








Review

Lactic Acid Bacteria: Food Safety and Human Health Applications

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Abstract: Research on lactic acid bacteria has confirmed how specific strains possess probiotic properties and impart unique sensory characteristics to food products. The use of probiotic lactic acid bacteria (LAB) in many food products, thus confers various health benefits to humans when they are frequently consumed in adequate amounts. The advent of functional food or the concept of nutraceuticals objectively places more emphasis on seeking alternatives to limit the use of medications thus promoting the regular consumption of fermented foods. Probiotic use has thus been recommended to fulfill the role of nutraceuticals, as no side effects on human health have been reported. Probiotics and lactic acid bacteria can boost and strengthen the human immune system, thereby increasing its resistance against numerous disease conditions. Consumer safety and confidence in dairy and fermented food products and the desire of the food industry to meet the sensory and health needs of consumers, has thus increased the demand for probiotic starter cultures with exceptional performance coupled with health benefiting properties. The potential of probiotic cultures and lactic acid bacteria in many industrial applications including fermented food products generally affects product characteristics and also serves as health-promoting foods for humans. The alleviation of lactose intolerance in many populations globally has been one of the widely accepted health claims attributed to probiotics and lactic acid bacteria, although many diseases have been treated with probiotic lactic acid bacteria and have been proven with scientific and clinical studies. The aim of our review was to present information related to lactic acid bacteria, the new classification and perspectives on industrial applications with a special emphasis on food safety and human health.

Keywords: lactic acid bacteria; health benefits; bio-preservation; probiotics

1. Introduction

Lactic acid bacteria (LAB) are important microorganisms that mainly produce lactic acid as a by-product during metabolic activities. Lactic acid bacteria play a multifaceted role in the agricultural, food, and clinical sectors [1]. Lactic acid bacteria is employed in many food fermentations with fermentation using this bacteria is one of the most conventional and recognized arts of food preservation. As lactic acid bacteria are very important in many food applications, the food industry is always

seeking strains with superior characteristics and properties to enhance sensory and product quality. Lactic acid bacteria also possess therapeutic properties that are vital for human health enhancement. Distinct nutritional properties of lactic acid bacteria coupled with enhanced adhesional adaptive features enable the bacteria to easily thrive in different environments such as in dairy-based foods, fermented foods, vegetables as well as in the human gut [1]. During fermentation, lactic acid bacteria produce organic acids and other metabolites that enhance flavor development in food, prevent spoilage, and are thus very useful in many applications, especially in the food and dairy industry. The dairy sector in particular benefits immensely from lactic acid bacteria hence the need to validate the potential of lactic acid bacteria as starter cultures are vital as product quality and sensory appeal are largely influenced by the role of dairy starter cultures [2]. The use of lactic acid bacteria in food preservation is known as bio-preservation which is a natural approach to using controlled microbiota as an alternative for shelf life extension and the preservation of food. Therefore, bio-preservation is considered as one of the many attributes derived from lactic acid bacteria under the scope of food safety/spoilage. Because lactic acid bacteria naturally produces bacteriocins that aid in food bio-preservation, they function as the antagonistic, inhibitory, and antimicrobial defense system that acts against pathogens and spoilage microorganisms [3]. As a result, lactic acid bacteria can be used as tool to ensure the safety and quality of food products. Probiotics are live microorganisms which when administered in adequate amounts confer a health benefit on the host. Probiotics such as lactic acid bacteria work by promoting and maintaining a strong human immune system. For example, a number of human health diseases have been reported to be prevented by the administration of probiotics and lactic acid bacteria. The regular consumption of probiotics and lactic acid fermented foods will thus benefit consumers nutritionally and serve as an immunity booster against diseases and infections. In this review, lactic acid bacteria, their classification and perspectives on industrial applications with a special focus on food safety and therapeutic benefits to human health was elucidated.

2. Lactic Acid Bacteria

Lactic acid bacteria are Gram-positive, non-spore-forming, non-respiring but aerotolerant, which produce lactic acid as one of the key fermentation products by utilizing carbohydrates during fermentation. These bacteria produce lactic acid as an end product of carbohydrate catabolism and also make organic substances that contribute to the flavor, texture, and aroma that result in unique organoleptic characteristics [4–7]. Orla Jensen (1919) [8] first published a monograph that laid the foundation for classifying lactic acid bacteria. This system of classification was linked to certain factors that entailed the following; glucose fermentation characteristics, cell morphology, capacity to utilize sugars, and optimum growth temperature range. This classification system thus recognized only four lactic acid bacteria genera: *Lactobacillus*, *Pediococcus*, *Leuconostoc*, and *Streptococcus* [4].

Lactic acid bacteria has also been classified into different genera/species based on their acid production characteristics by fermenting sugars and its growth at specific temperatures [9]. Additionally, the lactic acid bacteria can be classified as homofermentative or heterofermentative organisms based on their ability to ferment carbohydrates [10]. The homofermentative lactic acid bacteria such as *Lactococcus* and *Streptococcus* yield two molecules of lactates from one glucose molecule whereas heterofermentative lactic acid bacteria such as *Leuconostoc*, *Wiessella*, and some lactobacilli generate lactate, ethanol, and carbon dioxide from one molecule of glucose [11]. The conventional approach to lactic acid bacteria classification was based on physiological and biochemical characteristics; however, more recently, molecular characterization has become an important tool for classification and identification of lactic acid bacteria. Molecular characterization includes random amplified polymorphic DNA profiling, 16S rRNA gene sequencing, PCR-based fingerprinting, and soluble protein patterns [12] and differentiation of species by multiplex PCR assay by using specific recA derived primers [13].

2.1. Taxonomic Classification of Lactic Acid Bacteria

The genus *Lactobacillus* has recently been reclassified by scientists into 25 genera. This reclassification was necessitated due to the extent of how diverse the original genus was, which made it very challenging to classify, name, and distinguish between different lactobacilli [14]. The new genera are *Lactobacillus*, *Paralactobacillus* and the 23 novel genera. The twenty three (23) novel genera includes: *Amylolactobacillus*, *Acetilactobacillus*, *Agrilactobacillus*, *Apilactobacillus*, *Bombilactobacillus*, *Companilactobacillus*, *Dellaglioia*, *Fructilactobacillus*, *Furfurilactobacillus*, *Holzapfelia*, *Lacticaseibacillus*, *Lactiplantibacillus*, *Lapidilactobacillus*, *Latilactobacillus*, *Lentilactobacillus*, *Levilactobacillus*, *Ligilactobacillus*, *Limosilactobacillus*, *Liquorilactobacillus*, *Loigolactobacillus*, *Paucilactobacillus*, *Schleiferilactobacillus*, and *Secundilactobacillus* [14].

2.2. Niche or Habitat of Lactic Acid Bacteria

Lactic acid bacteria constitute a ubiquitous bacterial group that is widespread in nature in niches of dairy (fermented), meat and vegetable origin, the gastrointestinal and urogenital tracts of humans and animals, and soil and water [15]. The ecology of lactic acid bacteria has transitioned over time from their soil and plant habitats to the gut of mammals. The mammalian intestine is a repository of 100 trillion microorganisms generally called microbiota [16]. The microbiota colonizes the gastrointestinal tract and is essential for health by enhancing metabolism, digestion and boosts the immune system [16]. The microbiota is well adapted to the mammalian gut, based mainly on three factors which include adhesion to intestinal cells, resistance to host barriers, and substrate fermentation in the gut [17]. Bile salts and low pH also affect the lipid membrane composition of the microbiota [18].

The adhesion of lactic acid bacteria to the intestinal cells is facilitated by the action of peristalsis which is coupled with lubrication from mucins that protect and line the epithelial intestinal cells. This coordination thus ensures an increased adherence capacity of lactic acid bacteria to the intestinal cells [19]. Intestinal mucins are thus very important as their continuous production impedes and prevents pathogenic bacteria from adhering to the intestinal epithelial cells, thus promoting the activity of resident intestinal bacteria. Consequently, these gastrointestinal bacteria serve as a barrier system that acts against pathogens [20]. Antimicrobial substances that are produced by *Lactobacillus* and *Bifidobacterium* spp. have been confirmed to possess antimicrobial properties that are exerted against enteropathogenic bacteria linked to causing diarrhea against [21], and both genera can exert an inhibitory effect on the action of pathogenic enteric bacteria [20].

2.3. Lactic Acid Bacteria in Bio-Preservation

Fermentation is a process by which a carbon source is dissimilated by microorganisms yielding energy without net oxidation. The primary end products of microbial fermentation are generally alcohols and organic acids such as lactic acid, acetic acid, and propionic acid [22]. Food fermentation has been widely practiced using lactic acid bacteria which are able to preserve food and prevent spoilage. Consumer food preferences are now driven by nutrition and health benefits, resulting in choices that are trending more and more towards the sustainable use of natural ingredients as preservatives instead of chemicals [23]. As a result of this shift in preferences, the use of lactic acid bacteria in food applications has become more important. Lactic acid bacteria have thus been used extensively in food processing and many fermented foods as a result of their preservative capacity coupled with the health benefits that they provide to humans when lactic acid bacteria fermented foods are consumed. Lactic acid bacteria synthesizes small proteins called bacteriocins from ribosomes, and it is these bacteriocins that are inhibitory against foodborne pathogens, thus ensuring safe food. Moreover, bacteriocinogenic lactic acid bacteria are good candidates as dairy starter cultures that play an important role in food application processes [3].

Bacteriocins have been grouped into four major classes [10]. Class one bacteriocins are generally known as lantibiotics, and consist of nisin, an important and one of the most intensively used and studied bacteriocins. Group two, is characterized by large groups of small heat-stable proteins that are

subsectioned d into three groups [10]: (i) subgroup (2a), these bacteriocins inhibit *Listeria monocytogenes*, notable members in this group are Pediocin PA-1, Lactococcin A and B, Leucocin A, Sakacins A and P, Curvacin A, and Bavaricin MN; (ii) subgroup (2b) these bacteriocins are activated by two different peptides; hence, they are also called two-peptide bacteriocins. These two peptides are Lactococcin G and Enterococins. Lactococcins G and M, and lactacin F are examples in this group, and (iii) subgroup (2c), consists of circular cationic peptides that have an elevated antimicrobial property in comparison to other linear-shaped bacteriocins. An example of a circular bacteriocin is Enterococin AS-48. Group three bacteriocins are made up of larger heat-labile proteins with lactacins A and B, and helveticins J and V as members. Group four bacteriocins are considered complex due to their carbohydrate and lipid moieties. Leuconocin S, lactocin 27, and pediocin SJ-1 are part of this group based on their lipid or carbohydrate moieties.

A study by Yang, Lin, Sung, and Fang (2014) [24] further grouped Gram-positive bacteriocins into three distinct classes: Class A (modified peptides, also known as lantibiotics), Class B (unmodified peptides, also known as non-lanthionine), and Class C (consisting of large proteins, that are heat unstable). Another study by Cotter, Ross, and Hill (2013) [25] again subsectioned Class B into five sub-classes. It is noteworthy that, nisin is the only commercially available bacteriocin that exists in its purest form among all the different groups of bacteriocins.

Nisin has important commercial value as it is usually added as an ingredient to milk, and dairy-based products, mayonnaise, canned foods, and in most infant and baby foods [26]. Bacteriocinogenic cultures are also vital as ingredients in fermented and non-fermented foods as they are usually employed as starter cultures. In addition, harmless bacteriocins are at risk of being digested by some proteases due to their susceptible and sensitive nature [27]. Consequently, bacteriocins are considered as safe food additives and beneficial to the gastrointestinal system [4,24]. A summary of all metabolites including bacteriocins synthesized by lactic acid bacteria and its mechanism of action as well as their potential targets is shown in Table 1.

Table 1. Antimicrobial Substances produced by Lactic Acid Bacteria.

Antimicrobial Compounds/Metabolites	Characteristic Property	Species	References
Organic acids, hydrogen peroxide	Promotes significant inhibitory, antagonistic effect and an important target for pathogens (Gram-positives and Gram-negatives) and food spoilage microorganisms	<i>Lactobacillus</i> species	Nagpal et al., 2012 [28]; Papadimitriou et al., 2015 [29]; Ponce et al., 2008 [30]
Lactoperoxidase system	Thiocyanate and hydrogen peroxide have a broad-spectrum antibacterial action on pathogens	<i>Lactobacillus</i> species	Seifu et al., 2005 [31]
Bacteriocins	Characteristic Property	Species/Compound	References
Class I Bacteriocins (Lantibiotics)	Antimicrobial peptides synthesized ribosomally and have an inhibitory effect on pathogens. Widely used in food preservation operations. Lantibiotics are post-translationally modified and are low molecular weight peptides (<5 kDa). Consists of superior amino acids i.e., lanthionine and β -methyllanthionine	<ul style="list-style-type: none"> • <i>Lactococcus lactis</i> subsp. <i>Lactis</i>/Nisin • <i>Lb. Reuteri</i>/Reuterin • <i>Lb. delbrueckii</i> subsp. <i>Bulgaricus</i>/Bulgaricin 	Yang et al., 2014 [24]; Mokoena 2017 [10], Perez et al., 2014 [3]
Class II Bacteriocins (Non Lantibiotics)	Heat stable and small peptides with a high molecular weight (5–10 kDa). They are non-lanthionine molecules with or without post-translational modifications	<ul style="list-style-type: none"> • <i>Lb. helveticus</i>/Lactacin 27 Helveticin J • <i>Lb. plantarum</i>/Lactolin 	Yang et al., 2014 [24]; Mokoena 2017 [10], Perez et al., 2014 [3]
Class IIa Bacteriocins (Non Lantibiotics)	Functional peptides are synthesized from several genes as a requirement		Yang et al., 2014 [24]; Mokoena 2017 [10], Perez et al., 2014 [3]

Table 1. Cont.

Bacteriocins	Characteristic Property	Species/Compound	References
Class IIb Bacteriocins (Non Lantibiotics)	Two different peptides, mostly linear coupled with or without post translational modifications at the C-terminal are required	<ul style="list-style-type: none"> • <i>Lactococcus lactis</i> subsp <i>cremoris</i>/Diplococcin • <i>Lb. brevis</i>/Lactobacillin 	Yang et al., 2014 [24]; Mokoena 2017 [10], Perez et al., 2014 [3]
Class IIc Bacteriocins (Non Lantibiotics)	Bacteriocins have a circular structure with both the N- and C-terminals linked by covalent bonds	Lactobrevin	Yang et al., 2014 [24]; Mokoena 2017 [10], Perez et al., 2014 [3]
Class III Bacteriocins (Non-lantibiotics)	Large heat-labile peptides with molecular weight > 30 kDa. They are sub-classified under Class IIIa and Class IIIb.	<ul style="list-style-type: none"> • <i>Lb. fermenti</i>/Bacteriocin • <i>Lactococcus lactis</i> subsp<i>cremoris</i>/Diplococcin • <i>Lb. brevis</i>/Lactobacillin 	
Class IIIa Bacteriocins (Bacteriolytic)	Class IIIa they are mainly bacteriolysins. Lysostaphin, is an antimicrobial peptide produced by staphylococci that targets Gram-positives and destroys them.	Lactobrevin	Ibrahim, 2019 [32]; Ramu et al., (2015) [33].
Class IIIb Bacteriocins (Non-lytic)	Class IIIb (Helveticin) is a non-lytic protein produced from Gram-positive bacteria <i>Lactobacillus helveticus</i>	<ul style="list-style-type: none"> • <i>Lb. helveticus</i>/Helveticin • <i>Lb. fermenti</i>/Bacteriocin • <i>Lb. sakei</i>/Sakacin • <i>Lb. curvatus</i>/Curvacin 	
Class IV Bacteriocins	Bacteriocins classified as complex with compositions of lipids and carbohydrates moieties		Ibrahim, 2019 [32]; Ramu et al., (2015) [33].

2.4. Lactic Acid Bacteria in Fermented Foods

Lactic acid bacteria are essential, and their usefulness cannot be overemphasized in many food fermentation applications and preservation activities. Many traditional foods have been developed using lactic acid bacteria, which improve product characteristics and impart certain properties that enhance consumer acceptance and appeal. Most of the products that are developed by the use of lactic acid bacteria also provide superior health benefits to the consumer which is key to maintaining a healthy gastrointestinal system. Some of the fermented food products from lactic acid bacteria include kefir, cheese, butter, yogurt, sauerkraut, buttermilk, brined vegetables, sourdough, soya curd, koumiss, idly batter, uttapam, fermented meat, and beverages [34].

Fermented milk products, alternatively referred to as cultured dairy products, include dairy foods that have been fermented by a consortium of lactic acid bacteria that are responsible for milk curdling or the souring of milk [35]. Lactic acid bacteria are lactose fermenters that also preserve the taste and nutritional properties of milk. Bacterial members associated with fermented dairy products belong to the genera of *Lactobacillus*, *Lactococcus*, *Leuconostoc*, *Pediococcus*, *Bacillus*, *Propionibacterium*, and *Bifidobacterium*. These bacteria live in the same ecological niches and act mutualistically. There are approximately 400 traditional and fermented milk products comprising a diverse group of microorganisms that give rise to different sensory properties [36]. Table 2 highlights several traditionally fermented milk products that use lactic acid bacteria along with the accompanying health derived benefits.

Table 2. Beneficial properties of ethnically fermented food products and associated microorganisms.

Traditional Fermented Foods	Microbiota	Associated Action	References
Dahi	<i>Lactobacillus acidophilus</i>	Production of antibacterial substances	Balamurugan et al., 2014 [37]
Kefir	<i>Lactobacillus kefir</i> , <i>Lactobacillus kefiranoferiens</i> , and <i>Lactobacillus kefirgranum</i>	Production of bacteriocin enhances antibacterial activity Epithelial cells of the intestine have reduced inflammation Serum cholesterol level is reduced Produce an EPS known as kefiran.	Luo et al., 2011 [38]; Seo et al., 2018 [39]; Wang et al., 2008 [40]; Bonczar et al., 2016 [41]
Tofu	<i>Lactobacillus plantarum</i>	Antioxidant activity	Li et al., 2012 [42]
Koumiss	<i>Lactobacillus</i> sp.	Excellent antimicrobial properties against pathogens	Guo et al., 2015 [43]
Swiss Cheese	<i>Lactobacillus helveticus</i> R389	Enhancement of the immune system by increasing IgA and CD4 positive cells.	Ghosh et al., 2019 [36]
Nunu	<i>Lactobacillus plantarum</i> , <i>Lactobacillus fermentum</i> , and <i>Saccharomyces cerevisiae</i>	Produces EPS, and β -galactosidase Produces bacteriocins known as plantaricins promoting antibacterial activity against pathogens	Akabanda et al., 2013 [44]; Behera et al., 2018 [45]
Korean kimchi	<i>Lactobacillus plantarum</i>	Antimicrobial activity against pathogens	Kwak et al., 2017 [46]

2.5. Milk Fermentation with Lactic Acid Bacteria

Fermented milk products are classified into two groups. Group One: Bacterial lactic acid fermentation: (i) Fermentation by mesophilic bacteria (acidified milk, buttermilk, filmjolk, and langfil), (ii) fermentation by thermophilic and mesophilic bacteria (yogurt, dahi, Bulgarian buttermilk, zabadi). Group Two: Fungal and bacterial lactic acid fermentation: Fermentation by bacteria as well as fungi, e.g., alcoholic milk (*Acidophilus* yeast milk, Koumiss, and kefir) and moldy milk (Villi). Milk product varieties depend on the type of milk and starter culture used, sugars, and aromatic compounds [36].

These varieties are developed using primary starter cultures (which participate in primary acidification) and secondary starter cultures (which participate in generating aroma, flavor, and texture). Genera used in primary culture include *Lactobacillus* sp., *Leuconostoc* sp., *Streptococcus* sp. [47], whereas the genera associated with secondary starter cultures are *Propionibacterium* sp., *Brevibacterium* sp., *Debaryomyces* sp., *Geotrichum* sp., *Penicillium* sp., and *Enterococcus* sp. [36].

2.6. Lactic Acid Bacteria as an Essential Strain in Dairy Starter Cultures

The term "starter culture" is defined as a microbial preparation of large numbers of cells of at least one microorganism added to a raw material in order to produce a fermented food, which therefore accelerates and hastens its fermentation process. Lactic acid bacteria play a pivotal role in these processes and also have an established safe history of application and consumption in the production of fermented dairy food products and beverages [2]. Lactic acid bacteria causes rapid acidification of the raw materials through the production of organic acids, primarily lactic acid. They also produce many important by-products such as acetic acid, ethanol, aroma compounds, bacteriocins, exopolysaccharides, and several enzymes. These by-products effectively enhance product shelf life, microbial safety, improve texture, and ultimately contribute to the pleasant sensory profile of the end product. Starter cultures have a multifunctional role in dairy fermentations. Notable starter cultures used for manufacturing numerous fermented milk products include lactic acid bacteria, propionibacteria, surface-ripening bacteria, and yeasts, and molds [2].

Dairy starter cultures are unique, and their major role is fermenting lactose by producing lactic acid. This acid is responsible for developing the characteristic body and texture of the fermented milk product, thus contributing to the overall flavor of the product and consequently enhancing preservation. Lactic acid starter cultures also produce diacetyl, acetaldehyde, and acetic acid which aids in flavor and aroma development of the final product [2]. Some of the known dairy starter cultures used in fermented food productions are shown in Table 3.

Table 3. Starter cultures for fermented dairy foods and beverages.

Fermented Dairy Foods	Starter Cultures	References
Hard cheese without eyes	<i>Lactococcus lactis lactis</i> , <i>Lactococcus lactis</i> ssp. <i>cremoris</i>	Settani et al., 2013 [48]
Kefir	<i>Lactobacillus kefir</i> , <i>Lactobacillus kefiranoferiens</i> ,	Luo et al., 2011 [38]
Yogurt	<i>Lb. acidophilus</i> , <i>S. thermophilus</i> , <i>Lb. delbrueckii</i> ssp. <i>bulgaricus</i>	Panesar, 2011 [49], Hati et al., 2013 [2]
Swiss cheese	<i>Lactobacillus delbrueckii</i> ssp. <i>lactis</i> , <i>Lb. helveticus</i> , <i>Lb. casei</i>	Daly et al., 2010 [50]
Zabady	<i>Lb. delbrueckii</i> ssp. <i>bulgaricus</i> , <i>S. thermophilus</i>	Abou-Donia, 2004 [51]
Bulgarian butter milk	<i>L. delbrueckii</i> subsp. <i>bulgaricus</i>	Panesar, 2011 [49]
Nyarmie	<i>Lactobacillus</i> sp., <i>Lactococcus lactis</i>	Obodai & Dodd, 2006 [52]

Some heterofermentative lactic acid bacteria also produce carbon dioxide which aids in the texturization characteristics of some fermented dairy products, a classical example being the formation of unique holes or "eyes" in cheeses. During the ripening of cheese, the development of flavor and other textural changes are due to enzymes that originate from bacterial and fungal cultures that are largely dependent on the type of cheese [2]. Many studies have also confirmed dairy starters to possess direct and indirect functional health promoting properties such as the presence of live probiotics, prebiotic exopolysaccharides and oligosaccharides, bioactive peptides and lipids. Most dairy starter

cultures are selected for their desirable properties such as rapid acidification, flavor production, lack of associated off flavors, salt tolerance, exopolysaccharide production, bacteriocin production, and sensitivity to temperature [2,53]. The dairy industry also selects strains that are bacteriophage resistant. Bacteriophages are viruses that attack starter cultures and inhibit their fermentation performance [54]. Table 4 highlights some beneficial dairy starter cultures and their applications.

Table 4. Dairy starter cultures and their applications.

Starter bacteria	Functionality	Benefits	References
<i>Lactobacillus plantarum</i> , <i>Lactococcus lactis</i>	Production of Bacteriocins	Bio-preservation	Todorov et al., 2010 [55]; Biscola et al., 2013 [56]
<i>Lactobacillus</i> sp. (EPS efficient)	Formation of stabilizers and production of exopolysaccharides	Enhanced viscosity and body development (polysaccharide materials)	Cerning, 1995 [57]
Vitamins producing lactic acid (Streptococci and propionibacteria)	Vitamin content in fermented dairy products are improved	Enhances the overall health of the bacteria, Promotes vitamin malnutrition	Hati et al., 2013 [2]
<i>Leuconostoc</i> spp.	Acid production	Promotes flavor development, Formation of gels	Bintsis, 2018 [1]
<i>Lactococcus lactis</i> ssp. <i>cremoris</i>	Proteolysis and lipolysis	Ensures accelerated ripening and maturation of cheese	Hati et al., 2013 [2]

2.7. *Lactobacillus delbrueckii* subsp. *bulgaricus*

The discovery of *Lactobacillus bulgaricus* has been ascribed to Stamen Grigorov, a Bulgarian microbiologist who isolated the species from yogurt in 1905 in the laboratory of Professor Masole in Geneva and thereafter named the microorganism after the country of Bulgaria. “*Lactobacillus bulgaricus*” was formally described by Orla-Jensen in 1919 [8] and validated in 1971 with the study of Rogosa and Hansen (1971) [58]. Weiss, Schillinger, and Kandler (1983) [59], after a number of different studies, suggested the union of *Lactobacillus delbrueckii*, *Lactobacillus leichmannii*, *Lactobacillus lactis* and *Lactobacillus bulgaricus* under the name of *L. delbrueckii*. Thereafter, the name of the former “*Lactobacillus bulgaricus*” was then changed to become *Lactobacillus delbrueckii* subsp. *bulgaricus*. Sieuwerts (2009) [60], also confirmed the DNA of *L. delbrueckii* subsp. *bulgaricus* to be in ratio of 49–51% of the Guanine-Cytosine (G-C) content which is significantly higher compared to the G-C content of other lactobacilli in the genus [61]. This is primarily due to elevated G-C content in the third position in codons, which may be indicative of rapid ongoing genome evolution towards an overall higher G-C content. To further substantiate this hypothesis, the authors highlighted the unusually high number of rRNA and tRNA genes present along with a 47.5 kb inverted repeat located around the replication terminus.

These findings could be indications of recent genome reduction and a transient phase of evolution, away from other highly related GI tract bacteria like *Lb. Johnsonii* and *Lb. acidophilus*, towards the adaptation of *Lb. delbrueckii* subsp. *bulgaricus* to the environment of fermented milk [62]. The fermentation of carbohydrates by *Lb. delbrueckii* subsp. *bulgaricus* results in 99.5% D-lactic acid and 0.5% L-lactic acid, respectively. *Lb. delbrueckii* subsp. *bulgaricus* is therefore able to encode many partial carbohydrate metabolic pathways and shows a distinct preference for growth in lactose rich media. *Lb. delbrueckii* subsp. *bulgaricus* also maintains an extensive proteolytic and amino acid transport system which is very useful, especially in the protein rich milk environment [63]. *Lb. delbrueckii* subsp. *bulgaricus* belongs to a thermophilic group of lactic acid bacteria and tolerates optimal temperatures between 43–46 °C for efficient growth. They can also survive in both anaerobic and aerobic conditions. Their ability to efficiently survive in anaerobic environments is because they do not require oxygen in metabolizing energy. *Lb. delbrueckii* subsp. *bulgaricus* can be selectively enumerated from a product using a pH modified MRS (deMann, rogosa, and sharpe) agar, with pH of 4.6 and anaerobically incubated at 43 °C [64,65].

Lactobacillus delbrueckii subsp. *bulgaricus* is one of the two bacteria required in yogurt production. It was originally isolated from Bulgarian yogurt [8] and is also used in conjunction with *Streptococcus thermophilus* on an industrial scale for the production of yogurt. This bacteria plays a vital role in the development of the organoleptic [66], hygienic and perhaps probiotic properties of yogurt [67]. It has been shown to be a safe probiotic with several beneficial properties [68].

The close proto-cooperation between *Lb. bulgaricus* and *S. thermophilus* allows for increased acidification during milk fermentation. Cooperation in amino acid synthesis may also be a result of co-evolution and adaptation to the protein-rich milk environment. While *L. bulgaricus* lacks enzymes for synthesizing most amino acids, it possesses an extracellular caseinolytic protease. *Streptococcus thermophilus*, on the other hand, can produce almost all amino acids but lacks an extracellular protease [69].

3. History of Probiotics

The use of live microorganisms for beneficial purposes as probiotics such as those in fermented milk dates back to ancient times. Scientists such as Hippocrates and others considered fermented milk to be not only a food product but also medicine, and sour milk was prescribed for curing disorders of the stomach and intestines [70]. In 1908, a Russian bacteriologist, Eli Metchnikoff (Pasteur Institute, France) was the first to put forth a scientific explanation of the benefits of lactic acid bacteria in fermented milk [71,72]. Metchnikoff attributed the good health and longevity of Bulgarians to their high consumption of fermented milk called "yahourth".

He, thus, postulated his longevity-without-aging theory based on the principle that lactic acid bacteria were displacers of toxin-producing bacteria normally present in the intestine which in essence prolonged life. Metchnikoff also confirmed that lactic acid and other products produced by lactic acid bacteria in sour milk inhibited the growth and toxicity of anaerobic and spore-forming bacteria found in the large intestine [73]. In 1899, Henry Tissier (Pasteur Institute, France) isolated bifidobacteria from the stools of breast-fed infants and discovered that these bacteria were a predominant component of the human intestinal microflora [74]. Tissier, thus, proposed the administration of bifidobacteria to infants diagnosed with diarrhea, "believing" that bifidobacteria would displace proteolytic bacteria responsible for gastric upsets while re-establishing themselves as the dominant intestinal microorganisms [72]. Tissier's recommendation was confirmed by a study performed by El-Soud, et al. (2015) [75], whereby they supplemented milk formula with *Bifidobacterium lactis* for children diagnosed with acute diarrhea. It was evident that this therapy significantly decreased the frequency, sickness duration, and the hospitalization period of diagnosed children than the conventional treatment approach.

3.1. Origin of Probiotics

Probiotic lactic acid bacteria can be isolated from different sources such as fermented foods, animals, and from humans as well. However, for a probiotic strain to be considered for use by humans, it should be isolated from the human microflora system, thus having a high adhesion ability to the human intestinal cell walls. The strain must also be safe and not pose any threat to the host [34]. The most commonly used probiotics generally come from the genera *Lactobacillus* and *Bifidobacterium*. Other bacteria that could be considered and are similar include *Streptococcus thermophilus*, non-pathogenic strains of *E. coli*, *Enterococcus*, *Bacillus*, and yeasts, such as *Saccharomyces boulardii* [76]. Although the genus *Escherichia* belongs to the Gram-negative family Enterobacteriaceae, mainly known for its severely virulent serotypes (e.g., *E. coli* O157:H7), *Escherichia coli* is a very common inhabitant of the lower intestine and has a known probiotic strain: *Escherichia coli* Nissle 1917 (EcN). This strain together with other probiotics has been proven to effectively treat constipation and other related gastrointestinal disorders [77,78].

The genera *Streptococcus* and *Enterococcus* are considered members of the lactic acid bacteria group. Although, these bacteria contain several strains associated with severe health-care-related

infections such as *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and vancomycin-resistant *Enterococcus faecium* [79], there are other strains that form part of the commensal human microbiome of the mouth, skin, and intestine, such as *Enterococcus faecium* PC4.1 [80]. Moreover, some strains such as *Enterococcus durans* and *Streptococcus thermophilus* have probiotic properties [81]. The genus *Bacillus* includes Gram-positive spore-forming aerobic or facultative aerobic members with claimed probiotic properties including *Bacillus subtilis*, *Bacillus coagulans*, *Bacillus subtilis*, and *Bacillus cereus* [82]. *Saccharomyces boulardii* is used in medicine as a probiotic and forms part of the genus *Saccharomyces*.

3.2. Mechanism of Probiotics

Many studies have proposed various mechanisms underlying the action of different probiotics. However, it is pivotal to link the mechanism of action of the many different probiotics to the strain type, the dosage of probiotics consumed as well as the route of its administration. It is therefore noteworthy that the mechanisms of action cannot be generalized to all probiotics, yet, to a large extent, these actions will be depicted by many probiotics [74,83,84]. Moreover, although the mechanism by which probiotics exert biological effects on their host organisms is fairly well understood, the general non-specific terms widely used in elucidating their mode of action are colonization resistance and competitive exclusion [85]. Colonization resistance and competitive exclusion are terms that are linked to the phenomenon whereby indigenous anaerobic flora limits and impedes the concentration of potentially pathogenic flora in the gastrointestinal tract [86]. The notion of competitive exclusion first had an impact during the early 1970s when it was discovered that mixed adult intestinal microorganisms administered to newly hatched chicks conferred adult-type resistance against *Salmonella* infection [87].

According to Oelschlaeger (2010) [87], the effects of probiotics can be categorized under three modes of action as highlighted below:

- (i) Probiotics can modulate the host's defenses which include the innate as well as the acquired immune system. This mode of action is most critical for prevention and therapy for infectious diseases but also for the treatment of chronic inflammation of the gastrointestinal tract.
- (ii) Probiotics could also directly impact other microorganisms, commensal, and/or pathogenic ones in general. This property could be of immense benefit and vital in prevention and therapy for infections and the overall restoration of the microbial equilibrium in the gut.
- (iii) Additionally, probiotic effects may be linked to actions affecting microbial products such as toxins and host products, e.g., bile salts and food ingredients. This property may result in the inactivation of toxins and aids in detoxification in the gastrointestinal gut. It is also worth noting that the kind of effects depicted by certain strains of probiotics largely depends on the strain's metabolic properties, the molecules presented on their surfaces or on their secreted components.

In relation to the above mechanisms of action of probiotics as highlighted, many researchers have also generalized the mechanisms of probiotics which can be summarized as follows:

- Probiotics compete against pathogenic bacteria to bind to intestinal epithelial cells [86].
- Probiotics enhance the intestinal epithelial barrier function by increasing mucin production, preventing pathogens from causing injury to the epithelium and reducing cell permeability. In addition, probiotics also enhance the mucosal barrier function by inducing the expression of antimicrobial peptides such as defensins [86].
- They inhibit pathogenic growth through the secretion of antimicrobial peptides such as bacteriocins and reuterin. For example, lactic acid bacteria inhibit pathogen growth by creating an acidic environment through the production of organic acids [86].
- Probiotics also stimulate the production of serum Immunoglobulin A (IgA) and secrete IgA which plays a vital role in intestinal humoral immunity [86].
- They enhance phagocytosis, increase the activity of natural killer cells, promote cell-mediated immunity, and stimulate various other non-specific immune responses against pathogens [86].

- Probiotics down-regulate pro-inflammatory cytokine production, prevent apoptosis, and suppress the proliferation of T cells thus preventing various inflammatory conditions [86].
- They produce hydrogen peroxide which suppresses pathogens associated with bacterial vaginosis [88].

The general effectiveness of probiotics is associated with their ability to survive and withstand both the acidic and alkaline environment in the gastrointestinal environment as well as their ability to adhere and colonize the colon [28]. Improved mucosal barrier mechanisms of the gut are achieved by factors such as pH, redox potential, hydrogen sulphide production, and antimicrobial compounds/molecules produced in response to enteric pathogens. Furthermore, the mucosal barrier is also secured by several interrelated systems such as mucous secretion, chloride and water secretion, and the binding together of epithelial cells [86].

3.3. Probiotics and Human Health

Probiotic microorganisms colonize the mammalian gut and the intestinal system as confirmed by many research studies. The gastrointestinal tract has been ascribed to provide conducive environmental conditions for the proliferation and existence of probiotic bacteria. These essential microflorae directly confer immense health benefits to their host and in general are very vital for human health and nutrition. The most extensively isolated probiotic microorganisms from fermented foods, and from both the animal and human gut system, include *Lactobacillus*, *Pediococcus*, *Bifidobacterium*, *Lactococcus*, *Streptococcus*, and *Leuconostoc* [4,89]. *Bifidobacterium lactis* is one of the most studied probiotic strains as it has been used in many research studies to demonstrate its probiotic ability [90].

Presently, there are many diverse well-characterized strains of *Lactobacilli* and *Bifidobacteria* that are uniquely disposed for human use in the prevention and risk reduction for gastrointestinal (GI) infections or for treatment of infections [91].

The pivotal objective of the clinical application of probiotics is solely for the purposes of prevention and treatment of GI infections and diseases [9,34]. Some therapeutic applications of probiotics also include the prevention of urogenital diseases, alleviation of constipation, protection against traveler's diarrhea, reduction of hypercholesterolaemia, protection against colon and bladder cancer, and prevention of osteoporosis and food allergies [73,89]. The ingestion of lactic acid bacteria has been suggested to confer an array of health benefits including immune system modulation and increased resistance to malignancy and infectious illness [92,93]. These beneficial results were confirmed by a study conducted by Maldonado Galdeano et al., (2009) [94] on the effect of fermented milk containing *Lactobacillus casei* DN114001. This probiotic induced mucosal immune stimulation reinforcing the non-specific barrier and modulating the innate immune response in the gut of the host with the maintenance of intestinal homeostasis. The immune modulation of the host has been confirmed as one of the primary health benefits derived from the consumption of probiotic functional food [95]. One of the most challenging human health problems faced around the world is the mitigation of infectious diseases. Many recorded deaths are linked to intestinal infection as a result of the consumption of contaminated food and water containing pathogenic microorganisms. The advent of probiotics is a key solution for foodborne diseases, as the efficacy of probiotics for the treatment of these diseases has been confirmed by several scientific studies [95]. According to a study by Shu and Gill (2001) [96], *B. lactis* HN019 was shown to reduce the severity of infection caused by enterohemolytic pathogen *Escherichia coli* O157: H7, and it was thus inferred that this reduction may be associated with the enhanced immune protection conferred by the probiotic.

A summary of some of the salient and major health benefits conferred by probiotics and their proposed mechanisms are highlighted in Table 5.

Although the therapeutic properties of probiotics have been confirmed and are vital for human health, it is critical that probiotics conform to international standards and accepted norms for usage. According to the Joint FAO/WHO (2002) [97] guidelines on probiotics, the use of probiotic microorganisms to confer health benefits on the host must indicate the dosage regimens and duration

of use as recommended by the manufacturer of each individual strain or product based on scientific evidence, and as approved in the country of sale. Moreover, each probiotic product should prescribe the minimum daily amount that is necessary in order for the product to confer a specific health benefit or benefits. Evidence of this purpose should be clear and, where possible, should result from in vitro, animal, or human clinical studies.

Probiotics confer an array of human health benefits including the following: (1) Maintains the healthy microbiota balance of the intestine by competing and excluding harmful pathogens, as well as adheres to the gastrointestinal gut [98,99]; (2) Stimulate and enhance the immune response by increasing the release of serum antibodies (Immunoglobulin M (IgM), Immunoglobulin G (IgG), and Immunoglobulin A (IgA) and balancing pro-inflammatory and anti-inflammatory cytokines [28,100]. Probiotics also help to prevent or decrease the duration of intestinal diseases such as Inflammatory bowel disease, diarrhea, and constipation by colonizing and modulating the gut microflora, synthesizing antimicrobial compounds, and enhancing the immune response and secretion of mucus [101]. Additionally, probiotics are important in the prevention of metabolic disorders such as obesity, diabetes, and cardiovascular diseases by enhancing gut microbiota, restoring the antioxidant systems and decreasing insulin resistance and inflammation [9]. Probiotics inhibit the growth of *Candida* and *Helicobacter pylori*, thus preventing intestinal infection by competing and adhering to the mucosal surface and enhancing immune responses [28]. They also help to prevent the growth of cancer by acting as a therapeutic agent for cancer treatment by detoxification of chemical carcinogens, decreasing the release of toxic metabolites, enhancing the antioxidant system, modulating the immune response to inhibit self-proliferation of cancer and generating metabolites like butyrate which increases cancer cell death (apoptosis) and produces anti-mutagenic effects. Probiotics assist in the maintenance and alleviation of lactose intolerance by providing β -galactosidase (lactase) enzyme which breaks down lactose into simple sugars [28].

Another key benefit from probiotics includes the lowering of cholesterol levels by precipitating cholesterol with free bile salts into bile acids and thereby reducing cholesterol absorption [102]. Additionally, probiotics enhance the absorption of minerals such as calcium to help to prevent mineral deficiency diseases such as osteoporosis. They also enhance nutritional value by synthesizing cofactors and vitamins (K and B) and by producing various enzymes that are useful in the digestion of food [89]. A schematic display of how probiotics exert their beneficial roles in the gastrointestinal tract and in the intestines is shown in Figure 1.

Table 5. Health benefits of probiotic bacteria and speculated mechanisms involved.

Probiotic Strain	Health Benefits	Mechanism of Action	References
Lactic acid bacteria	Prevention and treatment of colon cancer	Ensures biodegradation of susceptible and potential carcinogens Boost the immune response system of the host and inhibits pro-cancerous enzymatic activity of colonic microorganisms	Kahouli et al., 2013 [103]
<i>Bifidobacterium bifidum</i>	Inhibition of enteric pathogens	Prevents and reduces diarrhea Inhibits invasive pathogens by secretion of acids and increases antibacterial action of the intestinal microflora	Gill & Prasad, 2008 [104]; Russell et al., 2011 [105]
<i>Bifidobacterium lactis</i> , <i>L. bulgaricus</i> , <i>L. plantarum</i> , <i>L. acidophilus</i>	Irritable bowel syndrome and constipation prevention and treatment	Alleviates symptoms of irritable bowel syndrome. Modulates and alters gastrointestinal microflora to offset abnormal conditions.	Guerra et al., 2011 [106]; Mena et al., 2013 [107]
<i>Lactobacillus</i> , <i>Bifidobacterium</i>	Treatment of <i>Helicobacter pylori</i> infection	Epithelial and mucosal cells are competitively colonized. Production of bacteriocins and organic acids to impede action of the bacteria.	Hsieh et al., 2012 [108]
<i>Bifidobacterium breve</i>	Rotaviral gastroenteritis treatment	Promotes and boosts the production of anti-rotavirus IgA or anti-influenza virus	Gonzalez-Ochoa et al., (2017) [109]
<i>Oxalobacter formigenes</i> <i>Lactobacillus</i> and <i>Bifidobacterium species</i>	Treatment of kidney or Urogenital infections	Metabolic and mopping up action on toxic compounds.	Roswitha et al., 2013 [110]
<i>Lactobacillus acidophilus</i> NCFM	Diabetes and obesity	Minimizes risks associated with type 2 diabetes mellitus and enhances host metabolic system ensuring weight management	Andreasen et al., 2010 [111] Sanchez et al., 2013 [112]

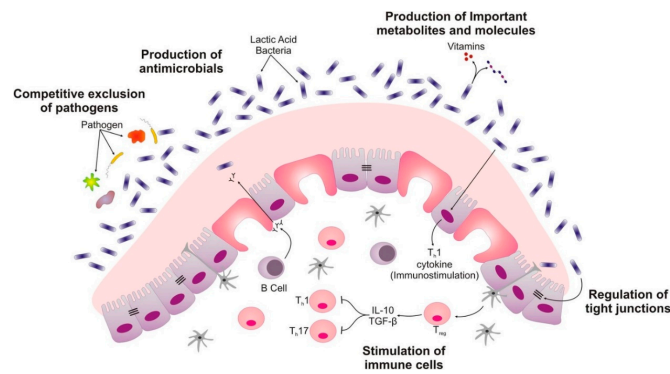


Figure 1. Schematic displaying different ways by which probiotics exert their beneficial roles in the intestine. Lactic acid bacteria isolated from dairy product are responsible for the competitive exclusion of pathogens, secretion of important metabolites and molecules such as bacteriocins. These probiotics create a mucus barrier by stimulating the goblet cells. The interaction of *Lactobacillus* with intestinal epithelial cells also differentiates immune cells and regulates the barrier function of intestinal epithelial cells [36].

3.4. Health Benefits of Probiotics in Some Disease Conditions

3.4.1. Lactose Intolerance

Lactose is a disaccharide and an important nutrient in all mammalian neonates and is broken down into glucose and galactose. In most human populations, the activity of lactase diminishes during mid-childhood (about five years of age), leading to low lactase levels from that period thereafter [113]. Many people, however, retain high levels of lactase activity throughout their adult life. It is worthy to note that the inherited trait of being lactase persistent (adults retain their ability to digest lactose) in humans is dominant while lactase-non persistent (adults lose their ability to digest lactose) is recessive [114]. The failure of the small intestine to produce adequate lactase when milk is ingested results in the condition known as lactose intolerance or lactose malabsorption [115,116]. The metabolism of lactose in the small intestine is shown in Figure 2. Lactose intolerance is thus defined as the pathophysiological situation in which the small intestinal digestion and or colonic fermentation is altered, which leads to clinical symptoms [117].

The unabsorbed lactose or lactose that is spilled over into the colon will thus be hydrolyzed β -galactosidase, the colonic bacterial enzyme (mostly produced by probiotics) through metabolism resulting in the formation of glucose and galactose. Consequently, glucose and galactose are transformed into lactate and short chain fatty acids (SCFA) hydrogen, acetate, methane, propionate, and butyrate as shown in Figure 3. Osmotic load thus occurs in the colon that is due to the formation of microbial biomass, the original substrate (lactose), and the intermediate and final products glucose and galactose. This phenomenon might increase transit time in the colonic, alter fermentation profiles and ultimately result in diarrhea [116,117].

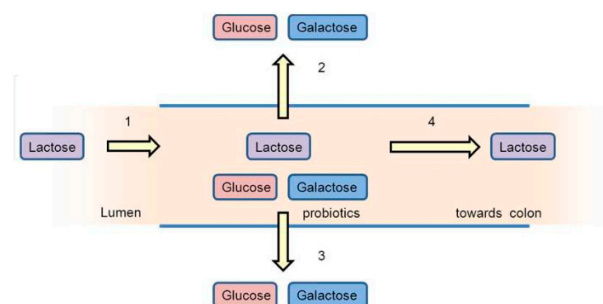


Figure 2. Small intestine metabolism of lactose. Lactose enters the small intestine (1) and is then converted by lactase from the host (2) or by probiotics (3). Excess amounts of lactose spill over into the colon (4). (Adapted from [117]).

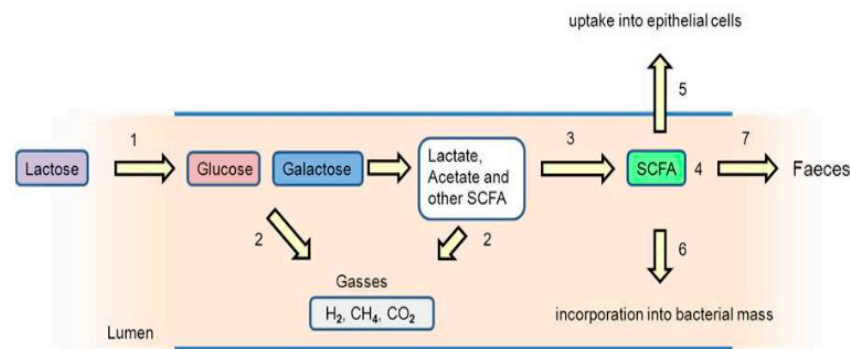


Figure 3. Colonic metabolism of lactose. Lactose enters the colon (1) and is fermented by the microbiota into glucose and galactose. Gases such as hydrogen, methane, and carbon dioxide are formed (2). Lactate is also formed and converted into short chain fatty acids (SCFA) (3,4). In this stage, gasses are also formed (2). SCFAs can be taken up by epithelial cells (5) or can be used by the microbiota (6) or excreted in the faeces (7). (Adapted from [117]).

Some lactose intolerance symptoms include abdominal pain, bloating, flatulence, and diarrhea. The administration of probiotic supplements or use of lactase tablets is highly recommended for conditions of low lactase activity in humans [113]. β -galactosidase mutants that were overproduced, alleviated the symptoms of lactose malabsorption as confirmed by Ibrahim and O’Sullivan (2000) [118] in their study (Ibrahim et al., 2010, [119]). Moreover, lactose absorption in lactose-intolerant individuals was improved with milk containing *L. acidophilus* [120]. The administration and usage of probiotics has been confirmed to change and improve the population of the colonic microbiota; thereby, a potential therapy for lactose-intolerant subjects [121,122]. Recently, Gyawali et al. (2020) [123] demonstrated *L. bulgaricus* strains can produce maximum amount of β -galactosidase further supporting the use of lactic acid bacteria as probiotics in the treatment of lactose intolerance.

3.4.2. Diabetes and Obesity

According to Ley et al. (2005) [124], gut microbiota plays a vital role in the pathology of insulin resistance (type 2 diabetes) and obesity. Furthermore, many human and animal studies have also suggested that gut microbiota enhances body weight gain and increases insulin resistance, and these phenotypes are thus transmittable with gut microbiota as observed in the implantation studies of microbiota from obese to normal and germ-free mice [125,126]. The established mechanism associated with gut microbiota-mediated pathology of obesity and diabetes is through, (1) increased energy harvest, (2) increased blood LPS levels (endotoxemia), and (3) low-grade inflammation [127]. Evidence-based knowledge has therefore confirmed that probiotic use has the potential to modulate gut microbiota, and is thus considered as a potential target to treat against diabetes and obesity [28].

There are two distinct bacterial phyla, the Gram-negative bacteroidetes and the Gram-positive firmicutes which are significantly dominant in the gut microenvironment. These two bacteria have an impact in metabolic diseases such as obesity and diabetes. Recent studies have confirmed that, an increased number of *Bacteroidetes* with a decrease in the levels of *firmicutes* over time has been linked to obesity [128,129]. It has also been proven that type 2 diabetes patients relatively have decreased levels of *Firmicutes* species than *Bacteroidetes*, thus increasing the bacteroidetes/firmicutes ratio which correlates positively with glucose concentration in the plasma [130]. Probiotic strains *Bifidobacterium longum*, *L. casei* and *Lactobacillus acidophilus* have also been credited with the prevention of obesity as they possess hypocholesterolemic properties [131].

3.4.3. Acute Diarrheal Disease

The application of probiotics in the treatment of acute diarrhea in both children and adults has been effective due to enough growing evidence in this regard. A meta-analysis confirmed that probiotics

reduced the mean duration of diarrhea by 13 h, reduced treatment failure by 38%, and thus was effective in preventing diarrhea in children [132]. Moreover, a recent Cochrane review of 63 randomized and quasi-randomized controlled trials, 56 of which involved infants and children, concluded that probiotics were very effective in reducing the mean duration of diarrhea by about 25 h. Therefore, the likelihood of diarrhea lasting ≥ 4 days was also reduced by 59%, the stool frequency also decreased approximately by one less bowel movement on day 2 after probiotic treatment which resulted in no adverse events [133].

The administration of *Lactobacillus reuteri* in a meta-analysis that consisted of eight randomized control trials with 1229 children as participants proved that it was effective in reducing the duration of diarrhea (25 fewer hours; 95% Confidence Interval (CI), 11 to 39 fewer hours) and significantly increased the rate of therapy on the first and second day [134]. Another meta-analysis of two randomized control trials involving 201 children diagnosed with diarrhea from rotavirus confirmed the efficacy of *L. rhamnosus* GG versus placebo (two fewer days; 95% CI, 0.6 to 3.6 fewer days) as there was a significant decrease in the disease condition [135].

3.4.4. Inflammatory Bowel Diseases and Irritable Bowel Syndrome

Inflammatory bowel diseases, such as pouchitis and Crohn's disease, as well as irritable bowel syndrome, has been confirmed to be due to aggravations or alterations of the normal intestinal microflora in the gastrointestinal gut [76]. Many research studies have proposed the administration of probiotics as a potential remedy in the treatment of these conditions as probiotics replenish or modify the gut microflora ensuring it, being healthy to support the host [76,136,137]. Globally, the intestinal microbiota plays a critical role in gut inflammatory conditions, probiotics thus have been recommended as potential support for treatment as they could remediate such conditions through modulation of the gut microbiota [97].

3.4.5. Cancer

There is scientific evidence proving that probiotic microorganisms can prevent or delay the onset of certain cancers. This stems from the fact that members of the gut microflora could produce carcinogens such as nitrosamines. Knowledge of this phenomenon thus is important as the administration of lactobacilli and bifidobacteria reduce the absorption of harmful mutagens as well as decrease β -glucuronidase and carcinogen levels through modification of the gastrointestinal flora [138]. There is ample evidence that cancer recurrences at other sites, such as the urinary bladder could be reduced by intestinal instillation of probiotics including *L. casei* Shirota [139].

3.4.6. Cardiovascular Diseases

There is scientific evidence buttressing the use of probiotics for the treatment of cardiovascular diseases. It has been established that the use of probiotic lactobacilli and metabolic by-products potentially confer benefits to the heart, which also pertains to the prevention and therapy of various ischemic heart syndromes [140] and lowering serum cholesterol [141].

Therapeutic benefits of probiotics in the management of cardiovascular diseases has been substantiated by recent clinical studies notably in the treatment of hypertension. Probiotics were reported to reduce systolic and diastolic pressures (estimatedly 14–6.9 mm drop) in patients diagnosed with hypertension [142]. Notable probiotic strains that have been clinically proven to alleviate the condition of hypertension are *L. plantarum*, *L. casei*, *L. plantarum*, *L. helveticus*, and *Streptococcus thermophilus* [143]. The decreasing effect of the blood pressure is linked to a reduction in the synthesis of nitrogen oxide in the macrophages, thus decreasing reactive oxygen species and promoting dietary calcium absorption via a different mechanism. This related mechanism is as a result of the synthesis of certain metabolites such as conjugated linoleic acids (CLA), angiotensin-converting enzyme (ACE) inhibitor peptides, and short chain fatty acids (SCFAs) [142].

3.4.7. Urogenital Infections

It is estimated that more than one billion women globally, have been diagnosed with non- sexually transmitted urogenital infections ranging from urinary tract infection (UTI), bacterial vaginosis (BV), and many other yeast infections [144]. Some notable species that are reported as causative agents of BV are *Ureaplasma urealyticum*, *Mycoplasma hominis* and *Gardnerella vaginalis* [145]. The vaginal microbial composition is described as a habitat that supports the growth and existence of more than 50 different beneficial species with the lactobacillus group regarded as an essential and critical regulator of the microbial ecosystem in the vagina. Some of the predominant lactic acid bacteria species include *Lactobacillus vaginalis*, *Lactobacillus casei*, *Lactobacillus reuteri*, *Lactobacillus salivarius*, *Lactobacillus brevis*, *Lactobacillus rhamnosus* and *Lactobacillus delbrueckii* subsp. *bulgaricus* [146]. Thus, an imbalance in the microbial composition greatly affects the health of the vaginal microbial ecosystem that increases the risk of contracting urogenital tract infections and the potential risk of bacterial vaginosis. The administration of probiotics can adequately restore the microbial ecosystem by balancing the number of lactic acid bacteria species [146].

3.4.8. Allergy

The benefits derived from probiotics cannot be overemphasized, and thus probiotics have been credited with the management and protection of allergic diseases in recent times as proven by many clinical trials. For example, in vitro studies using *Lactobacillus plantarum* L67, has proven to be effective in preventing allergy-linked disorders which thus promotes the synthesis of interleukin-12 and interferon-g in the host [147]. *Lb. plantarum* 06CC2 used in another study confirmed its efficacy in alleviating allergic symptoms which resulted in decreasing the levels of total Immunoglobulin E, histamine and, ovalbumin-specific immunoglobulin E as observed in the sera of ovalbumin-sensitized mice [146]. According to Kukkonen et al. [148], the administration of a complex probiotic which comprised of *Bifidobacterium breve*, *Lactobacillus rhamnosus* GG, and *Propionibacterium freudenreichii* to pregnant women were highly effective and decreases the risk of atopic dermatitis in children below the age of two years. Thus, administering probiotics to children helps in remedying and preventing eczema. Another study confirmed the efficacy of probiotics in the prevention of allergic reactions to dairy milk. Three strains (*Bifidobacterium longum* subsp. *infantis* LA308, *Lactobacillus rhamnosus* LA305, and *Lactobacillus salivarius* LA307) were used in this study and have thus been successful in preventing this allergic condition [149].

3.4.9. Gut–Brain Axis

The therapeutic application of probiotics has been acknowledged as a great benefit for human health. Although the mechanism of probiotics has a major role in the colonization of the gastrointestinal tract, which helps to prevent or treat many gastrointestinal disorders, attention has however been given to many studies that seek to elucidate the influence of the gut microbiota on the brain and the entire central nervous system (CNS) [146]. The connection between the gut microbiota and the brain has been established to be a bi-directional, interactive system by which regulatory signals are exchanged between the gut and the CNS. To buttress the effect of probiotics on the brain, many clinical studies have been conducted such as the administration of a daily dose of *L. plantarum* WCFS1 (4.5×10^{10} CFU/day) to children diagnosed with autism spectrum disorder. The administered probiotic significantly improved their performance in school and their attitude towards eating [150]. Another study confirmed a significant decrease in the cognitive reaction to the mood of sadness in healthy humans, when doses of a mix of different species consisting of *L. acidophilus* W37, *L. brevis* W, *L. casei* W5, *Bifidobacterium bifidum* W2, *B. lactis* W, *Lactococcus lactis* (W19 and W58), and *L. salivarius* W2 were administered [151].

3.5. Antiviral Activity of Lactic Acid Bacteria

The benefits derived from lactic acid bacteria cannot be overemphasized, as many studies have confirmed the potential use of lactic acid bacteria for the treatment of viral diseases and infections. It is also worth noting that there are diverse probiotic lactic acid bacteria with health-promoting antiviral properties. Some of these probiotic lactic acid bacteria are endowed with anti-influenza properties and have been confirmed to modulate and exert antagonistic effects on influenza virus in mice [152,153]. Lactic acid bacteria are therefore regarded as potent antidotes for many viral infections. Moreover, the emergence of viral infections such as the recent COVID-19 has presented a daunting challenge to scientists as they scramble to find a potent drug to combat this global menace. A natural alternative viral infection treatment approach such as the use of probiotics and lactic acid bacteria is thus highly warranted as the conventional prophylactic antiviral drugs and medications are often accompanied by many adverse side effects.

One of the greatest causes of mortality globally is the influenza virus which primarily results in an acute respiratory viral infection [154]. The most sensitive part of the human system to viral invasion is the immune system. The immune systems of high-risk populations, especially the elderly and children, are highly susceptible to viral attack as a result of poor immune function. In addressing immune function challenges in humans, it is important to consider boosting the natural immune defenses by adopting probiotic lactic acid bacteria as a tool against viral diseases. The need to embrace probiotic microorganisms and their derived metabolic products is thus a promising approach in the fight against many viral diseases and essentially vital in protecting public health.

The mechanisms by which probiotics and lactic acid bacteria exert their antiviral properties are varied. Some of the well-known probiotic antiviral mechanisms include direct viral interaction, synthesis of antiviral inhibitory compounds, immune system modulation, and stimulation. Many research studies have confirmed the antiviral property of probiotic lactic acid bacteria to be strain-specific and dependent [155].

3.5.1. Mechanisms of Probiotic Action on Viruses

Probiotic virus interaction: The most widely conceptualized mechanism of action of probiotic lactic acid bacteria has been linked to the interaction between the virus and probiotic lactic acid bacteria. The chain of reaction between the pair is perceived to be due to an adsorptive interaction [155]. This interactive property between probiotics and viruses was confirmed by Botic et al., (2007) [156] where they showed that probiotics had the ability to block and capture vesicular stomatitis virus (VSV) through direct cooperation between lactic acid bacteria cells comprised of *Lb. paracasei* A14, *Lb. paracasei* F19, *Lb. paracasei/rhamnosus* Q8, *Lb. plantarum* M1.1, and *Lb. reuteri* DSM12246 and VSV envelope. Another study conducted by Wang et al. (2013) [157] gave credence to the antiviral potential of *E. faecium* NCIMB 10415 in impeding the activity of influenza viruses during cooperation. A study by Al Kassaa et al., (2014) [158] demonstrated that *L. gasseri* CMUL57 a vaginally isolated microbiome, was also capable of impeding enveloped herpes simplex type 2 (HSV-2). However, this microbiome was not successful and capable of inhibiting coxsackie virus (CVB4E2).

Immune system induction: Modulation of the host immune system is a characteristic feature of probiotic lactic acid bacteria as they are strong promoters of antimicrobial and antiviral activity. Higher levels of interleukin 12-inducing activity were found in peritoneal macrophages of mice after isolating the strain *L. plantarum* YU from food products [158]. Strain *L. plantarum* YU was also confirmed to possess a superior and intensified activity of natural killer cells resident in spleen cells as well as a good level of IgA production from cells of Peyers' patch. Another confirmed characteristic property was the stimulation of Th1 immune responses and IgA production induced anti-influenza H1N1 virus activity [158].

There are various research studies on probiotic lactic acid bacteria that have confirmed their possessing superior antiviral properties. Some of these lactic acid bacteria are *Lb. casei* MEP221106 or MEP221114, *Lb. rhamnosus* CRL1505 [159]. Another strain of interest is *Lb. rhamnosus* (LGG) that has

been classified as safe and has also been found to be an enhanced immune system booster, particularly in HIV-infected patients [160]. *L. rhamnosus* GG has also been confirmed through several clinical studies as therapeutically safe for use by neonates and infants in the prevention of viral infections [161]. A general schematic illustration of the mechanisms of probiotic action against viral infection is shown in Figure 4.

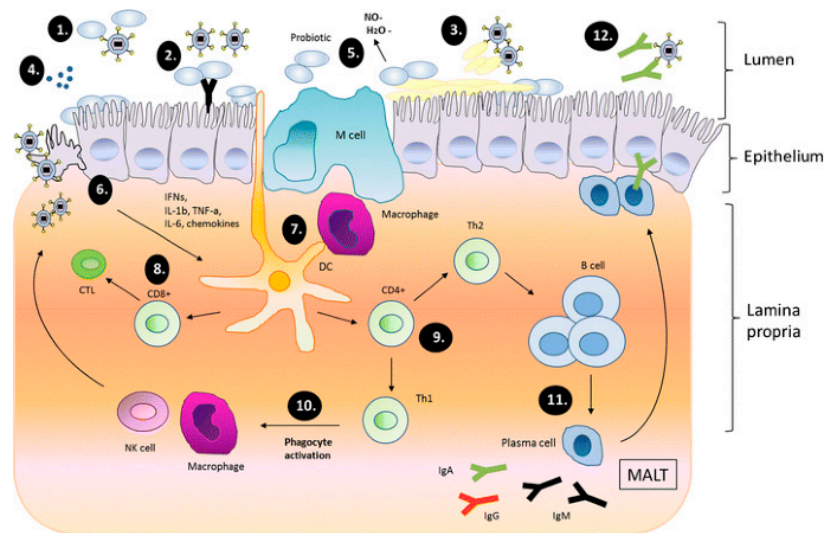


Figure 4. Mechanisms of probiotic action in the inhibition of viral infections (adapted from [162]).

A summary highlighting the probiotic mechanisms in Figure 4 is as follows [162]:

1. Probiotic bacteria is irreversibly attached to the virus, therefore limiting the virus' binding effect to the host cell receptor.
2. Probiotic adhesive property is capable of obstructing viral attachment on the epithelial surface through steric hindrance.
3. Virus replication is inhibited by mucin attachments produced by probiotics through the process of mucosal regeneration.
4. Antimicrobial metabolites produced by probiotics act against pathogens.
5. Synthesis of dehydrogenase by probiotics may possess and contribute to antiviral processes.
6. Epithelial cells generally promote the modulation of immune responses.
7. Macrophages and dendritic cells are induced, thus stimulating the immune response.
8. Viral cells are destroyed by the joint action of cluster of differentiation 8 (CD8) T cells and T lymphocytes that differentiate into cytotoxic T lymphocytes (CTLs).
9. Further differentiation of CD4 and T lymphocytes into helper T cells (Th1 and Th2) occurs.
10. Activated phagocytes eliminate viruses through induction of the Th1 cells.
11. B-cells are proliferated by stimulation of Th2, which migrates to secondary lymphatic organs resident in mucosa-associated lymphoid tissue (MALT). Differentiation of B cells into Ig producing plasma cells occurs afterward.
12. Antibodies activated during this immune response completely eliminate the virus.

3.5.2. Strain-Specific Antiviral Properties of Lactic Acid Bacteria

Many research studies have confirmed the antiviral characteristics of probiotic lactic acid bacteria to be strain-dependent. It is thus essential to know the different species of lactic acid bacteria and understand their mode of action in relation to inhibition of viral diseases and other related infections. A summary of some of the key antiviral characteristics is highlighted in Table 6.

Table 6. Some probiotic strains endowed with antiviral properties.

Lactic Acid Bacteria Strain	Origin of Strain	Virus Evaluated	Mode of Action	References
<i>L. fermentum</i> CECT5716	Human breast milk	Influenza virus	Enhances the response of antibodies	Boge et al., 2009 [163]
<i>Lactobacillus delbrueckii</i> ssp. <i>Bulgarius</i> OLL1073R-1 (1073R-1)	Fermented food (Yogurt)	Influenza virus	Promotes antagonistic antibodies	Nagai et al., 2011 [154]
<i>L. plantarum</i> YML009	Fermented food (Kimchi)	H1N1 Influenza virus	Activation of Th1 immune response	Rather et al., 2014 [164]
<i>L. rhamnosus</i> CRL1505	Commercial probiotic strains	Respiratory syncytial virus (RSV)	Production of IFN- γ and IIs	Villena et al., 2011 [165]
<i>Lactobacillus gasseri</i> SBT2055 (LG2055)	Human feces	RSV	Proinflammatory activity	Eguchi et al., 2019 [166]
<i>Enterococcus durans</i>	Goat milk	Herpes Simplex Virus (HSV-1) and Human papillomavirus (PV-1)	Decreases viral cell replication	Cavicchioli et al., 2018 [167]
<i>L. acidophilus</i> strain NCFM	Newborn feces	Reduce influenza like symptoms	Immunomodulation	Leyer et al., 2009 [168]
<i>Lactobacillus ruminis</i> SPM0211	Isolated from a young Korean girl	Rotavirus (ROV)	Immunomodulation and promotion of interferons (IFNs)	Kang et al., 2015 [169]
<i>L. rhamnosus</i>	Gut flora	HSV-1	Stimulation of macrophages and elimination of HSV-1	Khani et al., 2012 [170]
<i>L. plantarum</i> CNRZ 1997	-	H1N1 strain A	Proinflammatory response	Kechaou et al., 2013 [171]
<i>E. faecium</i> NCIMB 10415	-	Transmissible gastroenteritis virus) TGEV	Promotion of nitric oxide (NO) production and secretion of Interleukins (IL-6 and IL-8)	Chai et al., 2013 [172]
<i>L. acidophilus</i>	-	ROVs	Reduction in duration of diarrhea	Grandy et al., 2010 [173]

3.5.3. Antiviral Properties of Bacteriocins

Bacteriocins have been regarded as a promising antiviral alternative as compared to conventional antiviral agents. This has been necessitated as a result of the surge in increased resistance against commercially available antiviral agents [174]. Many scientists thus have explored the potential of bacteriocins largely produced from probiotic bacteria. Bacteriocins possess antiviral properties and generally enhances the immunomodulatory mechanism of the host against viral infections [175]. Bacteriocins have therefore been exploited in the treatment of many viral infections and diseases, and have thus proven to be successful in remedying these disease conditions [175]. *Bacillus subtilis* and *Bacillus amyloliquefaciens* are both associated with the production of a cyclic bacteriocin known as subtilisin, which has been confirmed to be effective against Herpes Simplex Virus (HSV) Type 1 and II [155,176]. Influenza virus activity has also been inhibited by a bacteriocin linked to *Lb. delbrueckii* subsp. *bulgaricus* 1043 [177]. Other known antiviral bacteriocins include enterocin ST5HA produced by *Enterococcus faecium*, Enterocin AAR-74 and Enterocin AAR-71 with both produced by *Enterococcus faecalis*, Enterocin CRL35 and Enterocin ST4V produced from *Enterococcus mundtii*, and a peptide, considered as a bacteriocin produced by *Lb. delbrueckii* subsp. *bulgaricus* [178]. Enterocin AAR-74 is reported to have decreased the proliferation of coliphage HSA significantly, by 10-fold; however, Enterocin AAR-71 was reported to have had no significant effect on phage HSA. Herpes viruses HSV-1 and HSV-2 were also inhibited by Enterocin ST4V in a dose-dependent system [178].

4. Conclusions

Lactic acid bacteria are a group of ubiquitous, heterogeneous, and ecologically diverse bacteria with significance in food fermentation processes. Lactic acid bacteria are also therapeutically useful as an antidote for many foodborne related diseases. The impact of lactic acid bacteria is therefore critical in promoting a healthy microbiota and increased immunity against diseases and infections. In addition, probiotics supplementation in human diets cannot be overemphasized based on the countless derived therapeutic health benefits. Probiotics and the advent of lactic acid bacteria are underpinned in the One Health Concept because stable-to-optimum health status requires a well-balanced microbiota composition and a strong immune system. The enlightened culture of food safety now advocates natural remedies that are environmentally friendly while inhibiting pathogens and food spoilage organisms. Thus, the concept of bio-preservation through lactic acid fermentation is a highly recommended alternative for product shelf life extension.

The COVID-19 pandemic has resulted in a greater focus on preventive health and innate immunity as pro-active approaches to dealing with this novel coronavirus. As a result, it has been suggested that the augmented use of probiotics and greater consumption of lactic acid fermented foods could be among the best ways to boost the immune system and ward off viral infection. As it is widely accepted that probiotics and lactic acid fermented foods are capable of boosting the body's immune system, the augmented use of these natural food products could be among the best ways to boost immunity and build the first line of defense as the virus [179]. Thus, another potential application of this immune system enhancement would be to explore the use of lactic acid bacteria as a live vaccine prophylaxis against COVID-19 [179]. Because lactic acid bacteria are capable of delivering antigens to the mucosal and systemic immune systems and generating specific antibody responses in serum and secretions, lactic acid bacteria as a live vaccine could build an effective immune response. It is also possible to construct biologically contained food grade strains for such a vaccine. This could be a promising vehicle not only for antigens but also for other biologically active compounds such as immunomodulators, antibodies, enzymes, or peptides [179]. In summary, lactic acid bacteria, probiotics, and fermented foods could help to serve as an effective, ongoing prophylaxis regimen during the current COVID-19 pandemic and beyond. However, additional clinical investigation and studies are warranted.

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