone contain non-bacterial fermentation may might improve substances its immunogenicity and other qualities, such as its anti-tumor activity. Physiologically active peptides generated from fermented milk serve a variety of tasks and purposes. Peptide fractions are released when Lactobacillus (L. helveticus) ferments milk (de Moreno de LeBlanc et al., 2005). Furthermore, yogurt containing live bacteria like Lactobacillus helps prevent colon cancer. As a result, eating yoghurt prevented the formation of tumors (Bedada et al., 2020).

6. Risks and Limitations Associated with **Probiotics:**

Unlike other types of functional foods, very little is known regarding the longterm protection of consuming such enormous quantities of probiotic bacteria. It is unclear how well these organisms tolerate acids and bile salts, despite the health claims made for probiotic supplements. When these properties have been studied, the findings have been inconsistent, contradictory, erratic, straindependent, and limited to in vitro settings (Anglenius *et al.*, 2023; da Silva *et al.*, 2021).

Probiotics have many health benefits, but there are growing concerns regarding their long-term safety when taken or in foods that have been supplemented with them. For their use, this presents a "doubleedged" dilemma (Imperial & Ibana, 2016).

Typical intestinal as well as systemic side effects of probiotic intake include lactic acidosis, gene transfer, mental fogginess, the introduction of certain bacteriophages, virulence factors, probiotic intestinal increased incidence, and many other problems (Oh et al., 2022) It is crucial to have a thorough understanding of the hazards and advantages of probiotics given how frequently consumers and healthcare professionals use them worldwide (Yao et al., 2010). When administering probiotics to some patient populations, especially premature or immunocompromised neonates, care should be taken. Despite the fact that probiotics have an outstanding overall safety record (Yao et al., 2010), these concerns must be carefully evaluated before patients are encouraged to utilize probiotic supplements.

6.1 Infections:

Some individuals should use probiotics cautiously owing to the possibility of getting sepsis. Before being marketed, microorganism strains must be evaluated for safety. As different strains of microorganisms can have incredibly particular effects and their effects may vary on health and disease as well as for different age groups, there is still much to learn about the proper mechanisms of action and care for these bacteria (Yao et al., 2010).

6.2 Sepsis:

Sepsis is a major area of threat with probiotic use (Venet & Monneret, 2018). Unlike probiotic products, Lactobacillus species are an infrequent but well-known cause of endocarditis in adults as well as many forms of sepsis in infants. According to investigations, taking probiotic several supplements has been connected to cases of Lactobacillus and other bacterial sepsis (Boyle et al., 2006). In healthy subjects, an infection linked to probiotic use has not been reported. According to Hennequin et al., (2000),individuals with primary immunodeficiency, chronic illness, or debility have been the target of every case of probiotic

bacteremia or fungicide (Hennequin et al., 2000).

6.3 The Relationship Between Probiotics and Antibiotic Resistance:

The majority of probiotics are frequently found throughout the human digestive system and are consumed in high quantities in functional meals; therefore, it is necessary to routinely screen for the existence of antibiotic resistance determinants in their genomes (Lahtinen et al., 2009). Vancomycin resistance is a common characteristic among Lactobacillus strains, which raises questions about whether it could spread to other harmful species, including Staphylococcus aureus and Enterococci. However, because vancomycinresistant genes are chromosomal in Lactobacillus. thev cannot easily be transferred to other species. The vancomycinresistant genes of Lactobacilli have not been discovered to be transferrable to other genera according to conjugation studies (Akpınar Kankaya & Tuncer, 2020; Tynkkynen et al., 1998). The ability to sporulate and the processes of contact with the human intestinal mucosa are two properties of probiotic Bacillus strains that set them apart from other probiotic bacteria (Sánchez et al., 2009).

The random administration of antibiotics resulted in transitional pressures being introduced into our natural settings, which hastened the establishment of bacteria strains that are resistant to antibiotics. To reduce these transitional pressures, using probiotics rather than antibiotics may result in specific health issues (Capita & Alonso-Calleja, 2013).

6.4 Harmful Metabolic Activities and Other Risks Resulting from Utilizing **Probiotics:**

flora is crucial Intestinal for metabolic processes such as the breakdown of complicated carbohydrates, the processing of and the regulation of glucose lipids, homeostasis. Probiotic manipulation carries a risk of metabolic side effects (Macfarlane & Macfarlane, 2012). Probiotic therapies may also carry other concerns, such as skin, eye, and/ or mucosal sensitivities or allergies.

Negative metabolic or toxic effects on the host as a result of the probiotics' microorganisms producing toxins and immune system overstimulation in families with weak immune systems (Doron & Snydman, 2015).

7. Current Probiotic Regulation and Future Perspectives:

Probiotics are increasingly being used as dietary supplements in the form of pills or capsules, while fermented dairy products and beverages remain the most popular source of probiotics (De Simone, 2019). The transition from traditional fermented products to dietary/nutritive supplements in pills has resulted in an average increase in the total number of live bacteria or yeast consumed by a thousand times, or from 10⁵-10⁸ live bacteria/gm of fermented products to $10^9 - 10^{12}$ of live bacteria/dose when taken as a diet supplement (Lin et al., 2023). Though there isn't an agreement worldwide over the right amount to consume per day, several countries have recommended that a dose of live microorganisms should include at least 10⁹ colony-forming units (Reid et al., 2018). It is essential that probiotics are produced and prepared in a manner that guarantees a significant level of microbial survivability for the duration of their shelf life, regardless of their quantity (Ozen & Dinleyici, 2015).

Probiotic supplements will be not only unsuccessful but also counterproductive and perhaps hazardous given the clinical risk and the increasing number of reports of antibiotic resistance worldwide (Anisimova *et al.*, 2022). We can assess the supposed health advantages and long-term well-being of using probiotic supplements by sharply focusing on the long-standing issues of antibiotic resistance, sensitivity to acids, and bile salt intolerance (Marttinen *et al.*, 2020).

Effectiveness, safety, manufacturing quality control, and health claim regulation are a few organizational factors that need to be taken into consideration. As complex organisms, probiotic preparations fall under the current biological laws and are categorized as medical or pharmaceutical items if they make a health claim that includes treatment, prevention, alleviation, or illness diagnosis. Due to the fact that they do not mention any specific diseases, the great majority are categorized as nutritional supplements. Additionally, a product can be categorized as a therapeutic food for a particular ailment, such as (sinusitis), when the clinical results are persuasive for a particular combination of probiotics. There is no system for regulating probiotics that is accepted worldwide and a framework for probiotic regulation has not been reached by all parties. In accordance with the Food Products Directive and regulations, probiotics and nutritional supplements are controlled in the European Union. All advantages and claims related to probiotics require EFSA (European Food Safety Authority) approval before they are made public. The majority of probiotic products are categorized as foods or dietary supplements and are therefore permitted to make structural or functional claims like "supports healthy digestion" (De Simone, 2019).

Probiotics show great promise for treating or preventing a variety of digestive ailments. It's important to keep in mind that there are currently a number of probiotic marketing claims that lack experimental evidence. Probiotics enable the replenishment of good microorganisms in our digestive tract, counterbalancing the negative ones. Moreover, the efficacy observed in a particular strain of bacteria may not necessarily transfer to other probiotic species. Furthermore, nothing is known about the fundamental mechanisms underlying the activity of probiotics. Accurate modeling of interactions between probiotic strains and native gut microbiota is still needed, as is a explanation of how thorough native microbiomes impact human health and wellbeing. It is quite possible that future probiotic supplements and food additions will embrace the "bugs as drugs" approach, which is predicated on customized treatment regimens and well-studied probiotic strains that are specific to each individual's microbiota and target specific diseases. Once these issues have been handled and evidence of probiotics' beneficial effects on health has been gathered, it would be quite legitimate to describe them as human buddies (Singh *et al.*, 2023).

Conclusions:

Probiotics are beneficial microbes, that scientists discovered thousands of years ago and they've been used safely for a very long time. Some are derived from a healthy person's gut microbiota, while others are nonhuman strains utilized for dairy product fermentation. Bifidobacterium and Lactobacillus bacteria are the most frequently utilized in treatment. Through our research, we highlighted that probiotics can be obtained and applied in many food products, some medicines and nutritional supplements and they are not only applied to humans, but also, they have been used in animal feeding. Research has been promising for these friendly critters. In spite of that probiotics have potential benefits and have been seen in the treatment or prevention of many clinical diseases they have non-neglected risks that threaten human health and safety. We recommend more studies about probiotics and their risks as well as their safe use as it is a double-edged currency that must be dealt with caution.

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List of Abbreviations:

CLRs: C-type lectin receptors

FMT: Fecal microbiota transplantation

HPA: Hypothalamic pituitary adrenal

IECs: Intestinal Epithelial Cells

LEE: Locus oof Enterocyte effacement

MAPK: Mitogen-activated protein kinase

MRS media: De Man, Rogosa and Sharpe Agar

MGB: Microbiota gut bacteria

MUC: Mucins

MUP: Mucus Binding Protein

NOD: Nucleotide oligomerization domain containing protein 1

NLRs: (NOD)-like receptors

PAMPs: Pathogen-associated molecular patterns

PELB: Plant extracts fermented with *Lactobacillus buchneri*

PPRs: Pattern recognition receptors

SCFAs: Short Chain Fatty Acid

TLRs: Toll-like receptors

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