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REVIEW

A systematic review on selection characterization and implementation of probiotics in human health

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Abstract
Probiotics are live bacteria found in food that assist the body's defence mechanisms against pathogens by reconciling the gut microbiota. Probiotics are believed to aid with gut health, the immune system, and brain function, among other factors. They've furthermore been shown to help with constipation, high blood pressure, and skin issues. The global probiotics market has been incrementally growing in recent years, as consumers' demand for healthy diets and wellness has continued to increase. This has prompted the food industry to develop new probiotic-containing food products, as well as researchers to explore their specific characteristics and impacts on human health. Although most probiotics are fastidious microorganisms that are nutritionally demanding and sensitive to environmental conditions, they become less viable as they are processed and stored. In this review we studied the current literature on the fundamental idea of probiotic bacteria, their medical benefits, and their selection, characterization, and implementations.

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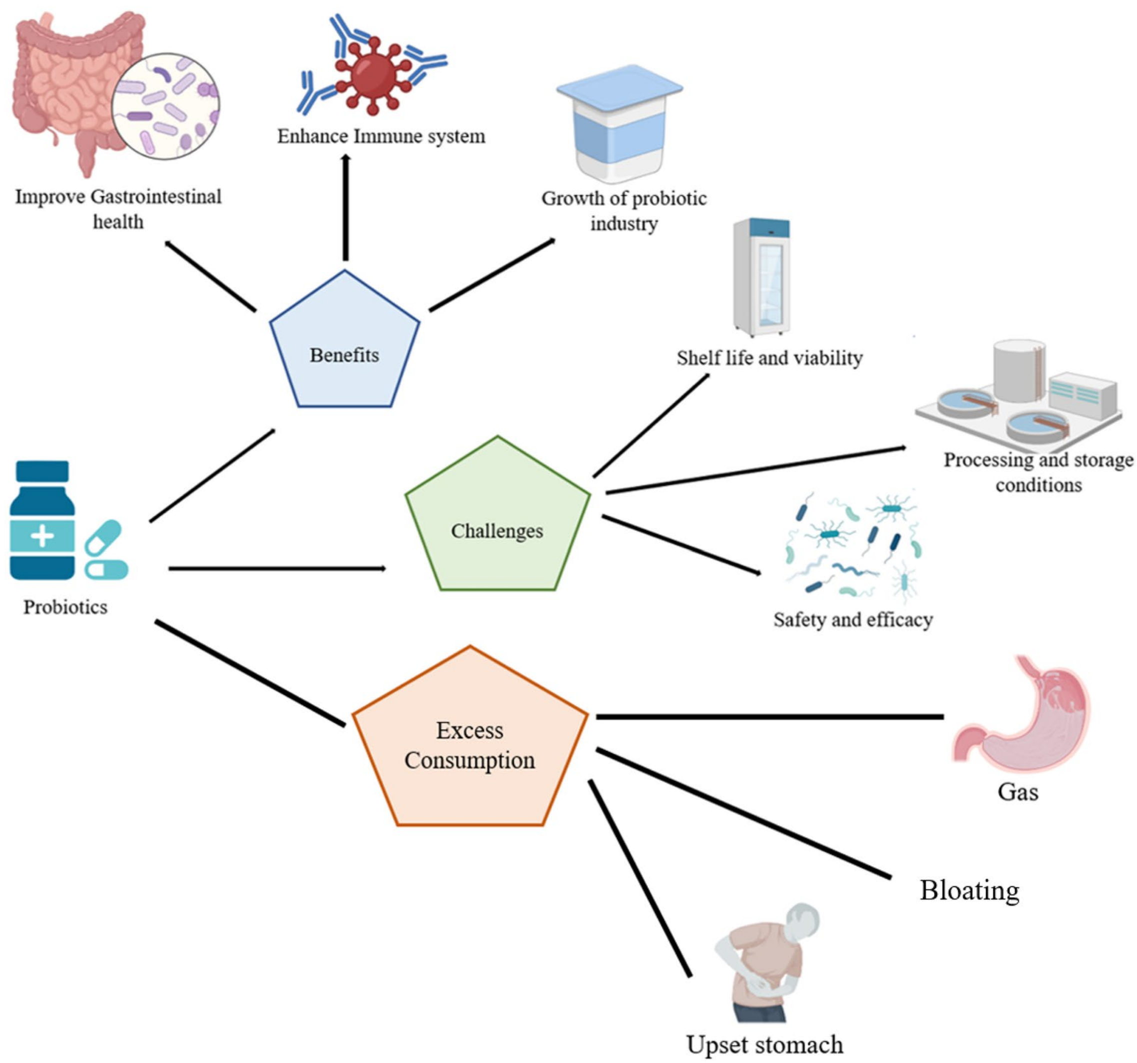
Graphical Abstract



Keywords Probiotics · Stability · Selection · Characterization · Applications

Introduction

Probiotic strains have seen increasing commercial interest in recent years. Since most of the probiotics currently available are fastidious microorganisms, nutritionally demanding and sensitive to environmental conditions, they become less viable as they are processed and stored. Elie Metchnikoff brought the idea of probiotics in the early nineties(Amara and Shibl, 2015a). Research in probiotics gradually gained pace in the past two decades and various advancements were observed with respect to the selection of probiotics, their isolation and characterisation. Probiotics fall under the category of functional food, a term that gained popularity as healthy foods in the past few years (Jackson et al., 2019a). Global markets have witnessed considerable interest in probiotics for various medical conditions, along with gaining popularity as health supplements among millions of people across the globe (Jackson et al., 2019).

Probiotics are bacteria, moulds, and yeasts with lactic acid bacteria being most common (Iqbal et al., 2021). A few examples include *Lactobacillus bulgaricus* (*L. bulgaricus*), *Lactobacillus plantarum*, *Bifidobacterium* species, and *Escherichia coli*. It is generally believed that these microbes contribute to the spread of diseases and, as a consequence, harm and deteriorate human health. There exist two kinds of bacteria, the good bacteria are required for the proper functioning of the body and are commonly found in the gut and other locations of the body including mouth, urinary tract, vagina etc. (Hemarajata and Versalovic, 2013). Probiotics are basically made up of these good bacteria, whose consumption can provide benefits such as supporting immune function(Nazir et al., 2018), controlling inflammation, increase digestion (Kaur et al., 2021), break down and absorption of medications(Nazir et al., 2018).

Certain medical conditions can be treated by increasing the amount of probiotics in the body which includes diarrhoea, gum diseases, irritable bowel syndrome, inflammatory bowel disease, yeast infections, lactose intolerance etc. (Foster and Zhou, 2015). However, the viability of probiotics continues to be a technological and marketing challenge for industries. Reduction of viability during processing and storage still continues to be one of the major challenges. This study focuses on the selection and characterisation of probiotics and their stability analysis to understands conditions under which the probiotic stability is affected to assist future research on solving this problem..

Literature search

Using the electronic databases Google Scholar, PubMed, and Web of Science without any limitations on language or time, a comprehensive search strategy was utilized to identify articles published by mid-2022. Research articles mentioning "probiotic" in the title and abstract were searched. To obtain more precise results, an advanced search was conducted with filters such as selection, stability, and characterization terms including "probiotics". We screened additional reviews and systematic reviews to identify potentially related citations. Manual searching was conducted to circumvent the elimination of pertinent articles.

Probiotics and food products

The gut microbes refer to a wide catalogue of microbes and their genes inhabiting the gut. The amount of microbes present in the human body outnumber the human somatic cells (Kerry et al., 2018). From the beginning of early life, the immune system's development and sustaining homeostasis are strongly affected by the configuration of microbial communities present in the gut (Yadav et al., 2018; Zhao, 2010). Probiotics have a lot of beneficial properties which are proven to be remediable and salubrious (Fig. 1). In addition, probiotics are coadjutants in treating metabolic disorders, which includes obesity, metabolic syndrome and type 2 diabetes. Probiotics exhibit many beneficial effects such as antimicrobial, anti-carcinogenic and anti-pathogenic properties (Shah and Swami, 2017).

Currently, there are a wide variety of food products containing probiotic strains (Table 1). Milk-based products

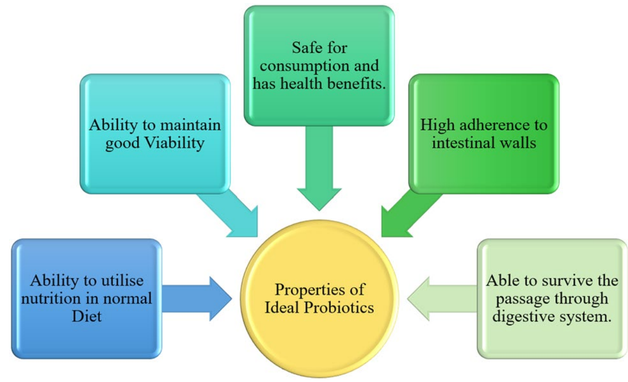


Fig. 1 Properties of an ideal probiotics

account for the majority of market sales, including fermented milks, cheese, ice cream, buttermilk, milk powder, and yogurts (Damián et al., 2022). As a non-dairy food application, soy-based products, nutrition bars, cereals, and juices can be used to deliver probiotics to the consumer (Aspri et al., 2020). As part of the evaluation of the effectiveness of probiotic strains added to foods and beverages, the product's safety and compatibility with the microorganisms, as well as its processing, packaging, and storage conditions, should be taken into account (George Kerry et al., 2018). The worldwide market for probiotic food has grown substantially every year due to the potential health advantages. However, certain food with probiotic claims is a problem because of the difficulty of surviving and maintaining the probiotic cells which are included in the food at the time of processing and storage (Rodrigues et al., 2020).

Engineering probiotics with tailored functional properties and its applications

The process of encapsulating one substance into another is referred to as encapsulation (Levi et al., 2011). Encapsulation is done to enhance their viability and stability during production and storage (Rodrigues et al., 2020). As carrier material, the substance used for encapsulation must be both safe and cost-effective. Electron microscopy can be used to analyse the size and structure of the microcapsule before and after incorporating the probiotics. Sometimes along with carrier material, some cryoprotectant or bioactive compounds might increase the stability (Šipailienė and Petraitytė, 2018). The process maintains cell viability even under harsh conditions in the gastric environment and allows the cell to be released in a controlled manner. The coating material selection is very significant since it determines the effectiveness of encapsulation.

Due to the recent development in research, probiotics have also found applications in treating ulcers (Khoder

Table 1 Various food probiotics, manufacturers and benefit on body

Food used for delivery of probiotic	Strain	Organism present	Amount to be consumed / dosage	Benefit on body	Manufacture s and country	References
DanActive fermented milk	*Lactobacillus casei* DN-114 001	*L. casei Immunitas*	200 g	Fosters digestion process, improves function of intestines, helping to avoid constipation	Danone (Paris, France)	(Rizzoli and Biver, 2018)
Kefir	*Lactobacillus, bifidobacterium*	*Lactobacillus*	200–300 ml	Boost immune system, improves bone health	Lifeway Foods, Kefir, USA	(Rizzoli and Biver, 2018)
Tempeh	Bacteria	Firmicutes	100 g	Reduce cholesterol, improve digestive health and reduce inflammation	Taiwan Tempeh Food Business Co., Ltd. Taiwan	(Stephanie et al., 2017)
Kimchi	*Lactobacillus*	*Lactobacillus*	0.5–7.5 oz (15 -210 g)	Regulate immune system, promote weight loss, fight inflammation	Madge's food company, USA	(Park et al., 2017)
Miso	*Saccharomyces*	*Saccharomyces cereviase*	6 g per day	Enhance gut bacteria. Overall physical and mental health	Hikari, Miso, Japan	(Ito, 2020)
Kombucha	*Acetic acid bacteria*	*Acetobacteraceae*	100–120 ml	Strengthening immune system, helps in gout, rheumatism, liver function	Zoh Probiotics, India	(Watawana et al., 2015)
Pickles	*L. plantarum, L. brevis, Enterococcus faecalis*	*Lactobacillus, Enterococcus*	–	Fight diseases	–	(Behera et al., 2020a)
Traditional buttermilk	*L. acidophilus*	*Lactobacillus*	8 oz	Helps in treating digestive health issues as irritable bowel syndrome	–	(Rawat et al., 2018)
Natto	*Bacillus subtilis*	*Bacillus*	100–200 g	Stronger bones, healthier heart and immune system	True basics, India	(Sella et al., 2021)
Cheese	*Bifidiobacterium longum, L. acidophilus*	*Bifidiobacteria, lactobacillus*	42 g	Beneficial for immune system	Nestle, India	(Hammam, 2020)
Miso soup	*T. halophilus, Saccharomyces cerevisiae*	*Tetragenococcus, Saccharomyces*	200 to 240 ml	Reduce risk of inflammatory bowel diseases	Hikari, Miso, Japan	(Allwood et al., 2021)
Sourdough bread	Lactic acid bacteria and yeast	*Saccharomyces cerevisiae*	56 g	Improves gut health,better digestion	Swiss bake, Switzerland	(Longoria-García et al., 2018)
Yoghurt	*L. bulgaricus, S. thermophilus*	*Lactobacillus*	3 cups	Strengthen immune system	Danone, (Paris, France)	(Meybodi et al., 2020)
Soft cheese	*L. lactis*	*Lactococcuss*	3 servings	Healthy weight gain, prevent osteoporosis		(El-Sayed and El-Sayed, 2021)
Acidophilus milk	*L. acidophilus*	*Lactobacillus*	–	Preventing intestinal infections		(Farag et al., 2020)

Table 1 (continued)

Food used for delivery of probiotic	Strain	Organism present	Amount to be consumed / dosage	Benefit on body	Manufacture s and country	References
Sour pickles	*L. plantarum*	*Lactobacillus*	–	Helps digestion		(Behera et al., 2020b)

et al., 2016), inflammatory bowel diseases (IBD), and tissue repair (Abraham and Quigley, 2017) and modulation of stem cells (Al-Yassir et al., 2021). Among others, when the stomach is subjected to damage, its surface may erode, which leads to cancer and ulcer. The protective effects of healthy multibacterial strains modulate the dividing stem cells and secretory cell lineage of the stomach. Cells of the stomach showed regeneration with increased stem cell proliferation and increased production of mucus which essentially protects the gut (Haghshenas et al., 2017). Probiotics have also shown the potential to treat IBD (Abraham and Quigley, 2017). Following the consumption of probiotics, cells that had previously displayed symptoms of IBD showed anti-inflammatory and pro-regenerative effects to revive the tissues and cells of the affected areas(Lee et al., 2018).

Probiotics enhance the healing of wounds present in the GI tract, and stimulate fibroblast proliferation migration. Probiotics also enhance the fortification of the epithelial barrier (Lee et al., 2018). Studies have shown that bacterial strains of probiotic bacteria react with compounds such as antioxidants, antimicrobial agents, and flavours, resulting in an effect that is a combination of the compounds as they interact (Markowiak and Śliżewska, 2017). A cumulative effect is generally observed by this, and composition variations may also influence flavour, microbial composition, and quality. Probiotics also improved disease resistance and broiler chicken performance. (Terpou et al., 2019a).

Furthermore, the encapsulation of the bacterial strains ensures the strains are delivered and protected under conditions like increased temperature, variation in pH, etc. essentially protecting the strains from degradation by gut physiological conditions (Markowiak and Śliżewska, 2017). Encapsulation increases the life of probiotic strain and enhances its activity. There are various methods by which bacterial strains (probiotics) can be encapsulated, which can be broadly categorised into two types: liquid delivery system or encapsulation by liquid system and solid delivery system or encapsulation by the solid system (Fenster et al., 2019).

Criteria of selecting probiotics and their action mechanism

Probiotics are often described as "a mono- or mixed culture of live microorganisms which, when applied to man or animals, beneficially affect the host by improving the properties of indigenous microflora" (Iqbal et al., 2021). The term "Probiotics" has its word root in Greek which means "pro-life" etymologically. With time various definitions evolved such as, "growth promoting factors produced by microorganisms", "Microbial cells which transit the GI tract and which, in doing so, benefit the health of consumer"(Liu et al., 2018a). To be considered as a probiotic, the bacteria is supposed to have certain characters (Fig. 1). *Lactobacillus* and *Bifidiobacteria* are the commonly used strain considered as probiotics. Many other strains are also used as probiotics. The important criteria to consider in a strain as probiotics includes (1) the ability to survive in a digestive tract environment which require acid and bile tolerance, (2) an inhabitant of a normal intestinal tract, (3) expected to be safe for host consumption, (4) should be able to adhere to the intestines and colonise there, (5) should be able to produce antimicrobial compounds like bacterions to fight off pathogens, (6) has to be non-pathogenic to host.

Currently, a wide array of commercial probiotics products are available and provide desired medical benefits when ingested in appropriate dosages (Vijayalakshmi et al., 2020). Even though a lot of strains from genera such as *Propionibacterium*, *Enterococcus,* and *Escherichia* are available (Plaza-Diaz et al., 2019), the criteria for selecting probiotics depend on factors that should enhance the efficiency and stability of probiotics. They include easy to store without loss of viability; easy to grow in cheap and straight forward fermentation medium to maximum concentration; should be able to withstand physical handling without losing viability, withstand processing, should process tolerance to digestive juices as it passes through the gastrointestinal tract and adhesion onto a specific body site (Yadav and Shukla, 2017). Probiotics possess different mechanisms of action which includes short-chain fatty acid production, immunomodulation, and stimulation of mucosal barrier function and lowering of gut pH. In several studies conducted, it was found that probiotics have an influence on acquired and innate immunity responses through induction of phagocytosis IgA secretion and modifying T-cell responses (Yeşilyurt et al., 2021). Most of the health benefits regarding the use of probiotics are related with gastrointestinal tract. Probiotic mechanisms in gastrointestinal tract can be classified into mucosal, luminal and submucosal (Lee et al., 2018).

Probiotics in food and human health

Food products containing probiotic strains are available in a wide variety. The most commonly used products in markets include diary based products like cheese, fermented milks, ice cream, buttermilk, yoghurts and milk powder (Sharifi-Rad et al., 2020). The other category of available products is non-dairy products like cereals, nutrition bars, juices, and so on (Table 1). A number of studies conducted on health benefits of probiotics have shown numerous results, which includes promoting intestinal health, reduction of serum cholesterol, improved immune responses, prevention of cancer, treatment of acute diarrhoeal diseases etc. (Martín and Langella, 2019).

Isolation of probiotics

Lactic acid bacteria (LAB) are generally considered as safe (GRAS) microorganisms. They are found in water, soil manure and in habitats with nutrient sources. LAB identification steps from natural resources are sampling and isolation, 16S rDNA fragment amplification and sequencing, PCR fingerprinting and data analysis, low pH and high bile salt tolerance assessment, antimicrobial activity. (Haghshenas et al., 2017). The first step in the isolation of probiotic LAB from uncommon sources or non-intestinal sources is to cultivate them on a high nutritional medium that is different or modified from the conventional de Man, Rgosa, and Sharp (MRS) medium. A medium consisting mainly of glucose, yeast extract, and peptone (GYP) was used to cultivate LAB isolated from paddy rice silage, crop and silage fermentation (Kerry et al., 2018). A GYP plus BM medium was successfully used to cultivate LAB isolated from soil (rhizospheres of fruit trees and soil around animal farms). To cultivate malolactic-producing LAB such as *Oenococcus oeni* from red wine-making in Japan, BM medium containing tomato juices, peptone, liver extracts, and glucose is used. A modified MRS medium is also used to screen different parts of the GI tract of animals in LAB. For LAB isolates from animals' GI tracts to grow properly, pH conditions and nutrients may be required as well as some substrates. A modified MRS medium containing 0.3–1% (w/v) CaCO3 was used to isolate LAB from the GI tracts of animals. Various animals, including chickens (Bayane et al., 2010), cattle (Puphan et al., 2015), and dogs (Nazir et al., 2018), have been successfully isolated using this medium. In addition to raising LAB from fermented foods made from fish (Plachom) and beef (Mum), the medium has also been used to cultivate LAB from a variety of raw materials. Fermented foods, such as pickles, were fermented in acidic conditions using a medium containing mainly glucose, yeast extract, peptone, and 0.5% (w/v) CaCO3.

The fermentation is carried out carefully, and after fermentation, the cells are separated from the spent medium through centrifugation resulting in a concentration of cells (Shokryazdan et al., 2017). Depending on the application of the final product, stabilizer solutions are added (cryoprotectants) to probiotic mixture before freezing. After mixing the probiotic concentrate with various freezing processes can be done for cryopreservation. These frozen cans are shipped to various companies for incorporating probiotics into food and beverages. After lyophilisation, it is milled into powder form with defined practical size and density (Loh et al., 2015). The milled materials are later blended with bulking agent, functional ingredients depending upon the needs of customer. This blend is then used to make finished products (Fenster et al., 2019).

Bioengineering of probiotics: technologies currently used to enhance cell viability

Bioengineered probiotics with numerous immunogenic or antagonistic properties could be useful for improving human health. In contrast to conventional drug administration methods, these bacteria are tailored to deliver drugs, therapeutic proteins, or gene therapy vectors precisely and with a higher degree of site specificity (Kumar et al., 2015).

Many factors are found to affect the viability of cells present in probiotics. Chemical factors such as oxygen levels, redox potential along with additives, antimicrobial compounds affect viability during storage, whereas biological factors are strain type, natural microflora product, enzymes produced, post acidification and various pathogenic or spoilage microorganism occurrences (Silva et al., 2016). Similarly, physical factors include drying conditions and temperature will affect the probiotic viability (Fenster et al., 2019). Strategies to enhance the cell viability include selecting suitable strain, which serves a crucial role in improving viability. In order to prompt cell inactivation and to intensify cell stability, physical stress is applied (temperature stress, osmotic stress, oxygen stress). The selection of proper food packaging systems can influence viability including packaging methods like oxygen scavengers, vacuum packaging can significantly improve probiotics viability (Terpou et al., 2019b).

Encapsulation technologies are expected to enhance stability, ensure better handling and storage of probiotic cultures (Ren et al., 2019). As most probiotics are of intestinal origin, they are unsuitable for growth on diary- based media and mostly get inactivated on exposure to high heat, acid during processing (Corcoran et al., 2005). Technological challenges associated with maintaining a high number of probiotic organisms in food, the capability of the culture to retain viability in the food matrix environment, maintenance of its characteristics during consumption are also of concern. These technological approaches used for the preparation of cultures may affect their viability and functionality. Sometimes, cell injury can also happen during the application of these technologies.

Probiotic encapsulation technology has rapidly emerged in the past decade. With the help of this technology, many microorganisms have been immobilised with semipermeable materials to facilitate their delivery (Hassan et al., 2019). Despite the benefit of increased viability and shelf life, it faces many challenges, including developing microencapsulation equipment, selection of non-toxic materials for encapsulation, development of beads or capsules from polymers, the determination of appropriate mechanism during probiotic release. One of the most important challenge is of the cost, encapsulated end products can be very costly. This is because their development demands both time and financial resources. The use of natural polymers will increase the cost further, such as milk proteins seems more costly than carbohydrates. These techniques also require certain raw materials, which includes oil and emulsifiers in order to stabilize the capsule (Aragón-Rojas et al., 2019).

Functionalities of probiotics

Probiotics are live microorganisms which upon ingestion in sufficient concentrations can exert health benefits on the host. The data obtained from the literature of probiotics in the treatment of various diseases are organized as a summary in Tables 2 and 3. The Food and Agriculture Organization of United Nations and the World Health Organization developed this definition, which has become the term of reference for science and regulation ever since (The Food and Agriculture Organization, 2021).

Probiotics in gastrointestinal ailments

Probiotics have advantageous benefits in treating gastrointestinal ailments like necrotizing enterocolitis, traveller's diarrhea, antibiotic associated diarrhea, irritable bowel syndrome (IBS), recurrent *Clostridium difficile*, inflammatory bowel disease (IBD), Crohn's disease, *Helicobacter pylori,* ulcerative colitis, etc. (Liu et al., 2018b). The gastrointestinal Tract (GI) sustains a diverse range of microbial population that actively or passively regulates the metabolism and immunological system of the host. The significance of intestinal microbiota, one of the priorities of probiotic therapies, on the physiology of immune cells can be emphasized to cure inflammatory conditions and gastric ailments (Sales-Campos et al., 2019).

Organisms that normally populate the gut may undergo dysbiosis due to antibiotic treatment (Kim et al., 2017). When the healthy balance in the gut is disrupted, harmful, threatening organisms, especially *Clostridium difficile* is known to colonize the gut. A study assessed the effectiveness of probiotics containing *S. boulardii* or *L. acidophilus* with *L casei* at a dosage of 10–50 billion CFU/day amongst participants taking antibiotics for preventing *Clostridium* difficile associated diarrhea (Johnson et al., 2012). They concluded that there was a 60% decrease in the risk of contracting *Clostridium difficile* associated diarrhea when probiotics are consumed with antibiotics (Goldenberg et al., 2017a).

There are copious studies that successfully enabled the effectiveness of probiotic strains on diverse gastrointestinal ailments. The consumption of multistrain probiotic consolidating *Streptococci*, lactic acid bacteria, and *Bifidobacteria* in notable amounts (6 g/day) can help maintain remission and prevent acute pouchitis a study illustrated (Amara and

Table 2 Probiotics in the treatment of various cancers and gastro-intestinal diseases

Name of gastrointestinal disease	Symptoms of the disease	Strain of probiotic recommended	Amount of Probiotic administered	Disease Cured in	References
Acute infectious diarrhea	Changes in bowel movement, increase in the water content, and frequency of stools	*Saccharomyces boulardii*	250 and 750 mg	~24 h-73 h	(Dinleyici et al., 2015)
Ulcerative Colitis	Diffuse mucosal inflammation, bloody diarrhoea, and abdominal pain	*E. coli* and *Lactobacillus* GG	100 mg to 200 mg per day	6 months	(Kaur et al., 2020)
Antibiotic-Associated Diarrhea	Severity to result in colitis, electrolyte disturbance, and bowel perforation	*L. acidophilus, L. casei*	5×10^9 viable bacteria	4 weeks	(Goldenberg et al., 2017b)
Crohn's Disease	Fever, fatigue, Blood in your stool, and mouth sores	*Bifidobacterium longum*	2×10^{11} freeze-dried viable	6 months	(O'Callaghan and van Sinderen, 2016b)
Traveller's Diarrhea	An urgent need to defecate, Nausea, Vomiting	*Lacticaseibacillus rhamnosus*	2×10^9 CFU	1 week	(Giddings et al., 2016)
C. difficile diarrhea	Waterydiarrhea, Rapid heart rate, nausea Lossof appetite, Weight loss	*S. boulardii*	1000 mg per day	4 weeks	(Moré and Swidsinski, 2015)
Irritable Bowel Syndrome	Discomfort or pain associated with an alteration in bowel habits constipation	*Propionibacterium freudenreichiis sp shermanii*	1×10^7 CFU	23 weeks	(Didari, 2015)
C. albicans-associated gut discomfort	Abdominal or pelvic pain, Blood in your urine	*L. rhamnosus*; *B. animalis subsp. lactis*	1×10^9 CFU	14 weeks	(Severance et al., 2017)
Colorectal cancer	persistent change in bowel habits, Rectal bleeding	*Lactobacillus* and *Bifidobacterial*	30×10^7 CFU	6 months	(Zaharuddin et al., 2019)
Head and neck Squamous Cell Carcinoma	A persistent sore throat, and pain or difficulty swallowing	*Bifidobacterium breve* lw01	1×10^9 CFU	3 weeks	(Johnson et al., 2020)
Severe acute pancreatitis	Fever, Higher heart rate, Swollen and tender belly	*L. plantarum*	3×10^7 cfu	2 weeks	(Oláh and Jr, 2014)

Table 3 Probiotic organisms and their applications

Genus	Species	Applications	Reference
Lactobacillus	*L. rhamnosus*	Reduction of viral-associated pulmonary damage; prevention and reduction of severity of atopic dermatitis in children; reduction of risk for developing allergic disease; reduction of risk for rhinovirus infections in preterm infants; protection of human colonic muscle from lipopolysaccharide-induced damage	(Ammoscato et al., 2013; Zelaya et al., 2014)
	L. acidophilus	Treatment of travellers' diarrhoea; reduction of hospital stay of children with acute diarrhoea; antifungal activity; prevention or treatment of bacterial vaginosis; treatment of *C. difficile*-associated diarrhoea; reduction of irritable bowel syndrome symptoms	(McFarland, 2007; Phavichitr et al., 2019)
	L. plantarum	Prevention of endotoxin production; antifungal activity; reduction of irritable bowel syndrome symptoms	(Cortés-Zavaleta et al., 2014; Lee et al., 2014; Wright et al., 2015)
	L. casei	Treatment of functional constipation in adults; immunomodulatory mechanisms; improvement of rheumatoid arthritis status; protection against *Salmonella* infection; prevention of *Salmonella*-induced synovitis; treatment of intravaginal staphylococcosis	
	L. delbrueckii subsp. *bulgaricus*	Antibiotic resistance of yogurt starter culture; enhancement of systemic immunity in elderly; antibacterial action against *E. coli*; modulation of brain activity	(Moro-García et al., 2013; Tillisch et al., 2013)
	L. brevis	Protective role in bile salt tolerance; reduction in plague acidogenicity	(Suzuki et al., 2013)
	L. fermentum	Prevention or treatment of bacterial vaginosis; blockage of adherence of pathogenic microorganisms on vaginal epithelium; antistaphylococcal action; potential for reduction of insulin resistance and hypercholesterolemia	(Tomaro-Duchesneau et al., 2014)
	L. reuteri	Reduction of low-density lipoprotein cholesterol; reduction of onset of gastrointestinal disorders in infants; reduction of frequency of proven sepsis, feeding intolerance and duration of hospital stay in preterm infants	(Caramia et al., 2013; DiRienzo, 2014)
Bifidobacterium	*B. infantis*	Reduction of irritable bowel syndrome symptoms; reduction of necrotizing enterocolitis in preterm infants	(Li et al., 2013)
	B. animalis subsp. *lactis*	Treatment of functional constipation in adults; reduction of total cholesterol; reduction of risk of upper respiratory illness	(Pinto et al., 2014)
	B. breve	Prevention and treatment of necrotizing enterocolitis in newborns; reduction of necrotizing enterocolitis with *Bifidobacteria* cocktail; reduction of cholesterol	(Bordoni et al., 2013; Janvier et al., 2014)

Table 3 (continued)

Genus	Species	Applications	Reference
Saccharomyces	*S. boulardi*	Treatment of travellers' diarrhoea; treatment and reduction of diarrhoea duration regardless of cause; treatment of irritable bowel syndrome; treatment of moderate ulcerative colitis; treatment and reduction of recurrent pseudomembrane colitis infection caused by *C. difficile*; treatment of acute gastroenteritis in children	(Fernandez et al., 2014)
Lactococcus	*L. lactis* subsp. *lactis*	Treatment of antibiotic-associated diarrhoea; antimicrobial and probiotic properties	(Lee et al., 2013)
Enterococcus	*E. durans*	Antibiotic and antioxidant activity; adherence to colonic tissue and anti-inflammatory activity	(Pieniz et al., 2013)
	E. faecium	Treatment of antibiotic-associated diarrhoea; efficient animal probiotic	(Cao et al., 2013)

Shibl, 2015a). It also demonstrated that the number of *Lactobacilli* and *Bifidobacteria* in the patients with pouchitis was elevated and also remained significantly increased later of the administration. Moreover, there was a substantial decrease/improvement in symptoms like involuntary defecation, abdominal cramps, faecal consistency, mucus, and urge to evacuate stools during the intervention period (LeBlanc et al., 2021). As we are well versed in the fact that our behaviour and mood is affected by the gut microbiota; patients associated with Irritable bowel syndrome most commonly exhibit the symptoms of depression and anxiety, as compared to the healthy population. The vagus nerve which is the 10th cerebral nerve plays a very significant role in the communication cascade of microbiota-brain axis (Breit et al., 2018). Administration of *Lactobacillus rhamnosus* JB-1 resulted in the benefit of amelioration of anxiety and depression- like disorders (Horvat et al., 2021).

Antipathogenic and antiviral activity

Probiotics is known to exhibit antimicrobial effect against numerous microorganisms, including pathogens and virus etc. (Denkova and Kostov, 2017). There are several mechanisms proposed on the action of probiotics manifesting the antipathogenic properties. When ingested orally, probiotics attach to the intestinal mucosa running through the stomach, hindering the pathogenic bacteria from adhering to the epithelial tissue (Islam, 2016). Marhamatizadeh et al., (2013) concluded that the growth of *Salmonella enteritidis*, *Staphylococcus aureus* or *Escherichia coli* was restricted by the intake of probiotics, whereas it had no considerable effect on the growth of certain selected LAB such as *Lactobacillus rhamnosus*, *L. plantarum*, *Leuconostoc mesenteroides* therefore inferring its anti-microbial properties positively. Probiotics also provided a barrier which was showcased by a reduced reactivity of the host epithelium to opportunistic pathogenic allergies (Clavel et al., 2017). *Lactobacilli* attach to the receptors on the surface epithelial cells and exhibit competitive inhibition with enteric pathogens. The study also suggested that the vitality and virulence properties of the *E. coli* 0157:H7 and other diarrhea-inducing *E. coli* could be reduced by lactic acid producing bacteria (Saxena et al., 2015).

Anti-cholesterol, anti-obesity and anti-diabetic effect of probiotics

Obesity has become an alarming disease as it leads to several chronic ailments such as cardiovascular diseases, diabetes, insulin resistance of hepatic and skeletal muscle, and few forms of cancer (Fruh, 2017). Medication through drugs gives undesirable side effects and there is a high risk of post-surgery infections which may lead to dysbiosis of gut microbiota. Comparative surveys of gut bacteria of obese patients showed fewer *Bacteroidetes* and more firmicutes (Puphan et al., 2015). Hence, dietary inclusions of probiotics may help upregulate and maintain the ratio of *Bacteroidetes* and firmicutes, therefore, improving the state of obese patients (Stojanov et al., 2020).

Bifidobacterium is a common bacteria found in the human intestine. It can aid *Bacteroides* in the degradation of polysaccharides and limit the absorption of exogenous cholesterol from the small intestine (O'Callaghan and van Sinderen, 2016a). According to a study, administering strain B. L66-5 resulted in BW reduction, and a reduction in hepatic adiposity, all of which aided in the management of obesity (Shen et al., 2013).

Cholesterol accumulation is a life-threatening condition in which the oxidation of cholesterol causes arterial plaque formation, which contributes to cardiovascular disease (Soliman, 2018). Probiotic products' efficiency in the enhancement of health and disease reduction is due to their bioactive components. Probiotics have been suggested as a beneficial dietary strategy for lowering total cholesterol, particularly in people with borderline blood cholesterol. Probiotic strains such as L5022, LA2404, LA2410, and BB5286 have witnessed the ability to remove cholesterol (Miremadi et al., 2014).

Antimutagenic and anticarcinogenic properties of probiotics

Cancer is defined as a spontaneous and unregulated division/proliferation of cells that results in the destruction of body tissue. Cancer is one of the most common malignant diseases, with significant fatality rates all around the world (Sawant and Shegokar, 2014). While chemotherapy destroys cancer cells over time, it also harms healthy cells and results in drug resistance (Sawant and Shegokar, 2014). Probiotics act on cancerous and mutagenic cells by exhibiting few mechanisms which include degradation, binding and inhibition of mutagens; probiotics also aid in prevention of procarcinogens and also alter deleterious and highly reactive carcinogens (Kumar et al., 2010). They assist in lowering the pH of the gut with the help of short chain fatty acids made during the catabolism of undigestible carbohydrates. They modulate and strengthen host's innate immunity by secreting anti-inflammatory molecules.

Live entire probiotic strains of *Lactobacillus fermentum* RM28 and *Enterococcus faecium* RM11 in fermented milks induced anti-proliferation in colon cancer cells (Amara and Shibl, 2015b). A study found that administration of *L. acidophilus* to tumour-bearing mice transformed their cytokine production into a Th1 protective pattern, which is good for anti-tumour immunity (Maroof et al., 2012a). As a result, decreased tumour growth rate and increased lymphocyte proliferation are also beneficial (Maroof et al., 2012b). Due to the key properties connected to the presence of arginine deaminase activity, *Lactococcus lactis* provides value to a probiotic product. This has metabolic features that can inhibit opportunistic infections by depriving them of arginine, a critical source of nitrogen, carbon, and energy for bacteria (Verdenelli et al., 2014).

Probiotics in urogenital infections

Probiotics containing *Lactobacillus* bacteria of human origin for ameliorating urogenital infections is proved to be very effective. Problems due to antimicrobial treatments such as yeast and bacterial resistance, recurrent infections have become prominent (Maroof et al., 2012a). Canadian urologist Andrew Bruce first conceived that *Lactobacilli* content of vaginal microbiota acts as a barrier and prevents urogenital infections. The *Lactobacillus* adheres to the vaginal epithelium and enhances anti-pathogenicity controlling vaginal microflora including *Candida albicans* (Verdenelli et al., 2014).

In a study, the bacteriocin produced by all *Lactobacilli* isolates against *Candida* strains was analysed using the method agar antagonism, however no inhibitory action was found, whereas the radial method yielded considerable antipathogenic results (Maroof et al., 2012a). *L. plantarum* 319 was shown to have potent inhibitory properties. This existence of normal intestinal *L. plantarum*, in the vaginal habitat has been linked to a lower incidence of bacterial vaginosis in the past (Martín et al., 2012).

Role of symbiotic probiotics

The human gut commensal microbiota thrives by maintaining a symbiotic relationship with the host, hence, forming a complex population of microorganisms. It plays a very prominent role in maintaining a balanced homeostasis and also aids in the formation of adaptive immune system. The human digestive system can be very challenging for the bacteria, especially, if it is prescribed to be taken orally and is poorly formulated. There is a possibility that the probiotic bacteria will not reach the intended location say, small intestine in the viable state. In such circumstances, the human gut microbiota will not be altered by probiotics. Hence, probiotic multi strain bacteria, known as symbionts confer additional and effective health benefits. The symbiotic preparation, symbiotic drink, administered in multi organ failure (MOF) patients, for 7 days resulted in positive alterations to improve the early lactate levels and late fibrinogen/D-dimer levels also, mucosa colonization by *Candida* (Martín-Consuegra et al., 2014).

Moens et al., (2019) concluded that the probiotic supplement (Symprove™), containing *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus rhamnosus* and *Enterococcus faecium* has displayed to ameliorate clinical symptoms, severity scores in IBS and to reduce abdominal pain and remarkably weaken manifestation of irregularity in bowel movements and menorrhoea symptoms in diverticular disease. Symprove proved to exhibit high tolerance against gastric acids in in-vivo studies anti-pathogenicity against *Clostridium difficile* (Moens et al., 2019).

Fortification of probiotics in food products

Food fortification, in general, is defined as adding one or more components of food as to enhance its nutritional concentrations for beneficial outcomes (Chadare et al., 2019). Food fortification is an essential technique for the enhancement of nutrition in quality and quantity of food. It is very cost-efficient and, considering the crucially of food safety and quality, it aims at promoting public health and safety. Consumption of fortified foods with probiotics is progressively increasing presently due to nutrition deficiencies in certain societies and at certain ages as evaluated from the literature on various probiotics (Table 1). Food fortification normally prioritizes natural resources such as fruit, cereals, milk, vegetables, grains, and so on, in the best way to improve the nutritional value with minimal side effects (Gahruie et al., 2015). The natural health-promoting factors provide benefits to the customers, such as maintaining normal blood pressure, and sustaining balanced cardiovascular, immune and nervous systems (Chadare et al., 2019).

Weaning foods

Weaning foods are the first solid foods consumed by an infant. Weaning foods provide the baby with nutritional benefits to nurture the baby's growth (Bassey et al., 2013). A shift from whole breast milk feeding to weaning foods might alter the infant's digestion and cause minor digestive issues like diarrhea. Hence, probiotic infant formula might help maintain homeostasis. *Bifidobacterium lactis* (BB-12) and *Lactobacillus reuteri* are normally comprised in the probiotic infant's formula. Porridge contains lactic acid bacteria that synthesize feruloyl esterase, was isolated and characterised for their probiotic potential. The strain *Lactobacillus fermentum produces* galactosidase and glutamate decarboxylase enzymes, as well as its potential to lower cholesterol in vitro, serves as a marker for use in the implementation of functional foods (Kumar et al., 2021).

Confectionary

Chocolate is, in essence, prepared in a butter matrix composed of cocoa mass and sugar suspended in it. Chocolates have been considered to be fortified with probiotic strains since long time due to its popularity among kids and also among the elderly. This is considered nutritionally and economically advantageous. Probiotic chocolates have a significant effect on the nervous system and relieve stress (Faccinetto-Beltrán et al., 2021). Probiotic strains are fortified along with other nourishing foods like dry fruits to make nutrition bars in the market. They provide as immediate energy and nurture the individual, providing homeostasis (Barat and Ozcan, 2018). Fermented ice cream formulation has the notable capacity to be used as a functional product. The use of soy milk or coconut milk gives an advantage as the growth of bifidum bacteria is enriched and also the final product can be consumed by lactose-intolerant individuals acting as a nutritious alternative (Palka and Newerli-Guz., 2018).

Health mix

Kefir grains and kefir cultures are used to make fermented milk called kefir. Kefir helps the body with healing and stabilizing functions as it contains essential vitamins, minerals, and amino acids (Egea et al., 2022), which also comprises easily digestible complete proteins. Kefir provides a wide range of benefits if consumed. It has been claimed to be effective against a variety of diseases. Various intestinal disorders, difficulty in bowel moments etc, can be treated by regular consumption of kefir (Leite et al., 2013). Fruit juices are popular for their rich nutritional values, fruit juices are fortified with probiotic enzymes to cater numerous diseases and also maintain a healthy system. Probiotic strain influences the viability, i.e., a few strains of *L. plantarum*, *L. acidophilus* and *L. casei* can thrive in fruit matrices as they are capable of sustaining acidic environs (Egea et al., 2022). Microencapsulation may create a more suitable anaerobic habitat for vulnerable probiotic bacteria, as well as act as an enhanced physical barrier from the fruit juice's severe acidic conditions, hence, being more effective.

Bakery products

One of the prominent item, when it comes to bakery products is bread. Bread is prepared in different forms and shapes to facilitate eating and preparation of desired food items. A study was conducted aimed at obtaining symbiotic bread. Encapsulation of *L. casei* 431 and *Lactobacillus acidophilus* LA-5 combined with calcium alginate starch with Hi-maize resistance and chitosan coating was achieved by emulsion process (Maroof et al., 2012a). The bread loaves were baked by encapsulating probiotics and inoculating them into the bread dough. After baking, the viability of encapsulated probiotics was analysed; also, the sensory assessment was performed. The standard requirement for probiotic products was met by the symbiotic bread (Ardabili et al., 2016).

Yogurt

Yogurt products supplement its customers with high levels of nutrition. Probiotic strains such as *L. acidophilus*, *S. acidophiles* etc. are used for fortification with yogurt (Chandan, 2017), which acts as a substitute for lactose-intolerant patients. The lactase enzyme contained in the yogurt bacteria digests the lactose in the gut lumen and is released into the small intestine where these bacteria are lysed by bile acids (Chandan, 2017). This helps balance gut homeostasis and treats diarrhea, constipation, and so on. There is a wide range of choices available in probiotic yogurt ranging from plain, flavoured, and Greek yogurts which are again available according to the composition of fats and protein, e.g., low fat, high protein etc. Greek yogurt is very famous in consumers as it offers high protein value. There are various brands selling yogurt in India namely epigamic, mother diary, milk mist etc. (Chandan, 2017).

Probiotics and food safety

Studies have been conducted on the health effects of probiotics on a wide variety of diseases. However, limited information is available about the safety and gastrointestinal tolerance of probiotic-containing products for long-term consumption and disorders caused by certain probiotics, such as Lactobacilli opportunistic pathogens. In some cases, these products may be sold without legal oversight. Populations at risk have reported cases of bacteraemia and adverse effects of probiotics (Nazir et al., 2018). Until recently, there has not been enough research on the long-term effect of prolonged probiotic use, particularly in new-borns.

A Probiotic Safety Assessment study uses a number of methods: 1. Probiotic strain intrinsic properties study. 2. Molecular mechanism of drug action of probiotic strains based on their pharmacokinetics. 3. An analysis of the interactions between probiotics and their hosts (Saarela et al., 2000). An immunocompromised host can be evaluated using animal models to determine the safety of the new probiotic. Assays of probiotic bacteria's safety have now been conducted using gnotobiotic mice with immune deficiencies (Amara and Shibl, 2015a). It is expected that the results of the animal studies will be reflected in the human studies as well.

Four broad categories can be used to categorize the need for further research on probiotics. First, a better understanding of host and microbial agents that contribute to lactobacillus infections is needed. A second requirement is to prove the efficacy of probiotics in treating or preventing diseases and infections. When probiotic efficacy is proven, it is necessary to understand the mechanisms of action of these organisms. Furthermore, based on previous criteria, it is necessary to research and develop improved probiotics, including new probiotic species being used as medical therapists or therapeutic supplements, as well as vaccines made from probiotics.

Dimensions of probiotic safety include the following characteristics (Amara and Shibl, 2015a):

1. Probiotic strains for human consumption should preferably come from human origin.
2. It is imperative that they are isolated from the healthy gastrointestinal tracts of humans.
3. It is important that they do not have any history of pathogenicity.
4. Infectious endocarditis or gastrointestinal disorders should not be linked to them.
5. Decongestion and hydroxylation should not destroy bile salts in the small intestine.
6. It is not recommended that they have genes that are transferable to antibiotic resistance. And so on.

To assess the safety of the new probiotics, it is important to identify them (Amara and Shibl, 2015a). There are two main reasons for identifying in the clinical setting: diagnostics and epidemiology. Since physiological characteristics are involved (Amara and Shibl, 2015a), molecular studies should be conducted for identification. Food supplements containing probiotics are not subject to any legal standards around the world. Based on the final consumer, the target species, the environment, and workers' safety during production or application, safety aspects are considered to be in contact with microorganisms (Amara and Shibl, 2015a).

Future perspectives of probiotics

Research on probiotics is abundant, but most of them are based on high-throughput analyses of the gut microbiota that provide snapshots of its diversity, but these studies yield little insight into how this complex system works. It is likely that future research efforts will focus on generating and combining data from multiple omics platforms. Using these tools, we will be able to characterize the microbiome from the genetic make-up and transcription products (metagenomics/metatranscriptomics), to the proteins and metabolic products (metabolomics/metabonomics). An important future challenge of microbiome research will be to link these meta-omics datasets through a mechanistic model of the microbiome to form a systems-level framework (Rao et al., 2009). These multiple technologies, however, will allow us to gain a deeper understanding of the workings of this complex ecosystem and identify the functionally important microbial components. Having a better understanding of this will allow for the creation of tailored probiotic treatments tailored to specific indications and diagnoses, which will ultimately lead to robust RCTs for clinical benefit based on individual strains.

The development of new technologies and methods for probiotics offers exciting possibilities for research and application. Enhanced tools allowing real-time studies in humans and following a microbe as it consolidates into an existing microbiota, as well as systems that can quantify levels of health, will drive this field forward (Spacova et al., 2020). In light of research, future physical exams will include information about microbes present, how they interact with the host, and the effect of environmental factors (like drugs, nutrients) (Lebeer et al., 2011).

Conclusion

Scientific studies have demonstrated how important probiotic consumption is for enhancing the quality of life, and probiotic-containing foods and supplements are becoming more and more ubiquitous. The viability of probiotics in the product up until consumption and during delivery throughout the gastrointestinal tract, sensory qualities of the product, consumers' favourable perceptions of foods versus drugs, the economic perspective, and even the shelf life of the products are some of the many variables that affect a customer's consumption patterns. Today's markets provide a diverse selection of foods containing probiotic strains, and it has been discovered that consuming them in the recommended dosage offers a number of health advantages. In recent years, probiotics have been bioengineered using a variety of cutting-edge fermentation technologies. The product may be exposed to a variety of conditions during production and storage that impact its stability and viability. Temperature, water activity, oxygen concentration, pH, and other microbes are a few of these variables. A financial burden on manufacturers precludes the implementation of probiotics into many product categories that may impairs efficacy.

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