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Use of Biotechnology to Develop Probiotics as Potential Functional Food

INTRODUCTION

A healthy diet is essential for good health and nutrition. A healthy diet is one factor that can reduce risks associated with many chronic diseases, such as cancer, cardiovascular disease, and metabolic and genetic disorders like diabetes, metabolic syndrome, and non-alcoholic fatty liver disease (NAFLD). Eating various healthy foods and consuming less salt, fructose, saturated, and trans-fats may be important for susceptible individuals to maintain good health. A well-balanced diet can provide adequate energy and an array of nutrients that support virtually all vital processes of our body that allow us to remain healthy and active. Many nutrients are essential for growth and development and for continual repair of all tissues during normal cellular turnover and following tissue damage. A healthy diet contains vitamins, minerals, and protein, preferably a blend of monounsaturated and polyunsaturated fats and an array of complex carbohydrates known as dietary fiber.

The concept of functional food came into existence to improve the nutritional quality of the diet beyond basic nutrition, thereby potentially reducing risks associated with noncommunicable diseases. This overview discusses the potential value of functional foods, their categories, global regulations associated with functional foods, and potential health benefits based on the current clinical evidence in humans. This discussion also provides a cursory introduction to emerging personalized and precision nutrition opportunities with their foundation in the nutrigenomics discipline.

WHAT IS FUNCTIONAL FOOD

These foods typically contain potential bioactive compounds, which have known physiological effects and possible clinical implications in various metabolic systems in the human body. (Kurek et al., 2022) Functional foods can be natural, fortified, or enhanced (**Figure 1**) and may provide health benefits such as improving digestion, supporting immunological functions, or contributing to cardiovascular health. (Essa et al., 2023) Consumers increasingly seek foods that satisfy hunger and contribute positively to their well-being. Foods that contain specific probiotics, various prebiotics, omega-3 fatty acids(specifically EPA and DHA), and possibly a myriad of antioxidants. Functional foods include fortified foods like calcium-fortified orange juice (Ca-citrate-malate) or vitamin D-fortified milk. (Baker et al., 2022)

Probiotics are one of the most well-known and popular components of functional foods. Probiotics are live microorganisms (typically non-pathogenic bacteria or yeast) that, when consumed frequently and in adequate amounts, tend to confer health benefits to the host. Probiotics are commonly found in fermented dairy products like yogurt and kefir (fermented milk drink) and select dietary supplements. They can promote gut health by creating a less-hostile intestinal microbiota environment. Collective clinical evidence since the days of Elie Metchnikoff (1845-1916) suggested that some probiotic strains may improve digestion, support immune functions, especially those associated with mucosal cells, and potentially reduce gastrointestinal disorders, such as diarrhea and rota viral infections. (Damián et al., 2022; Mackowiak, 2013; O'Toole & Cooney, 2008)

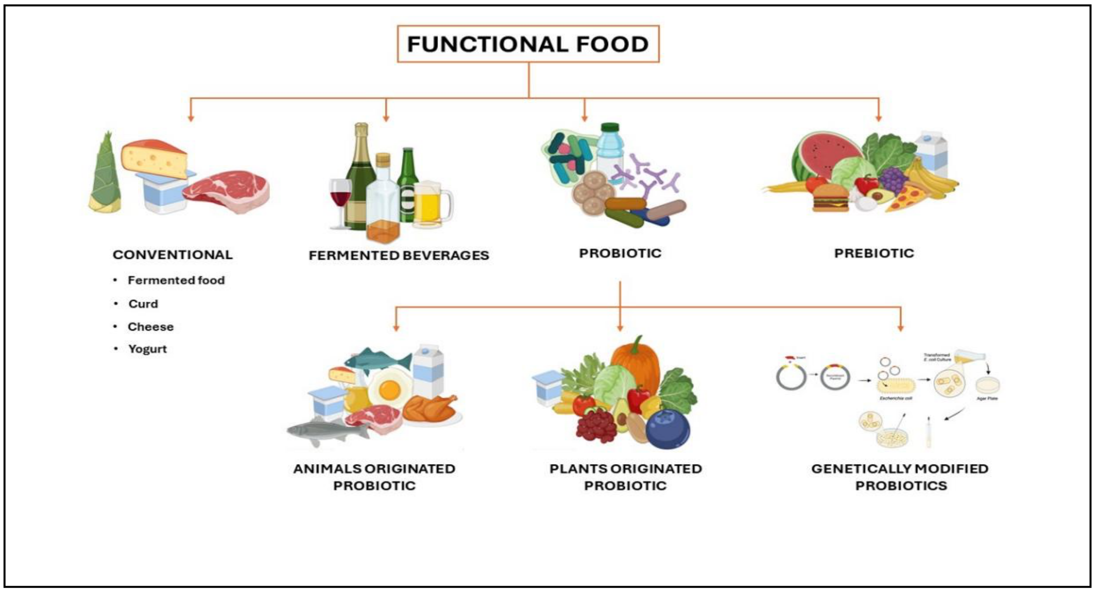


Figure 1: Functional foods and its classification

PROBIOTIC AS FUNCTIONAL FOOD

Probiotics are a prime example of functional food, recognized for their potential health benefits beyond basic nutrition. These live microorganisms, predominantly bacteria (such as lactobacilli and bifidobacteria) and some yeasts, are ingested in adequate quantities to positively affect the host's health.

The primary function of probiotics as functional food lies in their ability to support and modulate the gut microbiota, thereby triggering potential health in the gastrointestinal tract and possibly in other organ systems. This modulation is important for various aspects of health, including digestion, immune function, and even mental health. Probiotics achieve this by competing with harmful microorganisms for nutrients and adhesion sites in the gut, thereby reducing the colonization of pathogens and promoting a more healthful intestinal environment. (X. Wang et al., 2021; Zhou et al., 2024)

Contemporary research continues to examine and understand the mechanisms by which probiotics influence gut health. (Latif et al., 2023) The human gastrointestinal tract harbors a complex ecosystem of bacteria and other microorganisms, collectively known as the gut microbiota. Probiotics, such as strains of *Lactobacillus* and *Bifidobacterium*, typically contribute to this microbial community's diversity and stability. Research has shown that probiotics can modulate the composition of gut microbiota, enhance the barrier function of the intestinal lining, produce metabolites that support digestive processes, contribute to gut immune functions, and possibly reduce risks associated with a myriad of non-communicable diseases. (Kim et al., 2019)

Furthermore, probiotics can exert notable effects on immune function. Studies indicate that certain probiotic species, like *L. rhamnosus,* interact with immune cells in the gut-associated lymphoid tissue (GALT), influencing immune responses and inflammatory pathways. (Guo et al., 2023; Mazziotta et al., 2023) This modulation of immune activity suggests potential applications in managing inflammatory bowel diseases (IBD), allergies, and other immune-related disorders. Beyond gastrointestinal and immune health, emerging research explores the broader implications of probiotics on systemic health. For instance, there is growing interest in the role of probiotics in metabolic health, including their potential to regulate glucose metabolism, lipid profiles, and body weight. (Inchingolo et al., 2023; Wu & Chiou, 2021; Wypych et al., 2019)

PROBIOTICS FROM FERMENTED FOOD

Since probiotics may offer additional health advantages to their conventional nutritional role, they can be categorised as functional foods. To have a health benefit, a probiotic product must contain a sufficient amount of viable bacteria ($>10^8$ CFU/mL) and be administered orally at the right dosage each day. (Lin, 2003) Fermented foods may be logical sources of probiotics, exhibiting a "probiotic" effect through direct interactions between the host and ingested live microorganisms. (Shah et al., 2023)

The major microorganisms responsible for food fermentation are select non-pathogenic bacteria and food-grade yeast. (Chilton et al., 2015) On the international stage, these organisms must meet the WHO criteria of "live microorganisms` which, when administered in adequate amounts, confer a health benefit on the host" to be classified as probiotics. Studies showed that fermented foods and beverages contain large amounts of lactic acid bacteria (LAB). Major LAB genera, including *Alkalibacterium, Carnobacterium, Enterococcus, Lactobacillus, Lactococcus, Leuconostoc, Oenococcus, Pediococcus, Streptococcus, Tetragenococcus, Vagococcus,* and *Weissella,* of which select strains have been isolated from a variety of fermented foods and beverages worldwide. (Tamang et al., 2016) Fermented functional foods, particularly those based on probiotics, have had a resurgence in popularity since the early 2000s, primarily due to their potential to show health benefits and, importantly, demonstrated safety when used in foods for humans. (Kaur et al., 2022)

PROBIOTICS FROM PLANT SOURCES

Lactic acid bacteria (LAB) present in fermented plant-based foods are well-known probiotics that offer multiple health advantages when consumed. One of the safest and most effective ways to support the health advantages of these probiotics is by ingesting them with food or diet. Plants are one of the significant sources for producing fermented foods, which can be considered safe foods because it is made with precautions in which the possibility of the growth of viruses is very little. (Dimidi et al., 2019; Lye et al., 2017)

Cereals

Cereals and legumes are important sources of dietary fiber and oligosaccharides. These unique carbohydrates are non-digestible carbohydrates that may act as prebiotics and selectively stimulate the growth of the colon microflora. (Gupta & Abu-Ghannam, 2012) Moreover, the fermentation of cereals enhances protein digestibility and potentially allows microbial proteases to reduce some food allergens. (Küçükgöz & Trząskowska, 2022; Nkhata et al., 2018) Lactic acid fermentation of cereals has been used in Asian and African nations to produce drinks, gruels, and porridge. Fermentation enhances the flavor and may improve the nutritional quality of pulses, rice, and maize while lowering their anti-nutritional content, such as lignans, oxalate, and phytate. Soybean fermentation improves its digestibility while keeping its good-quality protein intact. (Elhalis et al., 2023)

a. Fruits and vegetables

Currently, the focus is shifting toward non-dairy probiotic foods from dairy foods. (El-Sohaimy & Hussain, 2023) Juices from fruits and vegetables can increase the viability of some probiotic strains by stimulating cells to synthesize nutrients from the source material, thus making the fermentation more favorable with growth substrates for some probiotic organisms. (Küçükgöz & Trząskowska, 2022) Fruit juice-based functional food products have an appealing taste profile to all age groups and can be fortified with probiotics and prebiotics. Beetroot juice fermented with *L. acidophilus NCDO1748* contained pigments, vitamins, and minerals. Fermentation of this juice with ABT-5 probiotics (*L. acidophilus* LA-5, *Bifidobacterium bifidum* BB-12, and *Streptococcus thermophilus*) enhanced the antioxidant capacity and improved zinc bioavailability. (El-Sohaimy & Hussain, 2023) The iron solubility of carrot juice increased 30-fold when fermented with LAB due to lactic acid production. Additionally, LAB improves the nutritional composition of fermented food by enhancing Vitamin B complex content. (Gupta & Abu-Ghannam, 2012)

b. Chocolate

Due to its content of minerals, proteins, carbs, flavonoids, and polyphenolic antioxidants, cocoa is considered a functional food. Studies indicate that since the lipid component of cocoa butter protects probiotics during storage and upper gastrointestinal tract passage, chocolate is a favorable substrate for probiotic bacteria. (Aspri et al., 2020a)

Probiotic bacteria *Lactobacillus casei* and *Lactobacillus paracasei* that have been freeze-dried and supplemented in dark chocolate may be stored for an entire year at 4-18°C. *Lactobacillus acidophilus NCFM* and *Bifidobacterium lactis HN019 (*10^8 *to* 10^9 *CFU/gm)* supplemented in chocolate remained viable throughout storage (15 ± 2°C) and transit through the upper gastrointestinal tract in humans. (Aspri et al., 2020b; Klindt-Toldam et al., 2016)

Table 1: Marketed functional foods from plant sources with probiotics

Product	**Preparation**	**Manufacturer**	**Probiotics present**	**Reference**
Grainfield Organic BE wholegrain Liquid Concentrate	Effervescent probiotic drink	Grainfields, Australia	*L. acidophilus,* *L. delbreukii,* *S. boulardii, and* *S. cerevisiae*	(Djorgbenoo et al., 2023)
KeVita Kombucha	Sparkling probiotic drink	KeVita, USA	*L.rhamnosus,* *L.plantarum,* *L.paracasei, Bacillus coagulans GBI-30 6086*	(Chaudhary, 2019)
Avenly velle	Oat based drink	Avenly Oy Ltd., Finland	*Lactobacillus and Bifidobacterium*	(Aspri et al., 2020b)
Gefilus	apricot/peach whey-based beverage	Valio, Finland	*Lactobacillus GG*	(Janasik, 2011)
Apple cider vinegar	Effervescent tables	Wellbeing nutrition, Maharashtra, India	*L. acidophilus,* *L. casei,* *L. rhamnosus,* *Bifidobacterium lactis,* *Bifidobacterium bifidum,* *S. thermophilus*	(wellbeingnutrition.com, n.d.)

PROBIOTICS FROM ANIMAL SOURCES

Probiotics isolated from animal resources like dairy products, animal meat, and honey can potentially benefit health. The marketed fermented foods, microbes isolated from these fermented foods, and their use are summarised below (**Table 2**).

a. Dairy products

b. Fermented dairy products are the optimal method for introducing probiotic bacteria into the human stomach and providing the right conditions for their growth. Previous studies showed that consumption of probiotic-containing yogurt, which is a blend of prebiotic (dietary fiber) and probiotic (Lactobacillus rhamnosus GG), helps reduce h putrefactive bacteria Clostridium difficile and Escherichia coli in the distal bowel. Thus, yogurt may help maintain a normal fecal microflora and may improve inflammatory bowel syndrome. (Kaur et al., 2022) Most marketed probiotic products are dairy-based, as given in Table 2.

c. Animal meat

Traditional fermented foods with fish, beef, pork, salted crab, and shellfish may contain LAB. (Sornplang & Piyadeatsoontorn, 2016) Numerous research studies have shown that probiotic Lactobacillus may be used for fermenting meat products. (Macedo et al., 2012; Y. Wang et al., 2022) These bacteria, however, can confer many health benefits. For example, *L. gasseri*, when used for fermentation, has shown improvement in the microbiological safety of fermented meat products. (Arihara et al., 1998) Starter culture *Lactobacillus rhamnosus FERM P-15120, Lactobacillus paracasei subsp. paracasei FERM P-15121*, and *Lactobacillus sakei* (10^7*CFU/gm)* inhibited *Staphylococcus aureus* growth and toxin generation in fermented meat products. (Sameshima et al., 1998)

E. faecium 1IS11 and *E. faecalis 4IS17* have been found in seafood and Thai fermented sea products and might be employed as starter cultures in fermented seafood. These bacteriocin-producing LAB strains may improve product safety and offer substantial health advantages. (Nanasombat, 2012) The most frequently detected LAB from various traditional Thai fermented foods with pork and fish are strains of *Pediococcus pentosaceous,* which can inhibit pathogenic bacteria such as *Pseudomonas aeruginosa, Salmonella typhimurium, Vibrio cholera, E. coli, Bacillus cereus,* and *Staphylococcus epidermidis*. (Siripornadulsil et al., n.d.) By enhancing the integrity of the intestinal mucosa and modifying the cytokines associated with inflammation and immunity, the two potential probiotic strains—*Lactobacillus salivarius ZLP-4b* from swine and *Bacillus velezensis JT3-1* from yak—improved the immune function of mice. Additionally, administering these probiotics to mice positively impacted their gut flora and enhanced their gastrointestinal health. This study provided evidence in favor of *B. velezensis JT3-1* and *L. salivarius ZLP-4b's* potential use as valuable probiotics. (Li et al., 2021)

d. Honey

Honey is considered a prebiotic due to the presence of non-digestible oligosaccharides and antioxidants such as polyphenol compounds (phenolic acids and flavonoids), vitamin C, vitamin E, enzymes (e.g., catalase, peroxidase) and trace elements like selenium (Se), zinc (Zn), iron (Fe), copper (Cu), phosphorus (P), and manganese (Mn) (Luchese et al., 2017) and was also recognized as a source of probiotics (predominantly yeast *Zygosaccharomyces rouxii*, *Schizosaccharomyces pombe*, and *Metschnikowia chrysoperlae* and LAB). (Abdel-Fattah et al., 2012) It has been reported that *Lactobacillus kunkeei*, isolated from the honey of giant honey bees, has antagonistic effects on yeast growth and its spoilage effects on honey. (Sornplang & Piyadeatsoontorn, 2016) Levan, a prebiotic formed by levansucrase, a type of fucosyltransferase produced by microbes, may elevate the contribution of select non-pathogens in the stomach, thereby possibly providing health benefits. Levansucrase was found to be produced by Achromobacter sp. (10A), *B. paralicheniformis* (2M), *B. subtilis* (9A), and *B. paranthas* (13M) isolated from honey. (Abdelsamad et al., 2022)

Table 2: Marketed functional foods from animal sources with probiotics

Product	**Preparation**	**Manufacturer**	**Probiotics present**	**Reference**
Actimel	cultured yogurt shot	Danone, Spain	*L.casei Immunitass/L.casei Defensi*	(*Actimel*, 2023)

Gefilus	low-lactose yoghurt-type product	Valio, Finland	*Lactobacillus* GG	(Janasik, 2011)
Hellus	Yogurt and yogurt-based drinks	*Estiko doybag, Estonia*	*L. acidophilus LA-5,* *Bifidobacterium BB-12,* *L. casei, and Lactobacillus fermentum ME-3*	(*Hellus*, n.d.)
Yakult	Fermented milk drink	Yakult Honsha, Japan	*Lactobacillus casei Shirota (LcS)*	(O'Connel et al., 2010)
Nutrifit	Probiotic milk	Mother Dairy, India	*L. acidophilus* and *Bifidobacterium animalis subsp. lactis*	(*Product | Motherdairy.Com*, n.d.)

GENETICALLY MODIFIED PROBIOTICS

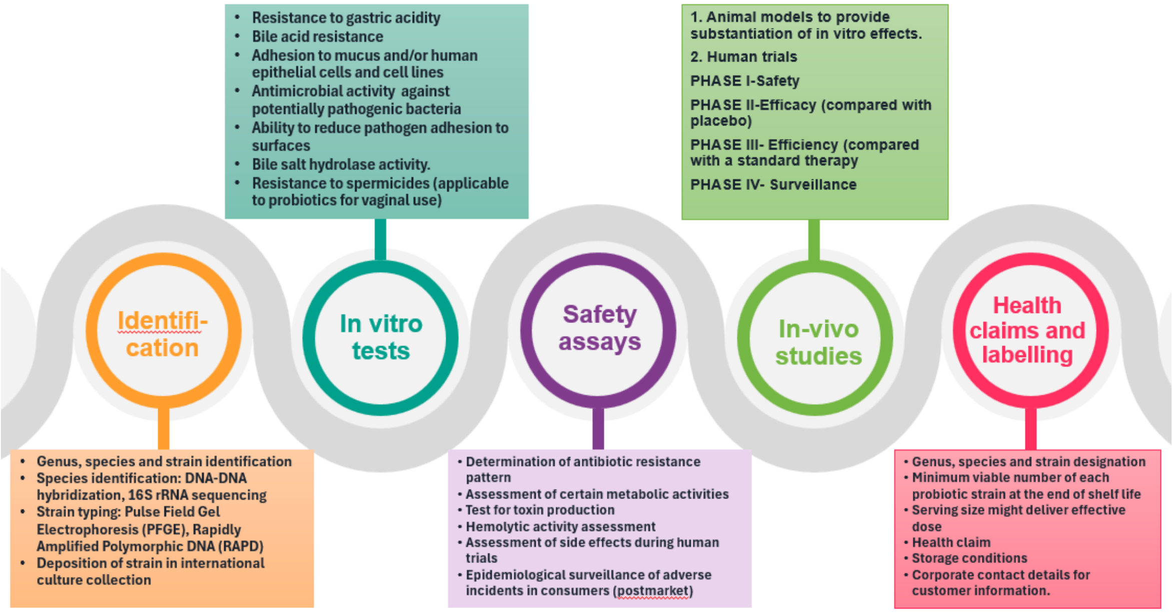
In recent years, the intersection of genetic engineering and probiotics has led to the emergence of genetically modified probiotics, heralding a new era in functional foods, health research, and food safety. These engineered microorganisms, typically derived from potentially non-pathogenic bacteria like lactobacilli or bifidobacteria, are equipped with enhanced functionalities to improve human health through various mechanisms. (Zuo et al., 2020) Cutting-edge biotechnology research is underway to explore the vast potential of genetic engineering and probiotics.

Recent research focuses on enhancing probiotic properties such as gut survivability and producing therapeutic molecules (like vitamins or antimicrobial peptides). For instance, ongoing trials investigate the efficacy of genetic engineering probiotics in controlling gastrointestinal disorders, modulating immune responses, and even preventing chronic diseases like diabetes and obesity.(Hitch et al., 2022) One notable study involves engineering a probiotic strain to produce specific enzymes that aid in digesting gluten, potentially relieving individuals with gluten intolerance. (Zuo et al., 2020) Another study explored genetic engineering and probiotics to deliver anti-inflammatory agents directly to the gut mucosa, promising breakthroughs in treating inflammatory bowel diseases. (Pesce et al., 2022) Genetically modified probiotics are poised to revolutionize the functional food industry by offering specific health benefits beyond conventional probiotics.

Probiotics, considered functional foods in many countries, may improve digestive health and deliver potential bioactive molecules that can positively impact overall well-being. This includes synthesizing essential nutrients, enhancing the bio availability of nutrients from ingested food, and fostering an improved gut microbiome, which is increasingly recognized as crucial for immune function. (Syngai et al., 2016).

GUIDELINES FOR EVALUATING PROBIOTICS

Guidelines for evaluating probiotics in food that could lead to the substantiation of health claims were developed in 2002 by the **Joint Food and Agriculture Organisation (FAO) of the United Nations/World Health Organisation (WHO).** Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics has standardized the requirements (**Figure 2**) to make health claims of probiotic agents. (*Joint FAO/WHO Expert Consultation On*, 2001) However, several countries made their guideline and regulations for the health claims of probiotics.



- Resistance to gastric acidity
- Bile acid resistance
- Adhesion to mucus and/or human epithelial cells and cell lines
- Antimicrobial activity against potentially pathogenic bacteria
- Ability to reduce pathogen adhesion to surfaces
- Bile salt hydrolase activity.
- Resistance to spermicides (applicable to probiotics for vaginal use)

1. Animal models to provide substantiation of in vitro effects.
2. Human trials

PHASE I-Safety

PHASE II-Efficacy (compared with placebo)

PHASE III- Efficiency (compared with a standard therapy

PHASE IV- Surveillance

- Genus, species and strain identification
- Species identification: DNA-DNA hybridization, 16S rRNA sequencing
- Strain typing: Pulse Field Gel Electrophoresis (PFGE), Rapidly Amplified Polymorphic DNA (RAPD)
- Deposition of strain in international culture collection

- Determination of antibiotic resistance pattern
- Assessment of certain metabolic activities
- Test for toxin production
- Hemolytic activity assessment
- Assessment of side effects during human trials
- Epidemiological surveillance of adverse incidents in consumers (postmarket)

- Genus, species and strain designation
- Minimum viable number of each probiotic strain at the end of shelf life
- Serving size might deliver effective dose
- Health claim
- Storage conditions
- Corporate contact details for customer information.

Figure 2: Guidelines for the evaluation of probiotics for food use as per Joint FAO/WHO working group report, 2002

SAFETY ASSESSMENT FOR CURRENT AND FUTURE PROBIOTIC STRAINS

The safety assessment for current and future probiotic strains is crucial for public health. Probiotics, live microbes that confer health benefits when administered in adequate amounts, rely heavily on rigorous safety evaluations due to their direct human consumption. Current safety assessment practices involve a multi-faceted approach, including comprehensive microbiological, genetic, and toxicological analyses. (Amalaradjou & Bhunia, 2012; Pradhan et al., 2020; Sanders et al., 2010) Initially, strains are screened for pathogenicity and virulence factors to confirm that they do not pose any risk of infection or adverse effects. This includes assessing the strain's ability to adhere to human tissues, antibiotic resistance, and genetic stability. (Mathipa & Thantsha, 2017; Sanders et al., 2010) Additionally, detailed studies are conducted to evaluate any potential for horizontal gene transfer, which could unintentionally introduce harmful traits to other microorganisms. (Lensch et al., 2024; Lerner et al., 2019)

With the advancement of biotechnology tools, future probiotic strains require refined and precise safety assessment techniques. Innovations such as genome sequencing and bioinformatics tools will enhance our ability to predict and monitor these strains' genetic stability and safety profiles. Advanced *in silico* models and predictive analytics can identify potential risks before they manifest, allowing for proactive measures. (Rouanet et al., 2020) Furthermore, new safety guidelines and frameworks are being developed to address the unique challenges posed by genetically engineered probiotics, ensuring they are both effective and safe for long-term consumption. As per the FDA guidelines, future probiotic strains will also undergo long-term clinical trials to monitor their safety and efficacy in diverse populations, providing real-world evidence of their benefits and potential risks. (*Early Clinical Trials with Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information; Guidance for Industry*, n.d.) Overall, the evolution of safety assessment methodologies using biotechnology tools will play a pivotal role in developing safe and effective probiotics to promote human health.

BIOTECHNOLOGY FOR FUTURE PROBIOTIC DEVELOPMENT

Biotechnology holds significant promise for advancing probiotic development in the future through a range of innovative applications. One of the key areas where biotechnology excels is strain selection and enhancement. Advances in genomic sequencing and bioinformatics allow researchers to identify and characterize microbial strains with specific probiotic properties, such as survival in the gastrointestinal tract, adhering to gut epithelial cells, or producing beneficial bioactive typically isolated from nature. These insights into the genetic makeup of probiotics enable genetic modifications using tools from synthetic biology, where genes responsible for desired traits can be inserted, deleted, or modified to enhance probiotic functionality. For instance, probiotic strains can be engineered to express enzymes that metabolize dietary components or pharmaceuticals, potentially improving nutrient absorption in the gut. (Romero-Luna et al., 2021) Moreover, biotechnology facilitates the development of advanced delivery systems that protect probiotics from harsh gastric conditions and ensure their controlled release in the intestine. Techniques such as micro-encapsulation, nanoencapsulation, or inclusion in polymeric matrices provide protective barriers that increase probiotic viability during storage and transit through the digestive tract, enhancing their therapeutic effectiveness. (Sbehat et al., 2022)

Developed probiotic formulations can also be tailored to release probiotics in response to specific environmental cues in the gut, optimizing their bioavailability and interaction with the host microbiota regardless of its critical sites in the host, particularly humans. In addition to strain modification and delivery optimization, biotechnology plays a crucial role in ensuring the safety and efficacy of probiotics. Through comprehensive safety assessments and clinical trials, biotechnologists can evaluate the health impacts of probiotics on diverse populations, identify potential adverse effects, and refine the formulations for maximum benefit. Among safety assessments, probiotics can be tested to determine antibiotic resistance patterns, toxin production, and hemolytic activity. (Roe et al., 2022) Furthermore, biotechnological tools enable researchers to monitor probiotic-host interactions at a molecular level using omics approaches (genomics, proteomics, metabolomics), providing insights into how probiotics influence gut microbiota composition and host immune responses. This mechanistic understanding supports the development of probiotics tailored to specific health conditions or personalized microbiome profiles, advancing the concept of precision probiotics medicine tailored to individual needs. (Kwoji et al., 2023)

CONCLUSION

Functional foods represent a fusion of nutrition and health science, aiming to optimize well-being and prevent disease through dietary choices. As research continues to uncover new bioactive compounds and their effects on the body, the range of functional foods available to consumers will likely expand, offering more personalized dietary options tailored to specific health needs. (Essa et al., 2023)

Integrating biotechnological innovations with ongoing research in microbiome science promises to unlock new frontiers in probiotic development. These advancements expand the diversity and functionality of available probiotic strains and pave the way for novel therapeutic applications in immune modulation, metabolic health, and disease prevention. By harnessing the power of biotechnology, future probiotics can revolutionize healthcare by promoting gut health and the health status of other tissues, enhancing nutrient utilization, and mitigating gastrointestinal disorders, thereby improving overall well-being and quality of life for individuals worldwide. Moreover, genetic engineering and probiotics hold promise in personalized nutrition, where strains can be tailored to address specific health needs based on an individual's genetic and microbiological profile. This personalized approach of probiotics may lead to more effective treatments and preventive measures against a spectrum of health conditions.

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This SIB was independently reviewed and approved by the IUFoST Scientific Council.

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