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Applications of Probiotics as a Functional Ingredient in Food and Gut Health

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Abstract Probiotics are live microbes which serve as excellent functional food ingredients, to improve human health. They provide essential metabolites with dietary and therapeutic characteristics which confers numerous health benefits. They ensure a proper maintenance of the gut health through complex interactions across the gut-brain axis. The probiotics enter into the body through food. Probiotics can exist naturally or be infused in food. Food products containing probiotics are viable modes for a healthy gut. Understanding the mechanism of action of the probiotic strains and their interaction with the gut microflora is absolutely necessary. This review elaborates on the applications of probiotics in food .It also describes the possible mechanism of action and its clinical significance.

Keywords: *probiotics, food formulations, gastroenteritis, clinical implications*

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1. Introduction

Probiotics are a group of health promoting functional foods with an emerging commercial interest [1]. They are incorporated as living microorganisms in food to enhance its nutritional content and protect the gut. Clinically, probiotics improve the intestinal microbiome contributing towards the immune potency of the host. They also counteract the pathogenic activity in the gut. Multiple mechanisms of actions are reported, including production of antimicrobial agents, competition for space or nutrients and immunomodulation [2]. FAO/WHO define probiotics as "live microbial food supplements or components of bacteria which when taken up in adequate amounts, confers a health benefit to the host" [3]. Probiotics have emerged as medical therapies for gastrointestinal and non-gastrointestinal diseases such as diarrhea, constipation inflammatory bowel disease, irritable bowel syndrome, asthma, atopic dermatitis, peptic ulcer, colon cancer, coronary heart disease and urinary tract infections [1].Evidences have supported the consumption of fermented milk especially yogurt, due to its nutritional properties in maintenance of gut health, due to its probiotic content.

This article summarizes the applications of probiotics as a functional ingredient in food, mechanism of action and its clinical significance in gut health.

2. Application of Probiotics in Food Products

The global market of functional foods including probiotics is growing exponentially. The emerging demand of consumers is incentivizing world markets to manufacture dairy and non-dairy products containing probiotic bacteria. Figure 1 and Table 1 show some dairy and non-dairy probiotic products available in world markets. Therefore, putting probiotic bacteria into products is an important issue with industrial and commercial consequences. This led to a shift in industries, focusing on the probiotics based food products, to fulfill consumer demand. Probiotic cells via food products are available in three different types for direct or indirect human consumption such as fermented or non-fermented form, dried or deep-frozen form for industrial or home uses and drugs in powder, capsule or tablet forms [4]. Some of the commercially available probiotic strains are listed in Table 2 [5,6].

2.1. Dairy Based Products

Dairy products serve as a good vehicle for probiotics. Some examples of dairy based products are; butter milk, normal milk, flavored liquid milk, fermented milks, dairy fermented beverage, milk powder, Whey-protein-based drinks, yogurt drink, ice cream, sour cream, yogurt, cheese,

frozen dairy desserts and baby foods are the most popular vehicles for probiotics [7,8]. Dairy foods are ideal for performing the delivery function because of their inherent environment stabilizing properties that promote the growth of probiotic bacteria, which can then be stored at refrigerated temperatures. In addition to probiotic strains, several useful compounds such as tryptone, yeast extracts, certain amino acids, nucleotide precursors, whey protein concentrate (WPC), fructooligosaccahrides (FOS) and caseinomacro peptides (CMP) are used in dairy products to enhance the growth and viability of the strains. Citrus fiber in these products enhances bacterial growth and survival of probiotic bacteria, whereas soy germ powder releases bioactive compound that protect probiotic strains from bile salt toxicity [9,10]. Recently, probiotic cheese, marketed in various forms (fresh, semi-hard and hard cheese), which are highly nutritious and have high energy and fat content, has shown a high rate of survival of probiotics at the end of its shelf life [11,12]. The utilization of probiotics in the cheese faces some challenges, such as low moisture content, the presence of salt, the development of acid and the influence on flavor during maturation; starter cultures can compete for nutrients and redox potential. Nevertheless, it acts as a potential carrier of probiotics [11]. Cheddar cheese, Feta cheese, Canestrato pugliese hard Cheese, Cottage cheese, white-brined cheese, Minas Fresco cheese, Minas fresh cheese, Argentine Fresco cheese, Iranian white-brined Cheese, Turkish Beyaz cheese are some of probiotic cheese products available on the world market [12,13]. That having been said, yoghurts with high fat content are the most common vehicles for probiotics among dairy products. Probiotic yoghurt contains cultures of *L. acidophilus*, *L. delbrueckii* subsp. *Bulgaricus* and *Streptococcus salivarius* subsp. *thermophilus* bacteria [14]. Some examples of Probiotic yoghurt widely marketed for human consumption are Corn milk yogurt [15]; Stirred fruit yogurts [13], Mango soy fortified probiotic yogurt, Iranian yogurt drink (Doogh) and Traditional Greek yogurt [12,16]. Other dairy-based products, used to carry probiotics are ice cream and frozen dairy desserts composed of milk proteins, fat and lactose as well as other compounds that are required for bacterial growth. These products are infused with certain commercialized probiotic strains such as *L. acidophilus* La-5 and *B. animaliss* sp. lactis Bb-12, *L. acidophilus* and *B. lactis*. Probiotic chocolate mousse is a good medium for *L. paracasei* subsp. *paracasei* LBC 82 which can exist by itself or together with inulin.

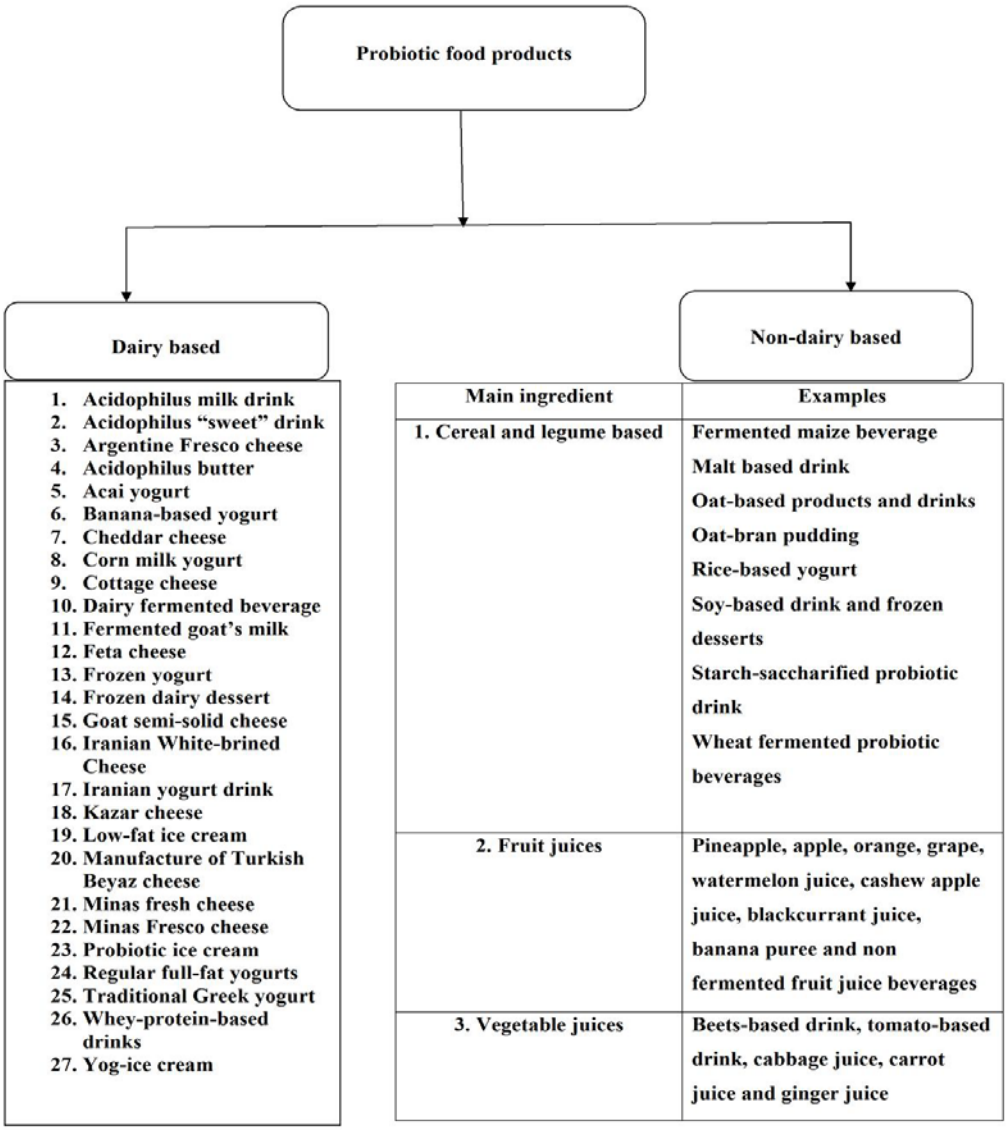

Figure 1. Probiotic products (dairy and non-dairy products) available in the world market [4,7,8]

Table 1. Probiotic products available in different countries [4,7,8]

Country	Probiotic products
Australia	F & N' s aLIVE fruit chunk yoghurt; Yo-plus digestive yoghurt; Wallaby organic yoghurt; Bio-life probiotic yogurt; Vaalia probiotic yogurt; Ombar probiotic chocolate
Brazil	Chamyto probiotic drink ,Nestle; Actimel *L. casei* Defensis; Danito *L. casei* Danone, Sofyl yakult
Canada	Bio Best Plant Steroid probiotic yoghurt; kraft LiveActive cheddar cheese and Chocolate Raspberry Bars; liberte yoghurt, Olympic Natural No Fat Probiotic yoghurt
Denmark	Klover drinkable yoghurt; Danimal Lactobacillus GG; Probio Arla cultura
Europe	Life way kefir; Culturelle probiotic Infant Formula; France Bravo Friscus; Yoplait yogurt; Danone Activia; Actimel probiotic yoghurt
Finland	Valio Gefilus® and Valio Kidius Gefilus® and Evolus® Milk drink and yoghurt (LGG); Yosa yoghurt oat product
France	b-Activ LGG Dukat Yoghurt and drink
Germany	Probiotic Vitality yoghurt; Soyoghurt
India	Nesvita' Probiotic yoghurt (Nestle, India); Probiotic Ice-cream 'Amul Prolife' (Amul Dairy, India); 'b-Activ' Probiotic Dahi (Mother Dairy); Probiotic curd Heritage Foods(India)ltd
Italy	Ganeden BC^{30}® probiotic low fat yogurt; Probiotic dairy drinks Latteria Sociale Merano; Danacol fermented dairy beverage, Yolive frozen yoghurt
Japan	Yakult; Meiji Bulgaria yoghurt and yoghurt drinks; Morinaga Bifidus yoghurt; Calpis Ameal S120
New Zealand	Biofarm Acidophilus Yoghurt
Spain	Kaiku Vita; Bio Herbal bifidus active green tea yogurt danone
Sweden	Provita yogurt; Yogenfruz yoghurt, biogia products; LiveActive probiotic products
USA	Activia Creamy yoghurt; Danone GYoPlus; Bluebunny-Sedona yoghurt Ice-cream; Chocolate Sweet Scoops-frozen yoghurt; Yovation-pierra's probiotic ice cream
UK	Vita-Yo creamy probiotic yoghurt; YeoValley Biolive yoghurt ; YeoValley natural fat free yoghurt; Unilever's flora proactive cholesterol

Table 2. Commercially available probiotic strains [5,6]

Probiotic strains	Source
*Lb. acidophilus*74-2; *Lb.acidophilus* 145; *Lb. bulgaricus* 1261; *Lb. plantarum*L2-1; *Lb. rhamnosus* 1091; *Lb. rhamnosus* LC-705; *Bifidobacterium* species 420; *Streptococcus thermophilus* F2	Danlac (Canada)
Lb. fermentum RC-14	Urex Biotech (Canada)
Lb. casei 01; *Lb. casei* CRL431	Chr. Hansen (Denmark)
B. lactis Bb-12 *Lb. acidophilus* LA5 *Lb. paracasei* CRL 431 *Lb. fermentum* VRI003 (PCC) *Lb. reuteri* RC-14 , *Lb. rhamnosus* GR-1 *Lb. paracasei* F19	Chr. Hansen (Milwaukee WI)
Lb. acidophilus LA-1	Chr. Hansen, Inc. (USA)
Lb. acidophilus DDS-1	Nebraska Cultures, Inc. (USA)
Lb. crispatus CTV05	Gynelogix, Colorado (USA)
Lb. acidophilus NCFM®	Rhodia, Inc. (USA)
Lb. rhamnosus ATCC 7469	MicroBioLogics (MBL) (USA)
Lb. casei var. *rhamnosus* (Lactophilus)	Laboratoires Lyocentre (France)
Lb. caseiImunitass (Defensis, DN114, DN-014001)	Danone (France)
Lb. casei Shirota (YIT 0918) ; *Bifidobacterium breve* strain Yakult	Yakult (Japan)
*Lactobacillus acidophilus*CK120; *Lb. helveticus* CK60	Matsutani Chemical Product (Japan)
Bifidobacterium longum BB536	Morinaga Milk Industry Co., Ltd. (Japan)
Lb. acidophilus SBT-2062 ; *Bifidobacterium longum* SBT-2928	Snow Brand Milk Products Co., Ltd. (Japan)
*Lactobacillus acidophilus*CK120; *Lb. helveticus* CK60	Matsutani Chemical Product (Japan)
Lb. paracasei F19	Arla Dairy (Sweden)
Lb. plantarum 299V ; *Lb. rhamnosus* 271	Probi AB (Sweden)
Lactococcus. lactis L1A	Essum AB (Sweden)
Lb. reuteri ATCC 55730 (" Protectis ")	Biogaia (Sweden)
Lb. salivarius UCC118	University College (Ireland)
Lb. johnsonii Lj-1(NCC533*; Lb. acidophilus* La-1)	Nestle (Switzerland)

2.1.1. Non-dairy Based Products

Non-diary based products are classified as fermented and non- fermented products. A limitation in the use of dairy products to deliver probiotics is due to the presence of allergens. This led to the development of other food matrices especially non-dairy probiotic products. Cereals are good nutrient substrates for the growth of probiotic strains. The fermentation of cereals in presence of probiotic microorganisms could be beneficial for health due to their availability of the vitamin B, the decrease of non-digestible carbohydrates and the improvement of the quality and level of lysine [17]. Boza is a fermented product based on maize, wheat and other cereals containing several lactic acid bacteria with probiotic characteristics. Malt medium supports the growth of all examined strains (*L. plantarum*, *L. fermentum*, *L. acidophilus* and *L. reuteri*) better than barley and wheat media due to its chemical composition. Malt, wheat and barley extracts exhibit a

significant protective effect on the viability of above probiotic strains under acidic conditions [12]. Oat, an important cereal contains high levels of β-glucans and provides the right nutrient for the growth of *L. reuteri*, *L. acidophilus* and *B. bifidum [18]*. Probiotic cassava-flour product, Starch-saccharified probiotic drink, Meat based products and Dry-fermented sausages are also the name of some other non-dairy probiotic foods [19,20]. Fruits are rich in several nutrients such as minerals, vitamins, dietary fibers, antioxidants and do not contain any allergens. This advantage of fruits has encouraged several food industries to manufacture healthy probiotic fruit juices like pineapple, apple, orange, grape, watermelon juice, cranberry, cashewapple juice, blackcurrant juice and many more. *L. plantarum*, *L. delbruekii*, *L. casei*, *L. paracasei* and *L. acidophilus* are main optimal probiotic bacteria widely used for the production of probiotic juices [21]. Probiotic beverage production from cashew apple juice fermented with *Lactobacillus casei* NRRL B-442 whereas watermelon juice is produced using four strains of Lactobacilli namely *Lactobacillus casei*, *L. acidophillus*, *L. fermentum* and *L. plantarum*. Probiotic tomato juice is produced by inoculating lactic acid bacteria namely *Latobacillus acidophilus* LA39, *Lactobacillus plantarum* C3, *Lactobacillus casei* A4 and *Lactobacillus delbrueckii* D7. Probiotic strains are able to grow without nutrient supplementation and pH adjustment in the tomato juice [22,23]. Similarly, probiotic bacteria such as *L. plantarum*, *L. casei* and *L. delbrueckii* grow in both beet and cabbage juices too [23,24]. Some examples of dairy and non dairy-based probiotic products along with their probiotic strains are listed in Table 3 and Table 4 [7,8,25,26,27].

Table 3. Probiotic products along with their respective strains

Probiotic products	Strains
Activia	*B. animalis* DN173010
Actimel	*L. casei defensis*
Attune nutrition bars	*L. acidophilus* NCFM, *L.casei Lc-11* and *B. lactis* HN019
Align capsules	*B. infantis* 35624
Adult Formula CP-1	*L. Acidophilus, L. Rhamnosus, L. Plantarum, B. Lactis and B. Bifidum*
Batavito, Bob Sponja	*L. casei*
Biofibras	*B. animalis* subsp. *lactis L. acidophilus*
Batavito, Bob Sponja	*L. casei*
Biofibras	*B. animalissubsp.lactis* *L. acidophilus*
Boza	*Lb. plantarum, Lb. acidophilus, Lb. fermentum, Lb. coprophilu s, Leuconostoc reffinolactis, Leuconostoc mesenteroides, Lb.brevis, Saccharomyce scerevisiae, Candida tropicalis, Candida glabrata, Geotrichum penicillatum,Geotrichum candidum*
Bio-K+ probiotic capsules	*L. acidophilus* CL1285 and *L. casei* LBC804
Bushera	*Lactobacillus, Lactococcus,Leuconostoc, Enterococcus and Streptococcus. Lb. brevis*
Chamyto	*L. johnsonii, L. helveticus*
Culturelle capsules	*L. rhamnosusGG*
Danito	*L. acidophilus, L. casei, B. animalis* subsp.*lactis*
DanActive cultured milk	*S. thermophilus* and *L. Bulgaricus* in addition to *L. casei* DN-114 001
Gefilus juice	*L. RhamnosusGG*
Good Belly fruit drink	*L. plantarum299v*
Injera	*L. plantarum, Aspergillus* spp., *Penicillium spp., Rhodotorula* spp., *Candida spp.*
Kishk, kushuk,	*L. casei, L. plantarum, L. brevis, B. subtilis,*
Kisra	*L. plantarum, L. brevis*
Kefir drinks	*L. acidophilus, Lb. Brevis, L. casei, Lb.casei* subsp. *Rhamnosus, Lb. casei* subsp. *Pseudoplantarum, Lb.paracasei* subsp. *Paracasei, Lb.delbrueckii* subsp. *Lactis*
Lective	*B. animalis* subsp.*lactis*
Mahewu	*Lactococcus lactis* subsp. *lactis*
Nesvita	*B. animalis* subsp.*lactis*
OWP probiotics	*B. longum, B. brevis, B.infantis, L. plantarum, L.rhamnosus, L. acidophilus*
Sofyl	*L. casei shirota*
Togwa	*Lactobacillus, Streptococcus, Lb.Plantarum* A6
VSL#3 saket	*B. breve, B. infantis, B.longum, L. acidophilus, L.bulgaricus, L. casei, L.plantarum and S. thermophilus*
Yakult cultured milk	*L. casei Shirota*
Yo-Plus yogurt	*B. animalis subsp lactis* Bb-12; *S. thermophilus* and *L. bulgaricus*

Table 4. Non-Dairy formulations containing Probiotic strains

Foods	Examples	Probiotic strains
Cereal based	Wheat, Malt, maize, oat	*L. plantarum, L. fermentum, L. acidophilu sand L. reuteri*
Fruit juices	Pineapple, apple, orange, grape, watermelon juice, cashew apple juice and blackcurrant juice	*L. plantarum, L. delbruekii, L. casei, L. paracasei. L. fermentum, L. plantarum* and *L. acidophilus*
Vegetable juices	Beets-based drink, tomato-based drink, cabbage juice, carrot juice and banana puree	*Latobacillus acidophilus* LA39,*Lactobacillus plantarum*C3, *Lactobacillus casei* A4, *Lactobacillus delbrueckii* D7 and *Lactobacillus plantarum* 299v (LP299V®)

2.1.2. Encapsulated, Spore Germinated and Genetically Engineered Probiotic Products

Micro-encapsulation serves as an important means for the survival of the probiotic cells. The encapsulated cells are introduced into different food matrices e.g. Yoghurt, cheddar cheese, ice-cream, yogurt-covered raisins, nutrient bars, chocolate bars, cocoa butter, biscuits, vegetable and frozen cranberry juice [28,29]. The encapsulated probiotic cells available in a tablet/capsule form are Forever Active Probiotic, Probiotic 7, Multi-probiotic or in the form of a powder e.g. Pure Baby Probiotic, Cernivet LBC ME10, Geneflora™ and ThreeLac™. Additionally, Probio-Tec capsules, encapsulated probiotic orange juice termed "Dawn", chocolate bar named "Attune", Innovance Probiotiques and an encapsulated yoghurt is available in the market under the brand name Doctor-Capsule. Syntol AMD and Ganeden BC^{30} deliver probiotic spores rather than living bacteria is known to be spore-germinated probiotics prepared by using spore germination technology. Though the use of these genetically engineered products has been quite limited but certain genetically modified probiotics strains have been used to increase physiological or immunological properties within the organism which can be useful in mucosal delivery system or in development of vaccine vector [30]. The use of any engineered strains has to be rigorously assessed for its safety before human use.

2.2. Mechanisms of Action of Probiotic Strains

About 10 trillion microbes of 500-1000 different microbial species colonize in the GI tract and remain in a complex equilibrium. These include *Bacteroides, Lactobacillus, Clostridium, Fusobacterium, Bifidobacterium, Eubacterium, Peptococcus, Peptostreptococcus, Escherichia and Veillonella*. Colonization of these microbes in the human gut start at birth and eventually get exposed to foreign microbial population and antigens derived from digested foods. Therefore, the intestine acts as an interface between the host and exogenous agents such as, pathogenic bacteria, viruses, allergens. The intestinal mucosa may play a central role in host microbiota-pathogen interactions [31].

Gut microbiota influences human health through an impact on the gut defense barrier, immune function, and nutrient utilization and potentially by direct signaling with the gastrointestinal epithelium [32]. The interaction between the host microbata and exogenous agents may disturb or alter the normal microbial balance or their activity in GIT. Alteration of such microflora is implicated in the pathogenesis of various diseases. Enteric diseases are caused by several pathogens like *Escherichia coli, Salmonella* spp., *Shigella* along with various other food borne pathogenic strains such as *Bacillus cereus, Staphylococcus aureus, Listeria monocytogenes* and *Vibrio cholera [33]*. They may cause infections in two steps. During the first step of the infection process, the pathogens may attach themselves to the surfaces of intestinal epithelial cell through certain adhesive receptors like glycoproteins and glycolipids and later on, in second step they cause direct cytotoxic injury, intracellular migration, and finally disrupt the epithelial tight junctions that leads to mucosal infection [34].

Probiotics promote the GIT homeostasis and stimulate the growth of indigenous beneficial gut microbata by inhibiting the growth of pathogenic or opportunistic pathogenic microbes. Therefore, probiotics are recommended as alternative bio therapeutic agents for intestinal pathogenic infections. These may act via several mechanisms such as, production of antimicrobial compounds, competition for nutrient substrates, competitive exclusion, enhancement of intestinal barrier function and immunomodulation [1,35,36,37].

2.2.1. Production of Antimicrobial Substances

LAB produces antimicrobial substances, such as organic acids, fatty free acids, ammonia, hydrogen peroxide and bio surfactant. It also produces a low-molecular-weight antibacterial peptide- bacteriocins that inhibits both gram positive and gram-negative enteric pathogens [38,39]. For example, probiotic *L. rhamnosus* GG inhibits the growth of pathogenic *Salmonella enterica* by producing lactic acid and other secreted antimicrobial molecules [40]. In order to exert a strong effect on a pathogen in vivo, the probiotic-derived antimicrobial compounds are produced in the right location in the intestinal tract at higher levels. Organic acids produced by LAB or any probiotic strains account for the alteration of bacterial flora due to the acidification of the colon by nutrient fermentation.

Homo-fermentative LAB strains produce lactic acid whereas hetero-fermentative strains produce the short chain fatty acids viz. acetic and propionic acids in addition to lactic acid by their respective metabolic pathways. Organic acids produced by certain probiotic strains lower the external pH that causes acidification of the cell cytoplasm. Nevertheless, these acids are partially in their undissociated at lower pH values. The undissociated organic acids are lipophilic and diffuse passively across the membrane that may cause intracellular acidification. On the contrary, at high intracellular pH values, they dissociate to produce hydrogen ions that interfere with essential bacterial metabolic functions. It also denatures protein and collapses the electrochemical proton gradient resulting in the disruption of substrate transport systems of infectious pathogens. Thus, it also alters the cell membrane permeability of pathogenic bacteria [41].

Production of free radicals along with hydrogen peroxide (H_2O_2) acts as a precursor that damages the DNA. In certain cases, the antimicrobial activity of H_2O_2 may result from the oxidation of sulphydryl groups thereby causing denaturation of a number of enzymes. The peroxidation of membrane lipids by H_2O_2 also causes the increased membrane permeability [41]. Carbon dioxide (CO_2) as end products of fermentative metabolism creates an anaerobic environment that may inhibit enzymatic decarboxylation reaction. In certain cases, it causes a malfunction in permeability due to the heavy accumulation of CO_2 in the membrane lipid bilayer. LAB also produces significant amounts of fatty acid, named as Reuterin, that show their antimicrobial potential under specific conditions [41]. *Lactobacillus paracasei* produces certain bactericidal bio surfactant that inhibits the growth of several pathogens [39].

2.2.2. Bacteriocins (*Antimicrobial peptide*)

Bacteriocins are ribosomally synthesized low-molecular-weight antimicrobial peptides with a good functional therapeutic activity against gastrointestinal pathogenic infections [42,43]. Bacteriocin activity adsorbs specific or non-specific receptors on the target cell surface and alters the membrane permeability, thus disturbing membrane transport, and finally inhibiting energy production. Numerous bacteriocins, such as nisin, lactobrevin, acidophilin, acidolin, lactobacillin, lactocidin and lactolin have been reported to be produced by Lactobacilli [42,43,44]. Table 5 presents the class of bacteriocins and its characteristics, based on structural, physicochemical and molecular properties.

Antimicrobial peptides (AMP) get attached to the anionic components of bacterial cell wall because of their cationic nature and cause disruption of cell envelope to reach into cytoplasmic membrane in a process known to be self-promoted uptake. A numbers of models including barrel stave model, carpet, toroidal or aggregate channel model represent different mechanisms of action. AMP become stave in a barrel like cluster around the outer membrane of pathogenic flora and the hydrophilic surfaces of peptides point facilitate pores. Leakage of cellular components through these transmembrane pores depletes proton motive force that ultimately interferes with cellular biosynthesis causing cell death [44,45].

2.2.3. Colonization Resistance and Competitive Exclusion

Adherence to human intestinal cells and intestinal mucus glycoproteins (mucin) as well as competitive exclusion of pathogens are most important characterization of probiotic strains to deactivate the pathogen in the intestine. Such competition may occur either for adhesion or for nutritional substrates and biogenic growth metabolites. Infection begins with the binding of the pathogen to intestinal epithelial cells via carbohydrate moieties of glycoconjugate receptor molecules. Probiotic strains compete with invading pathogens for the glycoconjugate receptors at the infection site of intestinal epithelium cells, which may block adhesion and penetration of infectious pathogens [46]. Gastrointestinal cell surface constituents, such as several glygoconjucates, can serve as receptors for bacterial adherence [47]. Adhesion may be specific or non-specific based on physico-chemical factors and involves adhesin molecules on the surfaces of adherent bacteria and receptor molecules on epithelial cell. Probiotic agents also compete for receptors or adhesion to intestinal epithelium that could prevent the colonization of pathogenic microorganisms from occupying this living space (colonization resistance or competitive inhibition) [36]. *Escherichia coli* binds to epithelial cells via mannose receptors in human intestinal epithelial cells; Probiotic *L. acidophilus* ATCC 4356 has shown similar adherence capabilities that could inhibit pathogen colonization at the same sites, thereby protecting the host against the infection [48,49].

Probiotics may also compete for an ecological niche creating an unfavorable condition for the invading pathogens to take hold in the intestinal tract and impair their colonization ability. A competition for nutritional substrates and biogenic growth metabolites (amino acid, methylamines, vitamins, short-chain fatty acids (SCFA) and bioactive peptides) amongst intestinal microbiota, probiotics and pathogens may occur. *Bifidobacterium adolescentis* S2-1 can better utilize vitamin K and inhibit the growth of *Porphyromonas gingivalis* by competing for the growth factor [50]. *Lactobacillus plantarum* 423 is able to colonize intestinal epithelial cells, thus preventing the adhesion of pathogenic *Clostridium sporogenes* and *Enterococcus faecalis [46]*.

2.2.4. Intestinal Barrier Function

The mucus layer is the first line barrier where pathogens penetrate it to reach the epithelial cells during infection, thus it provides protection by shielding the epithelium from potentially harmful antigens [51]. Disruption of epithelial barrier function or a loss of tight junction formation in the intestinal epithelium cells are another major reasons of intestinal pathogenic infections. Probiotics maintain a tight junction protein expression and enhancement of host mucin production, which improves the ability of the mucus layer to act as an antibacterial shield by preventing the increase of apoptotic ratio [36,52,53]. Probiotics can reduce the epithelial injury that follows exposure to *E. coli*O157:H7 and *E. coli* O127:H6 [54].

2.2.5. Immunomodulation

Several studies have shown an interesting physiological action of probiotics that modulate the immune system. Probiotics might be able to modulate the host's defenses including the innate as well as the acquired immune system [55]. One of the more precise mechanisms of action of probiotics is modulation of GI immunity by altering inflammatory cytokine profiles and down regulating proinflammatory cascades [56]. They enhance the production of serum IgA secretory IgA, as well as natural killer cells and phagocytosis, which play a crucial role in intestinal immunity. They prevent apoptosis and suppress T cell proliferation, thus preventing various inflammatory conditions [56,57,58]. *Lactobacillus reuteri* strains from human breast milk, either stimulate the key pro inflammatory cytokine, human tumor necrosis factor (TNF), or suppress its production by human myeloid cells [56,58]. Both in vitro production of g-IFN, IL-12, and IL-18 by lymphocytes and enhanced capacity to produce g-IFN in response to different lactic bacteria strains. *L. paracasei* is a potent stimulator of IL-12. However, IL-12 may down regulate the Th-2 response, decreasing IL-4 and IgE production. It may prevent an allergic tendency in humans.

Probiotics can also modulate toxin receptors and block toxin-mediated pathology by using enzymatic mechanisms. For example; *S. boulardii* degrades *Clostridium difficile* toxin receptors and blocks cholera-induced secretion in rat jejunum by the production of polyamines [59]. The presence of several probiotic bacteria regulate human beta defensin 2 (hBD-2) via the transcription factor NF-κB that would strengthen intestinal defenses [60].

Table 5. Classification of Bacteriocin

Class	Characteristics	Bacteriocin produced	FDA Approved
Class I	• small, cationic, hydro-phobic and heat-stable peptides. • usually contain unusual amino acids (e.g. the thioether amino acids lanthionine and/or 3 -methyl-lanthionine)	• Lantibiotics • Nisin	No Yes
Class II	• small, cationic, heatstable peptides	• Pediocin PA-1. • Mesentericin Y105 • Enterocin P, A • Curvacin A.	No
Class III	• large, heat-labile proteins	• Helveticin J • Lectacins A and B	No
Class IV	• Complex	• Sublancin • Glycocin F	No

2.3. Clinical Implications of Probiotics in Gut Health

A disturbed gut microflora, results in a wide range of symptoms, compromising the gut health and resulting in gastroenteritis. Gastroenteritis is caused by several pathogens such as *Shigellae*, *Salmonellae*, *Escherichia coli*, *Vibrio cholera*, and *Clostridium*, which may first colonize and then grow in the gastrointestinal tract. Then they invade the host tissue, or may secrete toxins that disrupt the function of the intestinal mucosa and normal gut flora (both their activity and balance) causing nausea, vomiting and diarrhea.

Diarrhea has become a foremost global health problem of late. It may be classified as (1) acute diarrhea (duration is less than 2 wk), (2) persistent diarrhea (duration varies from 2 to 4 wk), and (3) chronic diarrhea (duration is more than 4 wk). In many developing countries, infectious gastroenteritis such as shigellosis, traveller's diarrhea (TD), antibiotic associated diarrhea (AAD), acute diarrhea (AD), inflammatory bowel syndrome and irritable bowel syndrome are the common fatal diseases caused by more than 50 different pathogens including virus, bacteria, fungus and protozoa. Rotavirus and entero pathogenic *E. coli* (EPEC) are the leading causes of endemic pediatric diarrhea and Traveller's diarrhea. They affect all age groups. It has been estimated that severe enteric pathogenic diarrhea and dehydration are the main cause of morbidity and mortality each year worldwide [61]. Evidence suggests that oral consumption of microorganisms may have some preventive as well as curative effects on the gut flora [62]. They have a long history of safe use in foods and exert antagonistic effects on the growth of invasive and opportunistic pathogenic bacteria such as *Staphylococcus aureus*, *Salmonella typhimurium*, *Shigella*, *Yersinia enterocolitica*, *Vibrio cholera* and *Clostridium perfringens* [63].

2.3.1. Salmonellosis

Salmonellosis is an important health concern caused by Salmonella. A protective role of probiotic stains such as *Lactobacillus acidophilus* Bar13, *L. plantarum* Bar10, *Bifidobacterium longum* Bar33, *Enterococcus faecium* PCD71 and *Lactobacillus fermentum*ACA-DC179 and *B. lactis* Bar30 strains suppress the growth of Salmonella *typhimurium* and S. *enteritidi [64,65,66]*.

2.3.2. Antibiotic-associated Diarrhea (ADD)

Diarrhea is the most common gastrointestinal side effect of antibiotic therapy often associated with *C. difficile* infections in adults and children. Certain drugs (ampicillin, amoxicillin, cephalosporins and clindamycin) cause changes in the composition of intestinal microflora resulting in the proliferation of bacterial strains such as *C. difficile*, *C. perfringens* type A, *S. aureus*, *K. oxytoca*, *Salmonella* spp., *Candida* spp. The opportunistic proliferation of intestinal pathogens after breakdown of colonization resistance due to antibiotic administration releases two protein exotoxins, toxin A and toxin B responsible for diarrhea and colitis [67].

The role of probiotic strains of *Lactobacillus* (*L. rhamnosus*), *Lactococcus* spp., *Leuconostoc cremoris*, *Bifidobacterium* species, *Bacillus* spp., *Saccharomyces* spp., or *Streptococcus* spp. probiotics strains have been reported as a complementary therapy in the treatment of ADD [2,68]. The antimicrobial substances produced by *Lactobacillus* GG show a broad-spectrum activity against infectious *C. difficile* bacteria to control ADD. The most commonly used probiotics are administered as doses from 10^7 to 10^{11} for durations ranging from 5-49 days, generally paralleling the duration of antibiotic therapy [69] (McFarland, 2009). It was reported that after the completion of antibiotic therapy, administration of a mixture of certain probiotic strains notably, *L. casei*, *L. bulgaricus*, and *S. thermophilus* reduced the incidence of AAD [70]. The combination of two Lactobacillus strains, *L. acidophilus* and *L. casei* has been proved to be an effective oral therapy in the treatment of antibiotic associated diarrhea [71].

2.3.3. Traveller's Diarrhoea (TD)

TD commonly affect is healthy travelers in developing countries characterized by the excretion of a minimum of three unformed stools per day. Table 6 presents the classification of *E. coli*. *E. coli* produces one or more Shiga toxins that induce production of lesions on host intestinal epithelial cells, thus reducing intestinal epithelial barrier function [72]. Enteropathogenic *E. coli* (EPEC), rarely *Campylobacter*, *Shigella* and *Salmonella* are the main causative agent of TD responsible for inconvenience and discomfort [73]. In different clinical studies, the prevention of TD by the administration of *L. acidophilus*, *L. bulgaricus*, *Streptococcus thermophilus* and *S. cerevisiae* exhibit the antimicrobial potency of probiotics. *Lactobacillus* GG strains in a dose of 2×10^9 CFU for two weeks and *S. boulardii* probiotic yeast 5×10^9 - 1×10^{10} CFU for three weeks are effective against TD [74].

Table 6. Classification of Diarrheagenic *E.coli*

Categories
Enteropathogenic *E. coli* (EPEC)
Enterotoxigenic *E. coli* (ETEC)
Enteroinvasive *E. coli* (EIEC)
Enteroaggregative *E. coli* (EAggEC)
Enterohemorrhagic *E. coli* (EHEC)
Diffusely adherent *E. coli* (DAEC)

2.3.4. Acute Diarrhea

Acute diarrheal infection by rotaviruses is a major health problem worldwide. Acute diarrhea is defined as more often than usual bowel movements lasting 10-14 days. In a randomized study, it was reported that number of infectious pathogens like *rotavirus, adenovirus, Salmonella* spp, *Escherichia coli, Yersinia enterocolitica, Clostridium difficile, parasitices* (*Giardia lamblia, Cryptosporidium parvum*) are the main cause of this diarrhea [75]. Rotaviruses invade the columnar cells of the small intestinal epithelium where they replicate resulting partial disruption of the intestinal mucosa with loss of microvilli and increase intestinal permeability. *Lactobacillus rhamnosus* GG, *L. casei Shirota, L. reuteri, L. acidophilus* spec., *Bifidobacterium animalis* ssp. *Lactis* BB-12, *Enterococcus faecium* SF68, *Saccharomyces boulardii* are some of best-documented probiotic strains effective against acute diarrhea [76,77].

The mechanisms of actions by which Lactobacilli and *Bifidobacterium bifidum* reduce rotavirus-induced diarrhea, includes production of antimicrobial compounds, enhancement of the immune response and competitive blockage of receptor sites when lactobacilli bind to receptors [1,78]. The treatment with *Lactobacillus* GG promotes systemic and local immune response to rotavirus by enhancing IgA specific antibody-secreting cells (sASC) and serum IgA antibody level at convalescence, thereby, strengthening the gut immunological barrier. An analysis of the impact of probiotic strains as a milk supplement shows *Bifdobacterium lactis* in an amount of 1.9×10^8 CFU per 1 g of powder milk reduces the risk of rotavirus infection [79].

2.3.5. Helicobacter Pylori Gastroenteritis

Helicobacter pylori is an important etiologic agent of chronic gastritis, gastric and duodenal ulcers and increases the risk of gastric cancer as well as stomach carcinoma. Pathogenic *H. pylori* produces urease, which can hydrolyse urea to ammonium resulting in elevated pH in the stomach [81]. Clinical studies have established the value of probiotics, viz., *Lactobacillus acidophilus, L. casei strain Shirota* and *Lactobacillus fermentum* etc in treatment of *Helicobacter pylori* gastroenteritis [80]. In addition, the outcome of using a probiotic combination of *Lactobacillus rhamnosus* GG, *L. rhamnosus* LC705, *Propionibacterium freudenreichii* JS and *Bifidobacterium lactis* Bb12 for 8 weeks decreases urease and gastrin-17 activities found in H. Pylori-infected patients; whereas the probiotic *Lactobacillus reuter* suppresses *H. pylori* binding to the glycolipid receptors [82].

2.3.6. Inflammatory Bowel Syndrome

Inflammatory bowel syndrome (mainly Crohn's disease and ulcerative colitis) is more common among young people. Crohn's disease (CD) is chronic and idiopathic inflammation occuring from the mouth to the anus with the terminal part of the ileum mainly affected. Crohn's disease is associated with impairment of the barrier function and causes inflammation that extends much deeper into the layers of the intestinal wall. In general, it tends to involve the entire bowel wall, whereas ulcerative colitis affects only the lining of the bowel with characteristic patchy transmural lesions containing granulomas [83,84]. Ulcerative colitis is a chronic inflammatory disease of the inner lining (mucosa membrane) of the intestine or colon whereby, the colon becomes inflamed (red and swollen) and causes necrosis, ulceration (open, painful wounds), and perforation of the intestine along with diarrhea. Blood and mucus is f found in feces [83].

The administration of a formulated VSL#3 consisting of 8 probiotic strains (*L. acidophilus, L. casei, L. delrueckii subs. bulgaricus, L. plantarum, B. breve, B. longum, B. infantis*, and *Streptococcus salivarius subs. thermophilus*) in the amount of 3.6×10^{12} CFU twice daily, for 12 weeks provides a notable improvement in ulcerative colitis [85]. Moreover, inflammatory bowel syndrome diseases show a positive response to probiotics such as LGG, E. coli, Nissle1917,or a mixed culture preparation, containing 4 strains of Lactobacilli, 3 strains of bifidobacteria, and Streptococcus thermophilus (VSL#3) [86]. Studies on probiotic, VSL#3 for 9-12 months have reported a positive outcome in the prevention and treatment of pouchitis [87,88].

2.3.7. Irritable Bowel Syndrome (IBS)

Irritable Bowel Syndrome (IBS) is the most common functional gastrointestinal disorder with a collection of symptoms such as abdominal pain, bloating, incomplete evacuation, intestinal gas, straining, bowel function and constipation. The altered microflora or induction of an altered inflammatory state in the bowel may lead to malabsorption of bile acids in the colon and increased fluid and mucus secretion through the mucosa resulting in diarrhea and IBS symptoms [89]. This disease is chronic and 20% of adults, especially the women are predominantly affected. *Bifidobacterium infantis* 35624, *E. coli* Nissle1917, *Lactobacillus* GG and *L. plantarum* 299 v (Lp 299 v) are efficient against IBS [90,91,92].

3. Conclusion

The uses of probiotics in foods in on the rise and is gradually attracting attention. The applications of probiotics in food to preserve a healthy gut are one of the viable methods to maintain good health. The proposition of different foods as a vehicle to transfer probiotics in the body is a sustainable method. However, strain selection, processing, inoculation of starter cultures and selecting appropriate foods as a vehicle, needs strict regulations for transfer of health benefits to humans. Further studies are required to validate the interactions between probiotics, gut microflora and the gastrointestinal tract, across all

ages of the lifespan. Identification of new variants of probiotics derived from the microbiomes may be a good strategy to promote gut health in future.

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