Recent developments of lactic acid bacteria and their metabolites on foodborne pathogens and spoilage bacteria: Facts and gaps

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Hafize Fidan[a,*], hfidan@abv.bg, Tuba Esatbeyoglu[b], esatbeyoglu@lw.uni-hannover.de, Vida Simat[c], vida@unist.hr, Monica Trif[d], monica_trif@hotmail.com, Giulia Tabanelli[e], giulia.tabanelli2@unibo.it, Tina Kostka[b], kostka@lw.uni-hannover.de, Chiara Montanari[e], chiara.montanari8@unibo.it, Salam A. Ibrahim[f], ibrah001@ncat.edu, Fatih Özogul[g], fozogul@cu.edu.tr

[a]Department of Tourism and Culinary Management, University of Food Technologies, 4002, Plovdiv, Bulgaria

[b]Institute of Food Science and Human Nutrition, Gottfried Wilhelm Leibniz University Hannover, Am Kleinen Felde 30, 30167, Hannover, Germany

[c]University Department of Marine Studies, University of Split, Ruđera Boškovića 37, 21000, Split, Croatia

[d]Centre for Innovative Process Engineering (CENTIV) GmbH, 28857, Syke, Germany

[e]Department of Agricultural and Food Sciences, University of Bologna, 40127, Bologna, Italy

[f]Food Microbiology and Biotechnology Laboratory, North Carolina Agricultural and Technical State University, Greensboro, NC, 27411, USA

[g]Department of Seafood Processing Technology, Faculty of Fisheries, Cukurova University, 01330, Adana, Turkey

*Corresponding author.

Abstract

Lactic acid bacteria (LAB) are common microorganisms found in various ecosystems including in plants, fermented foods, and the human body. Exploring the biodiversity of lactic acid microflora and characterization of LAB is a new approach to form a variety of starter communities to create innovative nutritional food matrices. There has been growing interest in LAB isolated from non-dairy environments as these bacteria exhibit significant metabolic diversity and have unique taste-forming activities. Disease may be prevented, or treated by LAB but the treatment of disease conditions with LAB is highly dependent on the host's microbiome and diet and varies in both effectiveness and side effects from individual to individual. Future perspectives on the study of LAB may be related to the expansion of our knowledge in the fields of genetics and genetic engineering. The application of genetic science may help to improve existing strains and develop new strains with characteristics designed for specific purposes. Therefore, the preservative effects of LAB and their metabolites, as well as their interaction on the growth of food borne pathogens and food spoilage microorganisms were elucidated. In addition, the competitive models for microbial growth between LAB and other microorganisms as well as the role of LAB in the elimination of toxic compounds in food products were discussed. Moreover, the review provided an overview of the risks and benefits of using LAB in the food industry.

Keywords:

Lactic acid bacteria, Starter culture, Fermented products, Food-borne pathogens, Microbial interaction

Abbreviations

No keyword abbreviations are available

1 Introduction

The increase in global food production and estimated 35 percent rise in food demand by 2030 are bringing new challenges to the food sector with regard to quality, safety, and human health according to Food and Agriculture Organization (FAO, 2017). Moreover, there is increased consumer demand for natural and preservative-free ready-to-eat food products that tend to be more perishable and whose shelf-life is limited and dependent on temperature regime and handling. Food becomes undesirable or unacceptable for human consumption during the spoilage process in terms of sensory characteristics (development of off-odors, off-flavors, off-colors, softening, slime, etc.) and quality. The FAO estimates that 1/3 of the world's food is lost due to spoilage or wastage (FAO, 2020), resulting in significant adverse environmental and economic effects. Spoilage organisms are responsible for the unfavorable sensory characteristics of the foods.

Meanwhile, consumers are more aware of the numerous food safety risks that have increased as global trade has increased. Consequently, mitigation of food losses due to spoilage in today's food supply chain are becoming significant challenges and are also important global public health issues. The major foodborne pathogens (FBP), bacteria, fungi, parasites, and viruses, are responsible for many illnesses and food recalls worldwide each year with a persistent annual number of mortalities (Evivie et al., 2020; Narbad & Wang, 2018). The undesirable microorganisms can contaminate food along the production and supply chains (Abdelhamid & El-Dougdoug, 2020). Contamination of foods can occur at any point along the chain—during production, processing, distribution, or preparation. In addition, they pose a health risk to consumers by causing acute illnesses (mainly abdominal pain and gastrointestinal manifestations) as well as chronic cardiac or neurological disorders (Özogul & Hamed, 2018). The presence of undesirable microorganisms in foods can result in the formation of toxins that can cause allergic reactions and poisoning. For example, pathogenic bacteria can decarboxylate amino acids to biogenic amines such as histamine, cadaverine, putrescine, or tyramine that have various toxic effects on humans (Özogul et al., 2018; Özogul & Hamed, 2018; Šimat & Dalgaard, 2011). Strategies for controlling spoilage bacteria and FBP in food products include management of both intrinsic (pH,

water activity, NaCl content, nutritive components) and extrinsic factors such as temperature regime and conservation method that are essential for microbial growth in the food product. The use of chemical compounds (both synthetic and natural) and antimicrobials of biological origin are also necessary to control pathogens and prolong the shelf-life of food products. Due to concerns regarding the antibiotic resistance of some major food pathogens and the constant effort to eliminate or reduce the use of synthetic additives as antimicrobial agents, the search for new, effective alternatives is of the utmost importance with the development of new minimal processing technologies that can keep the quality and freshness for ensuring food quality and safety (Landete et al., 2008, LeBlanc et al., 2011).

Lactic acid bacteria (LAB) are a group of Gram-positive, catalase-negative, nonsporulating, aero-tolerant, acid-tolerant, and strictly fermentative cocci or rods bacteria that are generally recognized as safe (GRAS), natural bio-protective, and health-promoting microbes (Abdelhamid & El-Dougdoug, 2020; Ben Said et al., 2019; Özogul & Hamed, 2018). LAB are a heterogeneous group of bacteria that includes, but is not limited to the genera *Lactobacillus, Lactococcus, Streptococcus, Enterococcus, Leuconostoc, Carnobacterium, Oenococcus, Pediococcus, Tetragenococcus, Vagococcus*, and *Weissella* (Plavec & Berlec, 2020). These bacteria have been used for the fermentation of different food products since ancient times. More recently, they are considered biological alternative that may enhance food preservation, also known as bio-preservation (Ayivi et al., 2020; Laslo et al., 2020). The efficiency of bio-protective cultures was reported to reduce bacterial loads and inhibition of FBP in meat and vegetable products (LeBlanc et al., 2013, Sidari et al., 2020, Tamang et al., 2016). They are responsible for controlling yeasts and molds, inhibiting bacterial loads in bread production, and inhibiting *Listeria monocytogenes, Clostridium* sp. and spoilage microorganisms in seafood and dairy products (Ben Said et al., 2019; Lerner et al., 2019). The antimicrobial metabolites produced by LAB range from simple organic acids to more complex compounds such as antimicrobial peptides. These individually have been identified and characterized for their inhibitory potential against spoilage organisms and FBP (Plavec & Berlec, 2020; Siedler et al., 2019). The protective activity of LAB is described via three mechanisms: displacement/exclusion, competition for nutrients, and production of natural antimicrobial and antifungal compounds (Ayivi et al., 2020; Ben Said et al., 2019). In addition to food safety and spoilage prevention, LAB has beneficial effects on human health when correctly applied. In this review, the preservative effects of LAB and their metabolites, as well as their interaction with the growth of FBP and food spoilage microorganisms have been elucidated. The review also gives an overview of the risks and benefits of using LAB in food production.

2 The importance of LAB and their preservative effects for food

2.1 Characteristics of LAB

LAB belong to the group of gram-positive bacteria within the phylum Firmicutes (Bintsis, 2018; Laranjo et al., 2017). Representatives of these classified LAB show either a rod-shaped (bacilli) or spherical (cocci) morphology (Bintsis, 2018; Laranjo et al., 2017), while being non-motile, catalase negative and unable to form spores (Bintsis, 2018). Additional characteristics of LAB include their low guanine-cytosine content as well as their high tolerance to acidity e.g. the low pH in the human stomach, which enables the accumulation of food-origin LAB in the gut as part of the microbiome (Ammor & Mayo, 2007; Bintsis, 2018; Klingberg et al., 2005; Laranjo et al., 2017). Pasolli et al. (2020) analyzed the origin and prevalence of LAB species from human microbiomes using more than 9400 metagenomes. LAB were found in the following body sites: gut, oral cavity, skin, airways, vagina and breast milk, with the gut showing the highest diversity with 70 LAB species. Species such as *Lactobacillus* spp., *Lactococcus* spp., *Leuconostoc* spp., *Weissella* spp. and *Streptococcus thermophilus* showed prevalence higher than 0.1% (Diez-Gutiérrez et al., 2020). Due to the huge overlap of food-based LAB and the human intestinal species, food and especially the consumption of dairy products are the most important origin points.

LAB can be differentiated into homofermentative and heterofermentative species according to their metabolism (Bintsis, 2018; Laranjo et al., 2017; Wee et al., 2006). Even though both subgroups produce lactic acid as the main product by fermentation of carbohydrates such as glucose and fructose, the heterofermentative process forms some byproducts (Bintsis, 2018; Laranjo et al., 2017, 2019; Tangwatcharin et al., 2019; Wee et al., 2006). Independent of the fermentation pathway, most LAB are able to convert lactate to hydrogen peroxide, even if both lactate and glucose occur in the same ratio (Ammor & Mayo, 2007; Ito et al., 2003). The ability to produce lactic acid and hydrogen peroxide has led to the frequent use of LAB as a starter culture for food preservation (Gerez et al., 2015; Jung et al., 2019; Oh et al., 2020; Tangwatcharin et al., 2019).

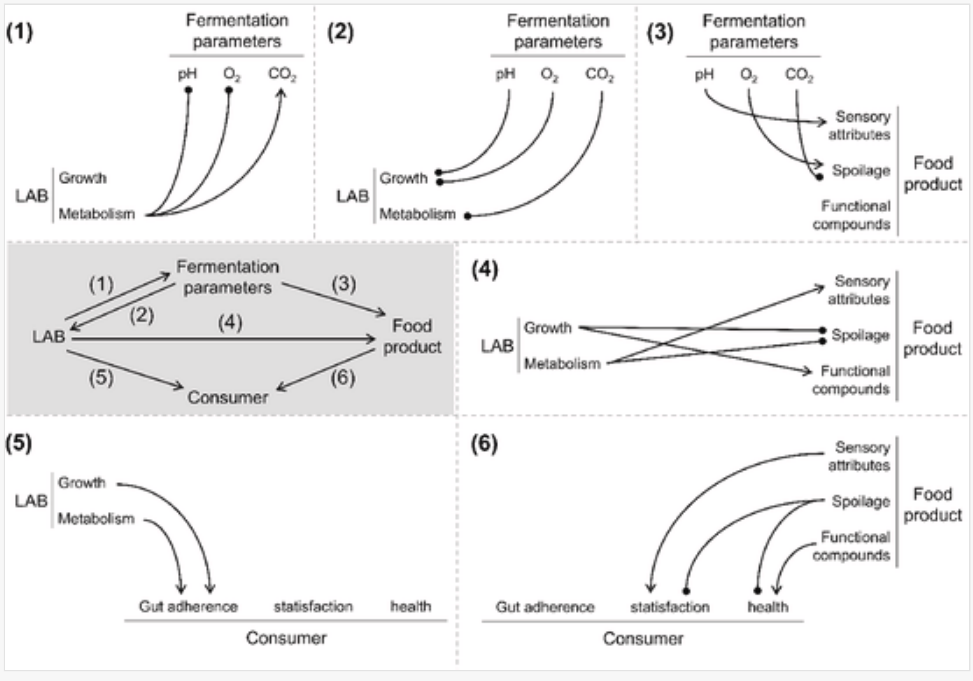
2.2 Effects of using LAB as a starter culture for food fermentation

In food fermentation, LAB are the most important microorganisms and belong to the following bacterial genera: *Lactobacillus, Lactococcus, Streptococcus, Leuconostoc*, and *Pediococcus* (Bintsis, 2018; Laranjo et al., 2017). In addition to the consistent quality, starter cultures can reduce ripening time and inhibit the undesirable and potentially pathogenic microorganisms, resulting in higher food safety (Laranjo et al., 2017). Due to these advantages, LAB appears to be an ideal option for food fermentation. However, the concentration, growth, and metabolism of these bacteria need to be stable during the entire process and should always be documented, even if a mixed starter culture or a co-culture with yeasts is used (Penido et al., 2019; Yu et al., 2017). The stability and effects of each LAB strain depend on a number of factors, which are part of a tight network with mutual interactions, including the fermentation parameters, the food product, and the consumer (Fig. 1, grey box). Details and examples for each interaction are described in the sections below.

(1) LAB-induced changes of fermentation parameters

alt-text: Fig. 1

Fig. 1



Mutual interactions (grey box) and corresponding examples (1–6) between LAB, fermentation parameters, the food product and the consumer. (1) LAB metabolism decreases pH and O_2 concentration, while CO_2 content increases; (2) Changes in fermentation parameters inhibit LAB growth and metabolism; (3) O_2/CO_2 ratio influences the food shelf live and spoilage, whereas the pH is an important sensory aspect for the consumer; (4) LAB inhibits food spoilage and can enhance functional compounds in fermented foods; (5) LAB growth and metabolism improves gut adherence of beneficial gut bacteria; (6) Food compounds define the consumer health and statisfaction. Arrows indicate a positive correlation and increase, while dots represent a negative correlation and decrease. Details are provided in the text.

One of the most affected parameters in fermentation is the pH value. LAB induce the acidification of food and a decrease in pH caused by lactic acid as a fermentation product **((Fig. 1 (1))**; Yu et al., 2017; Kang et al., 2003; Ribeiro et al., 2020; Bintsis, 2018). For example, such processes are used in wet coffee fermentation for the dissociation of bean mucilage (Ribeiro et al., 2020). Interestingly, Larsen et al. (2015) documented a slower decrease in pH under aerobic conditions, suggesting a heterofermentative metabolism under anaerobic conditions, leading to the formation of weaker acetic acid compared to lactic acid. Moreover, the CO_2 formed as a fermentation byproduct may react with water resulting in carbonic acid, which would further decrease the pH (Mitchell et al., 2010). Similar to the pH value, O_2 and CO_2 levels are specified by LAB. For instance, oxygen is used for oxidation reaction, while LAB switches from aerobic to anaerobic fermentation processes, resulting in the increased formation of CO_2 (Kang, 2003).

(2) Fermentation parameters influence the growth and metabolism of LAB

Fermentation processes depend on the growth activity of LAB. Consequently, limiting factors such as temperature, pH, salt concentration and atmospheric composition need to be adapted to bacteria-specific requirements as well as to the desired food product. For example, if probiotic or antimicrobial activities are desired, the LAB should be alive at 4 °C over a certain storage time. Gerez et al. (2015) analyzed the cell viability of *L. plantarum* in bread at 4 °C and −20 °C, noting a significant decrease in viability and lactic acid production at lower temperatures. These differences in acid production could also influence the final taste of the bread after thawing (Gerez et al., 2015). Thus, a compromise for all factors is warranted, with a normal range from 4 to 24 °C, 2–10% NaCl concentration and a pH of 4.2–6.0 (Ammor & Mayo, 2007; Oh et al., 2020). As mentioned above, LAB influence the fermentation parameters by formation of lactic acid, acetic acid and/or CO_2 (Kang et al., 2003). Consequently, LAB might be able to inhibit their own growth by decreasing the pH below the acceptable range or by increasing the CO_2 level to a critical point in order for there to be a decrease in bacteria viability **((Fig. 1 (2))**; Kang et al., 2003; Doulgeraki et al., 2012). These interactions are highly strain-specific and need to be analyzed for each application.

(3) Fermentation parameters influencing food products

As already described regarding the effects of fermentation parameters on LAB growth, fermented food or beverage is similarly affected by the pH and/or the oxygen level. The LAB-induced decrease in pH and oxygen level is widely used for food preservation by inactivating pathogenic or spoilage microorganisms **((Fig. 1 (3))**, while LAB adapt to these conditions (Ammor & Mayo, 2007; Tangwatcharin et al., 2019). Moreover, the acidic pH may induce the reduction of nitrite contained in processed meat products, resulting in the typical pink color that consumers associate with freshness (Ammor & Mayo, 2007; Laranjo et al., 2019).

(4) LAB directly modify the food product independent of the fermentation parameters.

In addition to lactic acid production, LAB are able to modify specific food compounds, induce the accumulation of health-improving substances (described in no. 5), and can directly form antimicrobial substances **((Fig. 1 (4))**. For instance, the high β-galactosidase activity of LAB is widely used in the dairy industry for lactose degradation (Colombo et al., 2018; Jung et al., 2019). *Lactobacillus reuteri*, *Lactobacillus fermentum*, *Lactobacillus crispatus* as well as *Lactobacillus plantarum* synthesize this enzyme, which converts lactose into short chain fatty acids. This means that LAB might be an effective preventive for lactose intolerance (Jung et al., 2019). Moreover, the degradation of lactose may also be useful for modifying the flavor of fermented food products (Jung et al., 2019). For example, Medved'ová et al. (2020) used a mixture of LAB in the manufacture of cheese in order to record a higher aroma intensity as well as enhanced overall acceptability. In contrast to this beneficial effect, LAB may also adversely affect the food product by their proteolytic or lipolytic activities. Such effects should be taken into consideration in order to avoid an undesired taste or texture (Ammor & Mayo, 2007). The high acidifying potential of LAB as a result of lactic acid formation as well as the synthesis of nitrite reductase enzymes promote the reduction of nitrite salts (e.g. in processed meat) to nitric oxide (Ammor & Mayo, 2007; Laranjo et al., 2019; Wang et al., 2016). Even if the reduction of nitrite seems to improve food safety (Laranjo et al., 2019), the formed NO may induce the formation of *N*-nitroso compounds (NOC) such as *N*-alkylnitrosamines or nitrosylated heme in meat products (Fahrer & Kaina, 2017; Kostka et al., 2020). These NOC possess a high carcinogenic potential by inducing DNA adducts and strand breaks, as well as mutations in *in vitro* assays, suggesting the association of NOCs with colorectal cancer formation (Fahrer & Kaina, 2017; Kostka et al., 2020). Another example and important point is the production of biogenic amines such as histamine, tyramine, tryptamine or spermidine by LAB (Barbieri et al., 2019; Tangwatcharin et al., 2019; Wang et al., 2016). These amines occur primarily in fermented meat in high concentrations and could induce an allergic reaction, hypertension or death in acute cases (Tangwatcharin et al., 2019; Yu et al., 2017). Therefore, the suitability and safety of LAB in food products must be paramount considerations prior to the application of LAB as a starter culture for fermentation (Barbieri et al., 2019).

As mentioned above, LAB are able to reduce the undesirable microbial content of a food product. Food preservation can be achieved by fermentation processes, influencing the growth-dependent parameters of the microorganisms, or otherwise LAB can directly form antimicrobial substances. (Ammor & Mayo, 2007; Cotter et al., 2005).

(5) LAB as probiotics

Beyond the fermentation process, LAB could also act as a probiotic, whereby LAB become part of the consumers gut microbiome and induce health-promoting effects **((Fig. 1 (5))**. In order for this health benefit to occur, several properties are essential. First, the bacterial strain must not have a pathogenic and/or toxic potential (Ammor & Mayo, 2007). Secondly, the LAB must be highly acid resistant in order to survive the conditions of the stomach (Ammor & Mayo, 2007; Erkkilä & Petäjä, 2000; Klingberg et al., 2005). Erkkilä and Petäjä (2000) analyzed the acid resistance of different LAB species, identifying *Pedicoccus acidilactici*, *P. pentosaceus* and *Lactobacillus curvatus* as the most acid tolerant strains up to pH 3. *L. curvatus* and *P. acidilactici* were also the most efficient in bile salt survival, the next critical step for probiotic bacteria (Ammor & Mayo, 2007; Erkkilä & Petäjä, 2000). With a fat-rich meal, bile salts are released from the gall bladder into the small intestine in order to promote digestion (Ammor & Mayo, 2007; Erkkilä & Petäjä, 2000). These salts may damage bacteria membranes, resulting in an antimicrobial effect, especially when the pH is low (Erkkilä & Petäjä, 2000; Urdaneta & Casadesús, 2017). *Lactobacillus plantarum* is also known for its high survival ability in extreme gut conditions (Jung et al., 2019). In addition to initial survivability, the adherence and persistence of probiotic LAB in the human gut is essential for beneficial effects (Ammor & Mayo, 2007; Klingberg et al., 2005). The extent of successful adhesion to gut cells is highly strain-specific, so starter culture strains should be screened individually (Ammor & Mayo, 2007; Klingberg et al., 2005; Li et al., 2015). For example, a high adherence was shown for *Lactobacillus plantarum* and *L. salivarius*, while *L. farciminis* was more than 20-fold lower in its adhesion capacity, suggesting its lack of acceptability as a probiotic starter culture (Klingberg et al., 2005).

(6) Enrichment of food-independent compounds by fermentation using LAB

Fermentation leads to desired biochemical changes responsible for significant changes in food. Fermentation is a natural way to improve the organoleptic characteristics and nutritional composition of foods by enriching them with vitamins, amino acids, anti-nutrients, and proteins **((Fig. 1 (6))**. Oh et al. (2020) analyzed the effects of *L. plantarum* PMO 08 on fermented beverages. The application of this LAB strain significantly increased the proline content and increased glutamine by 405%. Moreover, the polyphenol content of the plant-based beverage increased by more than 154%, which might also explain the high antioxidant activity, quantified as DPPH radical scavenging activity. Similar antioxidant effects were shown for *L. plantarum* Wikim 83 in three independent assays, suggesting its use in functional foods (Jung et al., 2019). In the development of functional foods, supplementation with the neurotransmitter gamma-aminobutyric acid (GABA) has likewise moved into focus (Diez-Gutiérrez et al., 2020). LAB such as *L. lactis* and *L. brevis* catalyze the production of GABA and CO_2 by glutamate decarboxylation (Yu et al., 2017). When used as a pharmacological agent or supplement, GABA can beneficially affect the cardiovascular and nervous system, control asthma, and it shows antidiabetic properties (Diez-Gutiérrez et al., 2020).

3 Antimicrobial effects of LAB

Fermentation processes provide optimal growth conditions for LAB starter cultures, enabling the conversion of ingredients to fermentation products and metabolites. However, these growth conditions can, unfortunately, be suitable for pathogens such as *Salmonella* spp. ~~*spp.*~~ and *Listeria* spp. ~~*spp.*~~ as well. Therefore, antagonistic activity against food pathogens is one of the most important considerations in starter culture selection where inoculated bacteria need to counteract over harmful microorganisms in order to guarantee food safety (Penido et al., 2019). Many LAB species fulfill this requirement and possess antimicrobial effects **(Table 1)**. In order to determine if LAB directly interact with pathogenic bacteria or if metabolites function as antibiotics, pathogens were incubated with cell-free cultures of LAB. For this purpose, LAB suspensions were centrifuged, and the acidic pH was neutralized and filter sterilized, followed by testing of the cell-free crude extract in antimicrobial assays (Heredia-Castro et al., 2015; Bungenstock et al., 2020). Cell-free cultures exhibit enhanced antimicrobial effects **(Table 1)**, which confirms the hypothesis of pathogenic growth inhibition induced by metabolites. The metabolites are fermentation products such as lactic acid, CO_2 or biogenic amines, whereas LAB produce strain-specific bacteriocins or other antimicrobial peptides (Balciunas et al., 2013; Drider et al., 2016).

alt-text: Table 1

Table 1

The table layout displayed in this section is not how it will appear in the final version. The representation below is solely purposed for providing corrections to the table. To preview the actual presentation of the table, please view the Proof.

Antimicrobial effects of several LAB and cell-free cultures against food pathogens.

Antimicrobial testing	LAB	Origin of LAB	Pathogens		References
Growth inhibition of pathogens by LAB	*Lactiplantibacillus pentosus*	Meat isolate	• *Escherichia coli* ~~*Escherichia coli*~~ • Bacillus cereus • Shigella flexneri	• Yersinia enterocolitica • *Salmonella typhimurium* ~~*Salmonella typhimurium*~~ • Listeria monocytogenes	Klingberg et al. (2005)
	Lactiplantibacillus plantarum	Meat isolate	• *Escherichia coli* ~~*Escherichia coli*~~ • Bacillus cereus • Shigella flexneri	• Yersinia enterocolitica • *Salmonella typhimurium* ~~*Salmonella typhimurium*~~ • Listeria monocytogenes	Klingberg et al. (2005)
		Strain collection: dairy isolate	• *Escherichia coli* ~~*Escherichia coli*~~	• Bacillus cereus	Klingberg et al. (2005)
		Cassava flour	• Bacillus cereus • *Escherichia coli* ~~*Escherichia coli*~~	• *Salmonella typhimurium* ~~*Salmonella typhimurium*~~	Penido et al. (2019)

		Camel milk isolates	• *Salmonella enterica* ~~*Salmonella enterica*~~ • *Escherichia coli* ~~*Escherichia coli*~~ • *Staphylococcus aureus* ~~*Staphylococcus aureus*~~ • Staphylococcus epidermidis	• Listeria monocytogenes • multi-drug resistant *Salmonella enterica* ~~*Salmonella enterica*~~ • Shigella flexneri • *Pseudomonas aeruginosa* ~~*Pseudomonas aeruginosa*~~	Rahmeh et al. (2019)
		Isolate from home-made mexican food	• *Staphylococcus aureus* ~~*Staphylococcus aureus*~~ • Listeria monocytogenes	• Vibrio parahaemolyticus • Bacillus cereus	Alvarado et al. (2006)
	Ligilactobacillus salivarius	Strain collection: meat isolate	• *Escherichia coli* ~~*Escherichia coli*~~ • Bacillus cereus • Shigella flexneri	• Yersinia enterocolitica • *Salmonella typhimurium* ~~*Salmonella typhimurium*~~ • Listeria monocytogenes	Klingberg et al. (2005)
		Camel milk isolates	• *Salmonella enterica* ~~*Salmonella enterica*~~ • *Escherichia coli* ~~*Escherichia coli*~~ • *Staphylococcus aureus* ~~*Staphylococcus aureus*~~ • Staphylococcus epidermidis	• Listeria monocytogenes • multi-drug resistant *Salmonella enterica* ~~*Salmonella enterica*~~ • Shigella flexneri	Rahmeh et al. (2019)
		Strain collection: human isolate	• *Escherichia coli* ~~*Escherichia coli*~~ • Bacillus cereus	• Shigella flexneri • Yersinia enterocolitica	Klingberg et al. (2005)
	Limosilactobacillus reuteri	Strain collection: meat isolate	• *Salmonella enterica* ~~*Salmonella enterica*~~ • *Escherichia coli* ~~*Escherichia coli*~~ • Bacillus cereus • Shigella flexneri	• Yersinia enterocolitica • *Salmonella typhimurium* ~~*Salmonella typhimurium*~~ • Listeria monocytogenes	Klingberg et al. (2005)
		Camel milk isolates	• *Salmonella enterica* ~~*Salmonella enterica*~~ • *Escherichia coli* ~~*Escherichia coli*~~ • *Staphylococcus aureus* ~~*Staphylococcus aureus*~~ • Staphylococcus epidermidis	• Listeria monocytogenes • multi-drug resistant *Salmonella enterica* ~~*Salmonella enterica*~~ • Shigella flexneri	Rahmeh et al. (2019)
	Pediococcus pentosaceus	Strain collection: meat isolate	• *Escherichia coli* ~~*Escherichia coli*~~ • Bacillus cereus	• Shigella flexneri • Yersinia enterocolitica	Klingberg et al. (2005)
		Camel milk isolates	• *Salmonella enterica* ~~*Salmonella enterica*~~ • *Escherichia coli* ~~*Escherichia coli*~~	• Listeria monocytogenes • multi-drug resistant *Salmonella enterica* ~~*Salmonella enterica*~~	Rahmeh et al. (2019)

		• *Staphylococcus aureus* ~~*Staphylococcus aureus*~~ • Staphylococcus epidermidis	• Shigella flexneri	
Lacticaseibacillus casei spp. ~~*spp.*~~ *casei*	Strain collection: dairy isolate	• *Escherichia coli* ~~*Escherichia coli*~~ • Bacillus cereus	• *Salmonella typhimurium* ~~*Salmonella typhimurium*~~	Klingberg et al. (2005)
Levilactobacillus brevis	Cassava flour	• Bacillus cereus • *Escherichia coli* ~~*Escherichia coli*~~	• *Salmonella typhimurium* ~~*Salmonella typhimurium*~~	Penido et al. (2019)
	Camel milk isolates	• *Salmonella enterica* ~~*Salmonella enterica*~~ • *Escherichia coli* ~~*Escherichia coli*~~ • *Staphylococcus aureus* ~~*Staphylococcus aureus*~~ • Staphylococcus epidermidis	• Listeria monocytogenes • multi-drug resistant *Salmonella enterica* ~~*Salmonella enterica*~~ • Shigella flexneri	Rahmeh et al. (2019)
Leuconostoc citreum	Kimchi isolate	• *Escherichia coli* ~~*Escherichia coli*~~ • *Salmonella enterica* ~~*Salmonella enterica*~~	• Salmonella aureus	Chang and Chang (2011)
Lacticaseibacillus rhamnosus	Strain collection	• Enterococcus faecium • Listeria greay • Listeria monocytogenes • *Staphylococcus aureus* ~~*Staphylococcus aureus*~~ • Streptococcus mutans • *Escherichia coli* ~~*Escherichia coli*~~	• Enteropathogenic *Escherichia coli* ~~*Escherichia coli*~~ • Klebsiella pneumonia • *Proteus mirabilis* ~~*Proteus mirabilis*~~ • *Pseudomonas aeruginosa* ~~*Pseudomonas aeruginosa*~~ • *Salmonella enterica* ~~*Salmonella enterica*~~	Coman et al. (2014)
Lacticaseibacillus paracasei	Strain collection	• Bacillus cereus • Enterococcus faecium • Listeria greay • Listeria monocytogenes • *Staphylococcus aureus* ~~*Staphylococcus aureus*~~ • Streptococcus mutans • *Escherichia coli* ~~*Escherichia coli*~~	• Enteropathogenic *Escherichia coli* ~~*Escherichia coli*~~ • Klebsiella oxytoca • Klebsiella pneumonia • *Proteus mirabilis* ~~*Proteus mirabilis*~~ • *Pseudomonas aeruginosa* ~~*Pseudomonas aeruginosa*~~ • *Salmonella enterica* ~~*Salmonella*~~	Coman et al. (2014)

			enterica • Shigella sonnei	
	Isolate from home-made mexican food	• Vibrio parahaemolyticus		Alvarado et al. (2006)
Lactococcus garvieae	Camel milk isolates	• *Salmonella enterica* ~~*Salmonella enterica*~~ • *Escherichia coli* ~~*Escherichia coli*~~ • *Staphylococcus aureus* ~~*Staphylococcus aureus*~~ • Staphylococcus epidermidis	• Listeria monocytogenes • multi-drug resistant *Salmonella enterica* ~~*Salmonella enterica*~~ • Shigella flexneri	Rahmeh et al. (2019)
Enterococcus faecium	Camel milk isolates	• *Salmonella enterica* ~~*Salmonella enterica*~~ • *Escherichia coli* ~~*Escherichia coli*~~ • *Staphylococcus aureus* ~~*Staphylococcus aureus*~~ • Staphylococcus epidermidis	• Listeria monocytogenes • multi-drug resistant *Salmonella enterica* ~~*Salmonella enterica*~~ • Shigella flexneri	Rahmeh et al. (2019)
	isolate from home-made mexican food	• *Staphylococcus aureus* ~~*Staphylococcus aureus*~~	• Listeria monocytogenes	Alvarado et al. (2006)
Pediococcus acidilactici	Camel milk isolates	• *Salmonella enterica* ~~*Salmonella enterica*~~ • *Escherichia coli* ~~*Escherichia coli*~~ • *Staphylococcus aureus* ~~*Staphylococcus aureus*~~ • Staphylococcus epidermidis	• Listeria monocytogenes • multi-drug resistant *Salmonella enterica* ~~*Salmonella enterica*~~ • Shigella flexneri	Rahmeh et al. (2019)
Lactococcus lactis	Camel milk isolates	• *Salmonella enterica* ~~*Salmonella enterica*~~ • *Escherichia coli* ~~*Escherichia coli*~~ • *Staphylococcus aureus* ~~*Staphylococcus aureus*~~ • Staphylococcus epidermidis	• Listeria monocytogenes • multi-drug resistant *Salmonella enterica* ~~*Salmonella enterica*~~ • Shigella flexneri	Rahmeh et al. (2019)
	Isolate from home-made mexican food	• *Staphylococcus aureus* ~~*Staphylococcus aureus*~~ • Listeria monocytogenes	• Vibrio parahaemolyticus	Alvarado et al. (2006)

Limosilactobacillus fermentum	Camel milk isolates	• *Salmonella enterica* ~~*Salmonella enterica*~~ • *Escherichia coli* ~~*Escherichia coli*~~ • *Staphylococcus aureus* ~~*Staphylococcus aureus*~~	• Staphylococcus epidermidis • Listeria monocytogenes • Shigella flexneri	Rahmeh et al. (2019)
Leuconostoc pseudomesenteroides	Camel milk isolates	• *Salmonella enterica* ~~*Salmonella enterica*~~ • *Escherichia coli* ~~*Escherichia coli*~~ • *Staphylococcus aureus* ~~*Staphylococcus aureus*~~ • Staphylococcus epidermidis	• Listeria monocytogenes • multi-drug resistant *Salmonella enterica* ~~*Salmonella enterica*~~	Rahmeh et al. (2019)
Enterococcus durans	Camel milk isolates	• *Salmonella enterica* ~~*Salmonella enterica*~~ • *Escherichia coli* ~~*Escherichia coli*~~ • *Staphylococcus aureus* ~~*Staphylococcus aureus*~~	• Staphylococcus epidermidis • Listeria monocytogenes • Shigella flexneri	Rahmeh et al. (2019)
Weissella confusa	Camel milk isolates	• *Salmonella enterica* ~~*Salmonella enterica*~~ • *Escherichia coli* ~~*Escherichia coli*~~ • *Staphylococcus aureus* ~~*Staphylococcus aureus*~~ • Staphylococcus epidermidis • Listeria monocytogenes	• multi-drug resistant *Salmonella enterica* ~~*Salmonella enterica*~~ • Shigella flexneri • *Pseudomonas aeruginosa* ~~*Pseudomonas aeruginosa*~~	Rahmeh et al. (2019)
Streptococcus infantarius	Camel milk isolates	• *Salmonella enterica* ~~*Salmonella enterica*~~ • *Escherichia coli* ~~*Escherichia coli*~~ • *Staphylococcus aureus* ~~*Staphylococcus aureus*~~ • Staphylococcus epidermidis • Listeria monocytogenes	• multi-drug resistant *Salmonella enterica* ~~*Salmonella enterica*~~ • Shigella flexneri • *Pseudomonas aeruginosa* ~~*Pseudomonas aeruginosa*~~	Rahmeh et al. (2019)
Lactobacillus delbruekii	Isolate from home-made mexican food	• Listeria monocytogenes		Alvarado et al. (2006)
Leuconostoc mesenteroides	Isolate from home-made mexican food	• *Staphylococcus aureus* ~~*Staphylococcus aureus*~~	• Vibrio parahaemolyticus • Enterobacter spp.	Alvarado et al. (2006)

			• Listeria monocytogenes		
		Isolate from home-made mexican food	• *Staphylococcus aureus* ~~*Staphylococcus aureus*~~ • Listeria monocytogenes	• Vibrio parahaemolyticus	Alvarado et al. (2006)
	Lactobacillus sakei	Meat isolate	• *Escherichia coli* ~~*Escherichia coli*~~	• Listeria monocytogenes	Pragalaki et al. (2013)
Growth inhibition of pathogens by cell-free cultures of LAB	*Enterococcus faecium*	Isolate from home-made mexican food	• *Staphylococcus aureus* ~~*Staphylococcus aureus*~~	• Enteropathogenic *Escherichia coli* ~~*Escherichia coli*~~	Alvarado et al. (2006)
		Rhizosphere of olive trees	• Listeria monocytogenes • *Staphylococcus aureus* ~~*Staphylococcus aureus*~~	• *Enterococcus faecalis* ~~*Enterococcus faecalis*~~	Fhoula et al. (2013)
	Lactiplantibacillus plantarum	Isolate from home-made mexican food	• *Staphylococcus aureus* ~~*Staphylococcus aureus*~~	• Enteropathogenic *Escherichia coli* ~~*Escherichia coli*~~	Alvarado et al. (2006)
		Meat isolate	• Listeria monocytogenes	• Listeria innocua	Bungenstock et al. (2020)
		Cheese isolate	• Bacillus cereus • Clostridium sporogenes • *Staphylococcus aureus* ~~*Staphylococcus aureus*~~	• Shigella sonnei • *Klebsiella pneumoniae* ~~*Klebsiella pneumoniae*~~	Hernández et al. (2005)
		Strain collection: dairy isolate	• *Staphylococcus aureus* ~~*Staphylococcus aureus*~~ • Listeria innocua	• *Salmonella typhimurium* ~~*Salmonella typhimurium*~~ • Escherichis coli	Heredia-Castro et al. (2015)
	Leuconostoc mesenteroides	Isolate from home-made mexican food	• *Staphylococcus aureus* ~~*Staphylococcus aureus*~~	• Enteropathogenic *Escherichia coli* ~~*Escherichia coli*~~	Alvarado et al. (2006)
		Rhizosphere of olive trees	• Listeria monocytogenes • *Staphylococcus aureus* ~~*Staphylococcus aureus*~~	• Enterococcus faecium • *Enterococcus faecalis* ~~*Enterococcus faecalis*~~	Fhoula et al. (2013)
	Limosilactobacillus fermentum	Strain collection: dairy isolate	• *Staphylococcus aureus* ~~*Staphylococcus aureus*~~ • Listeria innocua	• *Salmonella typhimurium* ~~*Salmonella typhimurium*~~ • *Escherichia coli* ~~*Escherichia coli*~~	Heredia-Castro et al. (2015)
	Lactiplantibacillus pentosus	Strain collection: dairy isolate	• *Staphylococcus aureus* ~~*Staphylococcus aureus*~~ • Listeria innocua	• *Salmonella typhimurium* ~~*Salmonella typhimurium*~~ • *Escherichia*	Heredia-Castro et al. (2015)

				coli ~~*Escherichia coli*~~	
	Lacticaseibacillus paracasei tolerans	Strain collection: dairy isolate	• *Staphylococcus aureus* ~~*Staphylococcus aureus*~~ • Listeria innocua	• *Salmonella typhimurium* ~~*Salmonella typhimurium*~~ • *Escherichia coli* ~~*Escherichia coli*~~	Heredia-Castro et al. (2015)
	Weissella halotolerans	Rhizosphere of olive trees	• Listeria monocytogenes • *Staphylococcus aureus* ~~*Staphylococcus aureus*~~	• Enterococcus faecium • *Enterococcus faecalis* ~~*Enterococcus faecalis*~~	Fhoula et al. (2013)
	Lactobacillus helveticus	Strain collection: dairy isolate	• Listeria monocytogenes • *Salmonella typhimurium* ~~*Salmonella typhimurium*~~ • *Staphylococcus aureus* ~~*Staphylococcus aureus*~~	• *Escherichia coli* ~~*Escherichia coli*~~ • Bacillus subtilis	Bian et al. (2016)
	Lactobacillus sakei	Meat isolate	• Listeria monocytogenes	• Listeria innocua	Bungenstock et al. (2020)
	Pediococcus pentosaceus	Meat isolate	• Listeria monocytogenes	• Listeria innocua	Bungenstock et al. (2020)
	Pediococcus acidilactici	Meat isolate	• Listeria monocytogenes	• Listeria innocua	Bungenstock et al. (2020)
	Leuconostoc citreum	Kimchi isolate	• *Escherichia coli* ~~*Escherichia coli*~~ • *Salmonella enterica* ~~*Salmonella enterica*~~	• Salmonella aureus	Chang and Chang (2011)

4 The metabolites of LAB

LAB are able to produce antimicrobial substances such as low molecular weight metabolites (reuterin, reutericyclin, diacetyl, fatty acids), hydrogen peroxide, antifungal compounds (propionate, phenyl-lactate, hydroxyphenyl-lactate and 3-hydroxy fatty acids) and bacteriocins. Moreover, they can be exploited for the production of other compounds of industrial importance (exopolysaccharides, bioactive peptides) but, at the same time, they can be responsible for the accumulation of dangerous molecules such as biogenic amines (Reis et al., 2012; Trias et al., 2008).

4.1 Organic acid production

Among the substances derived from bacterial metabolism, organic acid is the primary end-product of fermentation. LAB in particular are responsible for lactic acid fermentation, decreasing the pH of the surrounding environment and creating a selective barrier against non-acidophiles species. In this energy metabolic pathway, glucose and other monosaccharides are broken down into lactic acid alone as the main end product or in lactic acid and other end products (Gänzle, 2015; Halasz, 2009). In fact, there are two basic types of lactic acid fermentation, homofermentative and heterofermentative, each of which is dependent on the ability of the LAB to ferment glucose, differ in the main fermentation end products, and the ways in which these compounds are broken down.

Homofermentative: Only lactic acid is formed as the main end product via the fructose bisphosphate route (glycolysis). This pathway has been reported for *Streptococcus*, *Enterococcus*, *Lactococcus* and *Pediococcus* as well as some members of the genus previously named *Lactobacillus*. This type of fermentation is based on glucose, which is first broken down into pyruvate in glycolysis. It is then reduced to lactate by the enzyme lactate dehydrogenase with the coenzyme NADH. The NADH is oxidized to NAD+, with concomitant pyruvate reduction to lactic acid. The energy yield is two ATP moles/glucose mole (Wu et al., 2017).

Heterofermentative: The primary end products are lactic acid in the case of hexose degradation, ethanol and carbon dioxide (CO_2), and acetic acid (AA) in the case of pentose degradation. These bacteria lack the key enzyme in glycolysis, namely aldolase and include obligate heterofermentative cocci (*i.e. Leuconostoc* and *Weissella*) and obligate heterofermentative lactobacilli (*i.e.* Limosilactobacillus, *L*evilactobacillus, *Fructilactobacillus* etc.). Heterofermentative lactic acid fermenters can break down both hexoses (such as glucose or fructose) and, in particular, pentoses (xylose, ribose) via the xylulose-5-phosphate metabolic pathway. Thus, the breakdown of glucose does not take place via the fructose bisphosphate route. This metabolic pathway is initiated by the oxidation of glucose-6-phosphate to gluconic acid-6-phosphate. A pentose phosphate results from the decarboxylation that follows in the next reaction step. The resultant ribulose-5-phosphate is converted into xylulose-5-phosphate by means of an epimerase. Under the action of a phosphoketolase, xylulose-5-phosphate is converted into a triose phosphate (glyceraldehyde-3-phosphate) and an acetyl phosphate. The glyceraldehyde-3-phosphate is broken down into lactic acid via the fructose bisphosphate pathway. If a hydrogen acceptor is present, the acetyl phosphate is metabolized to acetic acid with energy gain. If no hydrogen acceptor is available, the acetyl phosphate is reduced to ethanol with the help of acetyl CoA and acetaldehyde (Zhou et al., 2019).

In this pathway, the NADH is re-oxidized by reducing pyruvate to lactate, corresponding to the last step of homofermentative lactic acid fermentation. During heterofermentative fermentation, the following relationships within the formation of LA, AA and ethanol can occur (Papadimitriou et., 2015; Nagpal et al., 2012; Ponce et al., 2008; Figalla et al., 2018; Oude Elferink et al., 2001):

- At the beginning of fermentation, approximately equal numbers of LA and AA molecules are formed (fermentation quotient approaches 1.0). During fermentation, the formation of acetic acid is reduced in favor of ethanol, with an increase of the fermentation quotient.
- The presence of oxygen or fructose as electron acceptors can have an effect on acetate formation, energy balance and end products. In addition to lactate and CO_2, the only end-product of acid metabolism is acetate (fermentation quotient = 1.0). Additional end products resulting from fructose fermentation (besides lactate and acetate) are 2 mol~~two mols~~ of CO_2 and 2 mol~~two mols~~ of mannitol.

Organic acids produced by microbial metabolism are widely used as antimicrobial agents in the food industry. In fact, alteration of environmental pH can affect the structure and permeability of cell membrane, resulting in leakage of the internal cell metabolites and other cell activities as protein synthesis (Coban, 2020; Hati et al., 2013). It is well known that organic acids can inhibit putrefactive (e.g. *Clostridia, Pseudomonas*), pathogenic (e.g. *Salmonella*, *Listeria* spp.) and toxinogenic (e.g. *Staphylococcus aureus, Bacillus cereus, Clostridium botulinum*) bacteria.

Weak acids, such as lactic acid, are also known to have a stronger antimicrobial effect at lower pH values. Another reason for the antimicrobial properties of LAB could also be the ability of the lactic acids to make the cell wall of bacteria permeable and thus potentiates the effect of other antimicrobial substances (Alakomi et al., 2000).

Lactic acid (LA) is one of the key substances in fermentation and is accumulated by LAB. The type of lactic acid formed (D +, L–, DL) and the structure of the murein are important determinants in LAB classification (Leroy & De Vuyst, 2004). LA is approved in the USA, the EU, Australia and New Zealand (i.e. E270) as a food preservative for its antimicrobial properties.Compared to LA, AA is a stronger inhibitor, with a broad spectrum of activity against yeasts, molds and bacteria. However, the two acids seem to have a synergistic effect, since a mixture of the two is more effective than either acid alone. In addition to the pH-lowering effect, lactic acid also has a permeabilizing effect on the cell membrane (stronger than HCl) and thus can potentiate the effect of other antimicrobial substances (Alakomi et al., 2000).

Other organic acids such as succinate, acetate, and formate with industrial importance can be produced by LAB through citrate metabolism.

4.2 Bacteriocin production

Bacteriocins are peptides produced by LAB endowed with antimicrobial activity against foodborne pathogens and spoilage microflora and include four classes: i) lantibiotics, mainly represented by nisin; ii) a wide group of small heat-stable proteins (further subdivided in three subgroups in relation to their structures) also containing Pediocin, Lactococcin, Sakacin, Curvacin, Enterococin; iii) heat-sensitive proteins; iv) an additional class defined as complex bacteriocins containing lipids or carbohydrate moieties. Their chemical characteristics and mode of actions have been widely described in the literature (El Issaoui et al., 2020; Ayivi et al., 2020). With regard to their application in foods, the use of bacteriocinogenic LAB can be a promising strategy since they are GRAS. However, it should be noted that several parameters can affect the ability of LAB to produce these compounds *in vivo* as well as the ability of bacteriocins to interact with food constituents (proteins, lipids, presence of enzymes, etc.) (Šimat et al., 2021). A summary of applications of LAB bacteriocins with commercially available products collected from recent literature (Chikindas, Weeks, Drider, Chistyakov, & Dicks, 2018; Daba & Elkhateeb, 2020; Del Rocio López-Cuellar et al., 2016) is reported in Table 2.

alt-text: Table 2

Table 2

The table layout displayed in this section is not how it will appear in the final version. The representation below is solely purposed for providing corrections to the table. To preview the actual presentation of the table, please view the Proof.

Application of bacteriocins available as commercial products (Chikindas et al., 2018; Daba et al., 2020; del Rocio López-Cuellar et al., 2016).

Main LAB producers	Bacteriocin	Target	Applications in food	Commercial product available
Lactococcus lactis	Nisin A	*Clostrid*ium spp, spoilage microflora	Cheeses	BioSafe® (Chr. Hansen)
		Spoilage microflora, *Listeria* spp.~~*spp.*~~, *Clostridium* spp., *Bacillus* spp.	Dairy products, bakery products, beverages	Nisaplin® E234 (Danisco DuPont)
Lactococcus lactis	Nisin A, Nisin Z	*Listeria* spp.~~*spp.*~~, *Clostridium* spp., *Bacillus cereus*	Dairy products, bakery products, beverages	Nisin A® and Nisin Z® (Handary)
Latilactobacillus curvatus	Sakacin A	*Listeria monocytogenes*	Fermented meats	Bactoferm F-LC® (Chr. Hansen)
Latilactobacillus sakei	Sakacin	*Listeria* spp.~~*spp.*~~	Meat products (packed under vacuum or MAP)	Bactoferm B-2® and B-FM® (Chr. Hansen)
Pediococcus acidilactici	Pediocin PA-1	*Listeria monocytogenes*	Fermented meats	Bactoferm F-LC® (Chr. Hansen)
		Psychrotrophic bacteria, yeasts and molds	Cottage cheese	MicroGARD® (DuPont)
Pediococcus acidilactici	Pediocin	*Listeria monocytogenes*	Smoked salmon, meat products	ALTA® 2341 and 2351 (Kerry Bioscience)
			Meat products	Fargo 23® (Quest International)
Leuconostoc carnosum	Leucocin	*Listeria* spp.~~*spp.*~~	Meat products (packed under vacuum or MAP)	Bactoferm B-SF-43® (Chr. Hansen)
Lactiplantibacillus plantarum	Plantaricin	*Listeria monocytogenes*	Fermented sausages, cooked ham	ALCMix1® (Danisco DuPont)

4.3 Reuterin production

Limosilactobacillus reuteri is a heterofermentative LAB found in a variety of ecological niches such as food fermentations (e.g. sourdough, meat, and dairy products) and considered a successful growth inhibitor of pathogenic microorganisms. Various mechanisms are responsible for it bioactivity, such as the excretion LA, AA, short-chain

fatty acids, hydrogen peroxide and antimicrobial substances. Indeed, certain strains of *Lim. reuteri* produce antimicrobial substances with unique antagonistic activity, including reuterin, reutericin and reutericyclin (Axelsson et al., 1989).

Reuterin, is a negatively charged, strongly hydrophobic molecule that acts as a proton ionophore, and is a dynamic multi-compound system consisting of 3-hydroxypropionaldehyde (3-HPA), its hydrate 1,1,3-propanetriol (3-HPA hydrate), dimer 2-(2-hydroxyethyl)-4-hydroxy-1,3-dioxane (3-HPA dimer), and acrolein (dehydrated form) (Asare et al., 2020; Engels et al., 2016). It is produced during glycerol fermentation by *L. reuteri* under anaerobic conditions. 3-HPA is a precursor for the production of chemicals such as acrylic acid and 3-hydroxypropionic acid (Stevens et al., 2011). Despite 20 years of investigation, the exact mechanism of action by which reuterin exerts its antimicrobial effects has remained elusive. However, it has been shown that reuterin induces oxidative stress in cells by modifying thiol groups in proteins and small molecules and inhibits DNA synthesis and, thus, bacterial growth (Singh, 2018).

In conjunction with other substances released by *Lim. reuteri*, reuterin has a bactericidal and bacteriostatic effect on a wide range of Gram-positive and Gram-negative bacteria, yeasts and protozoa, and is resistant to proteases and lipases. Reuterin is only stimulated by the direct interaction of *Lim. reuteri* with other microorganisms (Schaefer et al., 2010).

Reutericyclin (a tetramic acid derivative) is negatively charged, highly hydrophobic molecule with a molecular mass of 349 Da. It has a bacteriostatic or bacteriocidal effect on Gram-positive bacteria acting as a proton ionophore and dissipator of the proton motive force (Singh, 2018). Gram-negative bacteria and yeasts are resistant to reutericyclin due to the barrier properties of their outer membrane.

4.4 Hydrogen peroxide formation

Hydrogen peroxide (H_2O_2) is an oxidizing agent that can be produced by the metabolism of many microbial species. Usually, it is accumulated during the exposure to molecular oxygen generally by species that have an energy metabolism adapted to anaerobic environments. Bacteria can produce hydrogen peroxide in central carbon metabolism by oxidases such as pyruvate oxidase (Pox), lactate oxidase (Lox), and NADH oxidases (Nox). In aerobic and facultative aerobic bacteria, hydrogen peroxide is immediately intracellularly destroyed by the enzyme catalase. However, hydrogen peroxide can be accumulated in species that lack the main hydrogen peroxide-scavenging enzymes or if the activity of these enzymes is insufficient (Uhl et al., 2015). There are several ways in which LAB (*i.e. Lactococci, Lactobacillus, Lactiplantibacillus, etc.*) can form hydrogen peroxide when exposed to oxygen. They can oxidize lactate, pyruvate, α-glycerophosphate and/or NADH by means of flavin enzymes with the formation of hydrogen peroxide. LAB usually do not have a catalase, which results in an accumulation of hydrogen peroxide in the immediate vicinity. Because of their tolerance to hydrogen peroxide, LAB gain a selection advantage. The modes of action of hydrogen peroxide are well known and are related to the strong oxidizing effect on the bacterial cell as well as to the destruction of the basic molecular structures of cellular proteins, resulting in an increase in membrane permeability. Moreover, the reaction with other substances (e.g. thiocyanate) can lead to the formation of new inhibitors (Teusink et al., 2006). The production of hydrogen peroxide in food fermentation is undesirable, as it oxidizes existing lipids and thus leads to a rancid taste impression in fatty foods. Moreover, hydrogen peroxide can cause discoloration or green discoloration in meat products (Castellano et al., 2017).

4.5 Ethanol formation

The production of bioethanol is increasing globally; however, nowadays, the well-established technology includes the use of yeasts as the major production organisms, due to their ability to grow on cheap industrial media. In this perspective, in addition to the production of acids, LAB could serve as platform organisms for production of bioethanol, since they are known for their high tolerance toward alcohols. Moreover, LAB naturally ferment both hexoses and pentoses, even in harsh conditions and at low pH (Solem at al., 2013).

Ethanol is a valuable end product generated by the anaerobic conversion of carbohydrates together with lactic acid. The heterofermentative lactic acid fermentation produce as the main end-products lactic acid, ethanol and carbon dioxide in the case of hexose degradation. The growth rates of heterofermentative lactic acid fermenters are lower when hexoses are broken down than when pentoses are broken down, since the reduction equivalents are re-oxidized more slowly. This is due to the low activity of acetaldehyde dehydrogenase. In addition, coenzyme A is required as a cofactor for this degradation pathway. Therefore, the supply of pantothenic acid is necessary to maintain the degradation pathway as otherwise, the formation of ethanol will be inhibited (Castellano et al., 2017; Cayré et al., 2005).

Ethanol can have antimicrobial effects in foods due to its activity on membrane fluidity and integrity which can result in plasma membrane leakage and bacterial cell death (Kampf & Hollingsworth, 2008).

4.6 Carbon dioxide

Carbon dioxide (CO_2) is another low molecular weight compound formed by many LAB during heterofermentative metabolism.

The inhibitory effect of carbon dioxide is based on the creation of an anaerobic environment and on influencing the cell membrane properties (Singh, 2018). In fact, this molecule can interact with cell membrane lipids which hinder the possibility of ions being absorbed into the cell. The different microorganisms have very different degrees of sensitivity to carbon dioxide. Yeasts and molds are quite resistant to carbon dioxide, and considerable concentrations (≥20%) are required to inhibit them. On the other hand, Gram-negative psychrophilic bacteria species are very sensitive to this gas.

The influence and mechanism of action of carbon dioxide on the metabolism of microorganisms is still unclear (Singh, 2018).

4.7 Volatile compounds

As described above (section 5.1), the primary compounds produced by LAB through fermentation are LA and AA. Under specific conditions, part of the intermediate pyruvate can be converted into other compounds such as diacetyl, acetoin or acetaldehyde that play an important role in the flavor formation of many foods. For example, diacetyl and acetoin give a positive attribute to dairy products (cheese note), while their accumulation can be perceived as spoilage in other fermented products such as beer (Gänzle, 2015). These pathways are generally triggered by specific conditions such as the presence or absence of oxygen and pH modification and also depend on the specific metabolic features of the species considered. Indeed, obligatory homofermentative LAB generally produce LA as a unique product from glucose metabolism. However, in harsh condition (limitation of carbon sources, changes in temperature or pH) some of the homofermentative LAB can shift to mixed acid fermentation, with the activation of the enzyme PFL (pyruvate-formate lyase). The activity of this enzyme, and thus, the final products obtained, is influenced by oxygen availability and pH. In anaerobiosis and at pH higher than 7, PFL converts pyruvate to formate, acetate, acetaldehyde and ethanol, while in aerobiosis and at pH 5.5–6.5 pyruvate can be metabolized to acetate, acetaldehyde, ethanol and minor products acetoin, diacetyl and 2,3-butanediol, that can affect the sensorial profile of foods (Bintsis, 2018). Lactococci and *Leuconostoc* spp. can produce diacetyl, acetoin, 2,3-butanediol starting from citrate, that is first hydrolyzed to oxaloacetate and acetate by citrate lyase. The oxaloacetate is then decarboxylated to pyruvate, which is then transformed to other compounds. In lactococci, oxaloacetate is converted to acetate, acetoin, diacetyl, 2,3-butanediol and CO_2, while in *Leuconostoc* spp., it is converted to lactate, although in the absence of glucose or at low pH, this LAB can produce diacetyl and acetoin (Bintsis, 2018; Gänzle, 2015).

4.8 Other compounds for industrial applications

LAB are able to produce other non-volatile compounds that can be exploited at the industrial level. For example, extracellular polysaccharides (EPS) play an important role in improving the texture and mouth feel of bread and dairy products (cheeses, fermented milks, yogurt), acting as emulsifying and stabilizing agents. In addition to their technological properties, EPS can also have potential health benefits as prebiotics, antioxidants, anticancer and anti-inflammatory molecules and cholesterol-lowering agents (Bintsis, 2019; Nguyen et al., 2020; Zhou et al., 2019). The structure of these molecules can vary according to species or even strain specificity, although in general, they are branched heteropolysaccharides, intracellularly synthesized by strains belonging to several genera: former *Lactobacillus*, *Lactococcus* and *Streptococcus*, or homopolysacharides (glucans, fructans and galactans) obtained through the action of external enzymes of strains of *Leuconostoc*, former *Lactobacillus*, *Streptococcus* and *Weissella* (Garcia et al., 2020). Because of their technological potential in food texture and stability, many studies have been focused on the biosynthesis pathways leading to their accumulation, with the aim of selecting or modifying strains endowed with high EPS production ability (Teusink & Smid, 2006).

Beside technological properties, LAB can also influence the functional features of foods, thanks to their ability to produce bioactive peptides (BP). Indeed, proteolysis can result in the release of small peptides and free amino acids. These latter can be converted to other compounds also involved in the formation of the organoleptic profile (alcohols, aldehydes, acids or esters) while among peptides, fragments with specific amino acid composition and sequence can exert beneficial effects. In particular, health-promoting activities include antihypertensive, antioxidant, antimicrobial, anti-inflammatory, anticancer, hypolipidemic and hypocholesterolemic effects (Chai et al., 2020). In this context, LAB fermentation has been recognized as a promising strategy to obtain BP from different food matrices. A comprehensive review regarding suitable sources as well as peptide bioactivities and applications has been recently published (Chai et al., 2020). For example, among LAB, some strains of *Lactobacillus helveticus* and *Lactococcus lactis* have been reported to accumulate BP during milk fermentation. With regard to fermented meats, the use of some strains of *Lactiplantibacillus pentosus*, *Latilactobacillus sakei* or *Pediococcus pentosaceus* in combination with staphylococci as starter cultures for different types of fermented sausages determined the release of peptides with antioxidative, antimicrobial and immunomodulating activities (Nagpal et al., 2012).

LAB can also be exploited to enhance levels of other bioactive compounds such as γ-aminobutyric acid (GABA), known to exert several physiological functions such as neurotransmission, diuretic and hypotensive effects, etc. Indeed, fermentations carried out including species of lactobacilli and lactococci have been reported to increase GABA accumulation in edible seeds (chickpea, soybean, millet, oat, etc.) and sourdough (Gan et al., 2017).

Moreover, many studies demonstrated that LAB fermentation results in an increase in B group vitamins, suggesting the ability of these microorganisms to synthesize these essential nutrients in cereals and legumes (Gan et al., 2017).

Another advantage of the use of LAB in food products relates to the possibility of increasing antioxidant activity and changing the phenolic profiles in terms of the total content or ratio of specific compounds. This is due to the activity of enzymes such as β-glucosidase or esterase that can metabolize soluble phenolics or polymers. The food matrices in which LAB such as *Lacticaseibacillus paracasei*, *Lactiplantibacillus plantarum*, *Lactobacillus acidophilus* have shown these activities include fermented beverages obtained by pomegranate, blueberry mulberry, elderberry, cupuassu (Garcia et al., 2020) and cereal and legumes such as soybean and soy products, cowpea, runner bean, sorghum flour, wheat and rye bran (Gan et al., 2017; Verni et al., 2019). It is noteworthy that in many cases, these features are strain-specific and therefore the release of specific phenolic compounds, as well the improving of their bioavailability, can be strongly affected by many process parameters, e.g. microbial species, raw materials, environmental conditions. Moreover, since polyphenol stability is pH dependent, the accumulation of lactic acid due to LAB fermentation can stabilize the phenolic fraction, improving the nutritional and functional value of final products (Barbieri et al., 2019).

Regarding the functional properties of LAB, they are also able to degrade toxic and antinutritional compounds (tannins, phytates) present in raw material. Such is the case with cassava, in which LAB fermentation increases safety by reducing cyanogenic glucosides through the enzyme linamarase. In addition, with cereals and legumes, some strains of lactobacilli, pediococci or leuconostocs demonstrated the ability to reduce phytic acid content, with positive side effects on the bioavailability of minerals and proteins (Licandro et al., 2020).

Finally, in addition to the previously discussed bacteriocins, LAB are able to produce other antimicrobials such as short/medium chain fatty acids and phenyl lactic acid, known to exert antifungal activity (Mallappa et al., 2021). Due to the increasing demands of consumers for additive free foods, the use of these bio-based compounds is a promising strategy to ensure food safety and increase the shelf-life of food products (Coban, 2020).

4.9 Biogenic amines

Biogenic amines (BAs) are organic based generally produced by the microbial decarboxylation of specific amino acids in foods. BAs that can occur in food products are histamine, tyramine, putrescine, cadaverine, tryptamine, 2-phenylethylamine, spermine, spermidine, and agmatine. These compounds can be responsible for food poisoning, causing toxic effects in humans. A massive growth of spoilage bacteria, belonging to *Enterobacteria* and *Pseudomonas*, can lead to BA accumulation. Bas are considered a microbial quality index in fresh products (Baixas-Nogueras et al., 2005; Vasconcelos et al., 2021). BAs can also be present in fermented foods where LAB can be considered to be the primary BA accumulators, especially for tyramine (Barbieri et al., 2019). Indeed, LAB strains belonging to different species and genera *(i.e.* former lactobacilli, enterococci, lactococci, pediococci, streptococci, and leuconostocs) have been characterized for their decarboxylase activities and can harbor genes or operons coding for decarboxylating enzymes or other pathways implicated in BA biosynthesis. The role of LAB in fermented food BA content and the genetic organization of their decarboxylase clusters have been recently reviewed by Barbieri et al. (2019). Generally, enzymes responsible for specific amino acid decarboxylation are organized in clusters that include amino acid decarboxylase and corresponding antiporter permease genes.

The physiological reasons that lead to BA production pertain to several cell advantages, such as a cell response to acid stress through an increase of intracellular pH and a support to the primary metabolism of cells under environmental hazard conditions. In fact, the amino acid decarboxylation process belongs to the secondary transport system responsible for the delivery of a net positive charge outside the membrane and thereby replenishing the cells with the energy that they need (Perez et al., 2015).

In this regard, even if the genetic clusters responsible for BA production can show differences between the species and the strain, the decarboxylation mechanisms can be considered an important ecological tool for strain competitiveness in a stressful environment.

Such acidic and poor nutrition conditions can be easily found during the fermentation and ripening of foods, where non-controlled autochthonous LAB involved in the ripening process can contribute to BA accumulation. These non-starters LAB (NSLAB) can have an important role in the ripening phenomena (*i.e.* development of flavor and aroma profile), showing good adaptation to unfavorable conditions and possessing specific genetic mechanisms that lead to stress responses, *i.e.* decarboxylase activity. The presence of LAB strains that are able to produce BAs is a relevant food issue, due to their high BA accumulations in fermented sausages and cured meats, cheeses, fermented vegetables and fermented fish (EFSA, 2011).

Among these NSLAB, enterococci (*i.e. E. durans*, *E. faecium*, *E. faecalis, E. mundtii* and *E. casseliflavus* species), often involved in the ripening process of cheeses and dry sausages, have been recognized as strong tyramine producers (Bargossi et al., 2015; Ladero et al., 2012).

In addition, lactobacilli, such as *Latilactobacillus curvatus*, *Levilactobacillus brevis, Lentilactobacillus parabuchneri* and *Lentilactobacillus buchneri*, can accumulate tyramine, histamine and putrescine in fermented sausages and cheeses (Barbieri et al., 2019). In these products, the decarboxylating potential of strains belonging to *S. thermophilus* species has been reported. It is interesting to note that decarboxylase activity is often expressed independently of cell viability, and these enzymes maintain their activity after cell lysis (*i.e.* during cheese ripening) as well as in harsh environmental conditions (Gardini et al., 2012). Moreover, the aminobiogenic potential of strains belonging to *Pediococcus, Weissella, Leuconostoc, Oenococcus* and *Carnobacterium* has been studied (Barbieri et al., 2019).

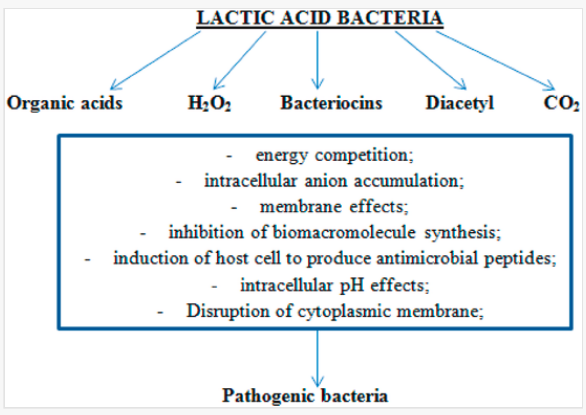
As with other LAB features, the ability to produce BAs is generally a strain-specific characteristic, and a strong variability in the amino biogenetic potential among different strains of the same species has been noted. This variability is affected by extrinsic, intrinsic and technological factors, which are closely interconnected (Gardini et al., 2016). Among these factors, the use of selected LAB starter cultures, not endowed with amino biogenic potential and able to inhibit the growth and activity of wild decarboxylating bacteria, is one of the primary strategies for counteracting BA accumulation in fermented foods. In addition, LAB capability to degrade BAs through the action of amine-degrading enzymes, such as amino oxidases, has been reported (Alvarez & Moreno-Arribas, 2014). This product of metabolism can be used by cells as a nitrogen source in poor media, and this activity has been demonstrated for several LAB strains of lactobacilli, *Pediococcus*, and *Oenococcus in vitro* and in a nitrogen poor matrix such as wine (Gardini et al., 2012).

5 Inhibition mechanism of LAB on the growth of microorganisms

The mechanisms of action of LAB on pathogens are not fully understood. Although opinions differ, most researchers agree that the bacteriostatic phenomenon is caused by several factors taken altogether. The factors explaining the inhibitory mechanism of LAB are presented in Fig. 2. Acid production is considered the most important mechanism by which LAB inhibit pathogens. The inhibitory effect of organic acids is provoked by undissociated molecules, which predominate in a low pH environment. High acidic conditions disrupt basic metabolic functions in cells associated with membrane transport of substrates and oxidative phosphorylation. In addition, LAB can reduce molecular oxygen to hydrogen peroxide and due to the lack of catalase activity, hydrogen peroxide concentration increases sharply. High H_2O_2 amount exhibits oxidative antibacterial action against various microorganisms (Klewicka & Libudzisz, 2004; Acai et al., 2019). LAB are characterized by their tolerance to low pH and growth, whereas other bacteria are unable to grow thereby ensuring food safety. The antimicrobial action of the organic acids is produced by the combined actions of the undissociated molecules and the dissociated ions. When an organic acid is added to the food environment, depending on the pH of the food, the pK of the acid, and the temperature, some of the molecules dissociate, whereas others remain undissociated. The lower antimicrobial effectiveness of lactic acid is probably a result of its low pKa. The antimicrobial action of the undissociated molecules is produced by dissociation of the molecules in the cytoplasm following their entry through the membrane. H+ released following dissociation initially reduces the transmembrane proton gradient and neutralizes the proton motive force and then reduces the internal pH, causing denaturation of proteins and viability loss. Moreover, the penetration of lactic acid into cell membranes leads to a decrease in intracellular pH. In addition to lactic acid, heterofermentative LABs produce products such as acetic acid, ethanol, and carbon dioxide. Ethanol is subsequently converted to CO_2 and H_2. Carbon dioxide interacts with cell membranes by lowering internal and external pH levels (Bungenstock et al., 2020). Diacetyl is a product of citrate metabolism and is responsible for the organoleptic properties of some fermented dairy products (Ghoul & Mitri, 2016). The action of diacetyl is associated with its interference with arginine-binding proteins. Studies have shown that diacetyl is antibacterial against Gram-positive and Gram-negative bacteria (Bungenstock et al., 2020). In combination with heat, diacetyl is more bactericidal than when used alone. In addition, diacetyl has an intense aroma, so its use is probably limited to certain dairy-based products in which its flavor is not unexpected. The antimicrobial action is probably produced by the deactivation of some important enzymes. The dicarbonyl group of diacetyl reacts with arginine in the enzymes and modifies their catalytic sites. Peroxide is the other component produced by LAB, and its antibacterial action is attributed to its strong oxidizing property and its ability to damage cellular components, especially the membrane. Peroxide also has the ability to oxidize membrane lipids and cellular proteins. Another mechanism for the manifestation of the antimicrobial activity of LAB is the result of bacteriocins, which are produced by LAB. Bacteriocins affect the integrity of the cell membrane, affecting the synthesis of DNA and proteins. Gram-negative and resistant Gram-positive bacteria injured by a physical or chemical stress become sensitive to bacteriocin. The bactericidal effect of the bacteriocins toward a sensitive bacterial cell is primarily a result of destabilization of the function of the cytoplasmic membrane (Coban, 2020). The bacteriocin molecules are initially absorbed on the membrane surface and form transient pores, leading to a loss of proton motive force as well as the pH gradient across the membrane (Hibbing et al., 2010). This alters the permeability of the membrane, causing the leakage of small nutrient molecules as well as affecting the transport of nutrients and the synthesis of ATP. These changes finally cause the cell to lose viability. In addition, some bacteriocins can cause lysis of sensitive cells. In the case of nicin, several molecules initially bind to the lipid of the cell wall. This subsequently helps the molecules to come in contact with the membrane, leading to pore formation. Pore formation by nisin requires a voltage difference between the inside and outside of the membrane. Nisin is thus, more potent against growing cells as opposed to resting cells of a target population (Coban, 2020).

alt-text: Fig. 2

Fig. 2



Inhibition of foodborne pathogens by LAB.

In contrast, the action of pediocin is not dependent on the voltage difference of the membrane, so it is effective against both growing and resting cells (Oscáriz & Pisabarro, 2001; Cizeikiene et al., 2013; Heredia-Castro et al., 2015).

5.1 Interaction of LAB on the effect of microorganisms

Current nutritional trends related to improved health and longevity have resulted in greater consumer focus on natural and minimally processed foods that guarantee certain health benefits. For example, chemical preservatives are either proscribed or not accepted by the consumer which has caused an increase in usage of so-called biological preservation in order to ensure the safety and quality of foods. Consequently, the application of a natural preservative in the form of a prebiotic substrate responds to consumer concerns, providing the development of a useful endogenous microflora and the technological safety of the nutrient medium. For instance, fermentation is one of the oldest known food preservation methods, a typical example of which is dairy fermentation that is widely used in the manufacturing of various dairy products (Mokoena, 2017; Siedler et al., 2019).

The ability of LAB to produce a variety of biologically active metabolites that act as carriers of dairy's healthy and flavor-rich potential is well-known. For example, LAB are responsible for the flavor and textural characteristics of the final product. With lactic acid fermentation, a number of physico-chemical, biochemical and microbiological

changes to the nutrient medium have been observed in the course of the biotechnological process, all of which have had a positive effect on the qualitative indicators of the final product (Marianelli et al., 2010; Mokoena, 2017).

A microbial ecosystem is a delicately balanced population of microorganisms in which each organism interacts and influences other population members. Microorganisms can interact with another organism in a manner by which they harm the other without leading to a negative effect. There are several types of microbial interactions, such as commensalism, inhibition, competition for food, parasitism and synergism, all of which can affect the functioning of the microbial ecology. For example, commensalism is a relationship that benefits bacteria but does not help or harm the host. Most bacteria that are part of the normal microflora are found on epithelial surfaces that are in contact with the environment. These bacteria are common on the skin surface, in the respiratory tract, and in the gastrointestinal tract. In some cases, commensal bacteria can become pathogenic and cause disease, or they can provide a benefit to the host (Crowley et al., 2013).

However, pathogenic parasites that cause disease oppose the protection of the host and grow at the expense of the host. A parasitic bond is one in which bacteria benefit while the host is damaged. These bacteria produce poisonous substances called endotoxins and exotoxins, which are responsible for disease symptoms. Disease-causing bacteria are responsible for meningitis, pneumonia, tuberculosis, and many others (Sivamaruthi et al., 2019). LAB produce organic acids (lactic and acetic acid), which are effective inhibitors of pathogenic microorganisms. These organic acids have the ability to lower the pH of the environment but at the same time have an inhibitory effect by releasing H + ions, which acidify the cellular cytoplasm. Other LAB antimicrobials such as bacteriocins, H_2O_2, and fatty acids are also considered as growth inhibitors of some organisms (Langa et al., 2014).

Sometimes, the antimicrobial activity is associated with the microbial consortium in which microorganisms participate rather than with each strain individually. Microbial growth studies provide essential information regarding the mechanisms of food spoilage, foodborne diseases, food bioprocessing, and strain improvement. Microorganisms are present in mixed cultures in food and can interact with each other while growing. Knowledge of the diversity of organisms and their symbiotic, parasitic or commensal interactions is essential for understanding species' coexistence, distribution, productivity, and ability to survive (Reis et al., 2012). Microorganisms can form an endosymbiotic bond with other organisms. The microorganisms that make up the intestinal flora in the gastrointestinal tract synthesize vitamins such as folic acid and biotin and absorb complex, indigestible carbohydrates. Some microorganisms that are considered to be beneficial to health and are part of the normal intestinal microflora are called probiotics (Bian et al., 2016).

Antimicrobial activity is a sought-after quality in the selection of strains (Bungenstock et al., 2020). Due to the ability of LAB to produce various antimicrobial substances, they inhibit the development of pathogenic microorganisms. LAB are known to have antimicrobial activity against many Gram-positive and Gram-negative bacteria and fungi (Coman et al., 2014; Sharma et al., 2018). The diversity of food processing methods and the specificity of the selected technological processing of some dairy products favor the microbiological status and organoleptic quality of the product and the development of foodborne pathogenic bacteria. The presence of pathogenic bacteria such as *Listeria monocytogenes, Staphylococcus aureus, Escherichia coli*, and *Salmonella enterica* would lead to irreversible biochemical and flavor-lowering changes that lower the quality and safety of the fermented product. The usage of starter cultures with indicated antimicrobial potential would thus be a suitable alternative for maintaining the microbiological status and organoleptic qualities of the product throughout the biotechnological cycle (Alvarado, 2006).

As alternative forms for reducing microbial contamination, LAB with high antimicrobial activity can be used widely as a bioconservative. Cizeikiene et al. (2013) reported that LAB strain supernatants (*P. pentosaceus* KTU05-10, *P. pentosaceus* KTU05-9, *P. pentosaceus* KTU05-8, *P. acidilactici* KTU05-7 and *L. sakei* KTU05-6) effectively inhibited the growth of Gram-positive *B. subtilis* strains, *B. thuringiensis*, and Gram-negative *S. typhimurium*, *P. gladioli* pv. *aliicola* 3.1, *P. cepacia* 1.1, *P. fluorescens* biovar. Kim (2005) studied more than 120 isolates of LAB obtained from Kimchi and their antifungal activity against *Aspergillus fumigatus*. The author reported that approximately 10% of the isolates showed inhibitory activity and only 4.16% (five isolates) exhibited strong activity against the indicator fungus *A. fumigatus*. Marcia et al. (2018) reported the antifungal activity of 32 strains of LAB and propionibacteria alone and then in combinations performed in yogurt and cheese models against four major spoilage fungi previously isolated from contaminated dairy products (*Penicillium commune, Mucor racemosus, Galactomyces geotrichum*, and *Yarrowia lipolytica*). Their results showed that the combinations delayed the growth of *P. commune, M. racemosus* and *R. Mucilaginosa* on sour cream for 2–24 days. In another study, Juodeikiene et al. (2018) focused on finding a strategy for the reduction of *Fusarium* mycotoxin in malting wheat grains using the treatment with LAB on deoxynivalenol, zearalenone, T-2 and HT-2 toxins. The test of LAB strains revealed a broad spectrum of antimicrobial activity against fungi, especially *Fusarium culmorum* and *Fusarium poae*.

5.2 Competitive models for microbial growth between LAB and other microorganisms

In their life path, microorganisms compete for favourable environmental conditions in order to exist. Competition for food and environmental resources is carried out in two main ways - through indirect and direct competition. Competition can be categorized as indirect competition (competition for exploitation), in which microorganisms seek to use the organic resource quickly without entering into direct competition with other members of the population. Direct competition (intervention competition) involves direct, antagonistic interactions between competitors, with the “winner” appropriating the resources (Hibbing et al., 2010). Cadavez et al. (2019) compared competition models for *L. monocytogenes* growth as a function of the intrinsic properties of a traditional Brazilian soft cheese and the inhibitory effect of LAB during refrigerated storage. As a result of the applied model, they concluded that water activity (a_w) did not improve the fit quality of the Huang-Cardinal [pH] model. Such models are considered as important due to the potential for using dynamic data (i.e., microbial population data as driven by food intrinsic properties over time) to make predictions. For example, Valík et al. (2018) reported that the incorporation of averaged competition coefficients resulting from individual co-culture trials improved the prediction of *S. aureus* behaviour in co-culture with LAB in milk at different temperatures and LAB inoculums ranging from 12 °C to 30 °C and 10^3–10^7 CFU ml^{-1}, respectively.

Breidt and Fleming (1998) developed a mathematical model for co-culturing of pure and mixed cultures of *L. lactis* and *L. monocytogenes* growing in a vegetable broth medium. The model described bacterial cell growth that is limited by the accumulation of protonated lactic acid and decreasing pH.

Due to the inherent limitations of the current mathematical models used to predict microbial growth, Nev et al. (2021) proposed a modelling approach that incorporates growth parameters as a function of initial nutrient concentration. They conducted growth experiments on a range of microorganisms, including human fungal pathogens, baker's yeast, and common coliform bacteria and observed that the maximal nutrient uptake rate and biomass yield were both decreasing functions of the initial nutrient concentration. Cauchie et al. (2020) studied the growth parameters of specific spoilage microorganisms, *Brochothrix thermosphacta*, *Leuconostoc gelidum*, and *Pseudomonas* spp. (*P. fluorescens* and *P. fragi,* (isolated in minced pork) and developed a three-spoilage species interaction model under different storage conditions. As a result, the food packaging showed the highest impact on bacterial growth rates, which in turn had the strongest influence on the shelf life of food products.

5.3 The role of LAB in the elimination of toxic compounds in food products

Fermented foods are widely consumed worldwide and are one of the primary sources of toxins and pathogenic microbes. Mycotoxins (aflatoxins, fumonisins, sterigmatocystin, nivalenol, deoxynivalenol, zearalenone, ochratoxin and alternariol), bacterial toxins (shiga toxin and botulinum), biogenic amines and cyanogenic glycosides are the most common toxins in microorganisms. Fermented products and meat sausages are highly vulnerable to contamination due to the chemical composition and nutritional value of the food products. Consequently, chemical preservatives such as calcium propionate, potassium sorbate, and sulfur dioxide are usually added to food to avoid spoilage caused by yeast and mold. The addition of these preservatives runs counter to the objective of developing ‘purely labeled’ foods that do not contain synthetic chemical preservatives (Zhao et al., 2017). Some other methods to remove or detoxify mycotoxins in food include physical (use of heat, ionizing radiation, and ultraviolet light) and chemical processes (use of acids or alkaline chemicals and various reagents), including hydrolytic, chlorinating, oxidizing processes (Hathout & Aly,

2010). However, these methods also prove insufficient for control, particularly with strains of certain fungal species as their mycotoxins are resistant to these processes. In addition, many of these methods adversely affect product quality. In these cases, biopreservatives are used in food due to the growing demand of consumers for more natural approaches to food preservation instead of using synthetic chemicals. LAB are the most promising candidates to be used in food as fungal antagonists. LAB are known to have the ability to bind highly toxic compounds such as heavy metals (Ameen et al., 2020; Halttunen et al., 2008; Hasr Moradi Kargar et al., 2020), food mutagens (Thyagaraja & Hosono, 1994; Turbic et al., 2002), microbial toxins such as aflatoxins (Peltonen et al., 2001; Fazeli et al., 2009) and cyclopeptide toxins (Zhao et al., 2017).

6 Health benefit or risk of LAB

The use of LAB in the food industry has been one of the oldest and the most studied methods of preservation (fermentation). The health benefits of consuming fermented foods are well known and accepted by consumers, so introducing an adequate amount of live microorganisms (probiotics) into one's daily diet in the form of supplements (pills, powder, or liquid drops) is considered to be a healthy habit (Liu et al., 2018). Some of the main health benefits of the LAB are presented in Table 3.

alt-text: Table 3

Table 3

The table layout displayed in this section is not how it will appear in the final version. The representation below is solely purposed for providing corrections to the table. To preview the actual presentation of the table, please view the Proof.

Health benefits of LAB.

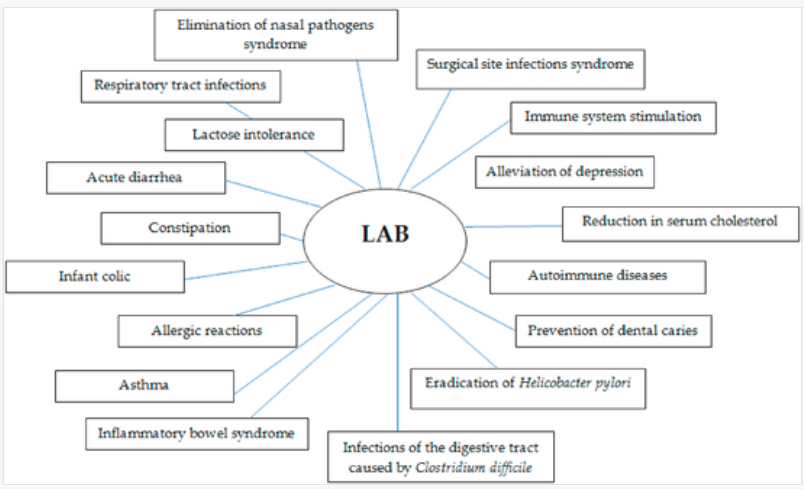
LAB strains	Health benefits	Reference
• Lactobacillus • Pediococcus • Weissella	• Enzymatic activity of the strains; • High β-galactosidase activity; • Presented resistance to simulated gastric (3_h) and intestinal (4_h) conditions *in vitro*; • The ability to auto- and co-aggregate with indicator microorganisms and a high cell surface hydrophobicity.	Colombo et al. (2018)
• Levilactobacillus brevis • Lacticaseibacillus casei • Lactiplantibacillus plantarum	• Improvement in level of urinary 3-IS.	Fukuchi et al. (2020)
• *Limosilactobacillus fermentum* • *Lactobacillus* sp G3_4_1TO2	• Showed maximum potential probiotic characters; • Produced amylase enzyme; • Play role in gastro intestinal tract.	Padmavathi et al. (2018)
• Limosilactobacillus fermentum CRL1446 (CRL1446) • Lactococcus lactis CRL1434 (CRL1434) • Lacticaseibacillus casei CRL431 (CRL431)	• Treatment to obesity and overweight; • Regulation of the immune system; • Decrease in plasmatic glucose, cholesterol, triglycerides, leptin, TNF-α, IL-6 levels; • Increase of IL-10.	Fabersani et al. (2021)
• *Lactobacillus gasseri* NT	• Participate in lipid metabolism; • Fat synthesis reduction.	Yonejima et al. (2013)
• Limosilactobacillus *reuterin* 263	• Cardiovascular diseases; • Hypolipidemic pharmacological effect.	Huang et al. (2015)
• Limosilactobacillus fermentum NCMR 2826	• Reduced serum cholesterol levels; • Reduce macrovesicular steatosis and hepatocyte ballooning;	Thumu & Halami (2020)

	• Intestinal microbial modulation.	
• Limosilactobacillus fermentum CCM 7421	• Alter the composition of intestinal microbiota and metabolites (organic acids), and modulate the physiology (serum biochemical parameters) and immunity parameters.	Strompfová et al. (2017)
• Lactiplantibacillus plantarum 299v	• HIV-1 infection; • May stabilize $CD4^+$ T cell numbers in HIV-1 infected children and are likely to have protective effects against inflammation and chronic immune activation of the gastrointestinal immune system.	Cunningham-Rundles et al. (2011)

Probiotics include genera *Lactobacillus, Bifidobacterium, Leuconostoc, Pediococcus*, and *Enterococcus* (Sundararaman et al., 2020). The increasing list of medical and non-medical indications that can be improved, prevented, or treated by probiotics consumption is affecting the global probiotics market, which is expected to exceed $3.5 billion by 2026 (Ahuja & Mamtani, 2019, p. 5). In this regard, both the demand and the range of food products containing probiotics are constantly growing. When probiotics are applied to dairy and non-dairy foods, these products become functional and can interact directly with the consumer (Gobbetti et al., 2010). However, special maintenance of probiotics through food processing, packaging, and storage is needed in order to ensure product viability and stability (Kechagia et al., 2013; Suez et al., 2019). In the last few decades, numerous researchers have reported a wide range of health benefits from foods containing probiotic microorganisms, especially *Lactobacillus* and *Bifidobacterium* genera that are the dominant microorganisms in the probiotics industry (Gobbetti et al., 2010; Suez et al., 2019). *Lactococcus* spp., *Streptococcus thermophilus*, *E. coli* Nissle 1917, and the yeast *Saccharomyces boulardii* have also been well studied. The proposed mechanisms for the beneficial effects of probiotics include induction of immunomodulation, protection against physiological stress, suppression of pathogens, microbiome modulation, and improvement of the barrier function of the gut epithelium (Suez et al., 2019). Medical conditions that may be prevented, improved, or treated by probiotics were presented in Fig. 3. Moreover, probiotics have showen antimicrobial, antimutagenic, and anticarcinogenic properties (Gobbetti et al., 2010; Kechagia et al., 2013; Lerner et al., 2019; Liu et al., 2018; Mathur et al., 2020; Plavec & Berlec, 2020; Suez et al., 2019). Recently, it was found that some probiotic strains may suppress virus-induced cytokine storms through modulation of host immune responses, maintenance of gut homeostasis, and the production of interferon, all of which can be beneficial to patients with COVID-19 infections (Singh & Rao, 2021; Sundararaman et al., 2020).

alt-text: Fig. 3

Fig. 3



Medical conditions that may be prevented, improved, or treated by LAB.

The use of probiotics has been greatly popularized and promoted among the general public in recent years, primarily through the use of health-benefit claims that are not yet supported by proper studies. This brings into question the suitability and safety of different strains, especially over-the-counter probiotics that are regulated as dietary supplements for which proof of efficacy is not mandatory for their sale. Such products claim to be capable of preventing many diseases by restoring the human microbiome to its natural (normal) state (Anonimus, 2017); however, both the European Food Safety Authority and the US Food and Drug Administration have yet to approve any probiotic formulation as a replacement for medical therapeutics (Suez et al., 2019). The treatment of human disease conditions with probiotics is highly dependent on the host's microbiome and diet and varies in both effectiveness and side effects from individual to individual. However, when administrated in adequate quantities for sufficient periods, probiotics are safer than most pharmaceuticals (Liu et al., 2018). Thus, not surprisingly, research on probiotics has intensified in the last two decades. According to PubMed, a total of 212 papers were published on probiotics in 2000 compared to 4447 papers on this topic in 2020 (PubMed, 2021). This demonstrates the level of interest and focus on moving probiotics to a place at the forefront in the field of therapeutic agents. However, authors agree that more evidence-based *in vitro* and *in vivo* research is required, taking into consideration all of the complexity of the system such as the human microbiome (diet, colonization resistance, strain specifics, etc.). By standardizing the experimental techniques, clinical trials, safety explorations, and strain selections it may have the ability to draw objective conclusions and avoid undesirable outcomes. The risks and adverse effects response to different probiotic strains and formulations, treatments/intakes have been reported and discussed in detail elsewhere (Daliri et al., 2018; Lerner et al., 2019; Suez et al., 2019). The authors confirm that additional caution is needed especially for the immunocompromised patients; however, it does not diminish the beneficial effect of probiotic strains.

7 Facts and gap of LAB use in food industry

LAB constitute a large industrial microbial group and are primarily used as starter cultures and probiotics due to their potential as safe and efficient cell factories for food ingredients and the production of high-value chemicals. These bacteria are currently being exploited in various biotechnological processes as delivery vehicles for preventive and therapeutic drugs and as biological catalysts for the production of value-added products (Hatti-Kaul et al., 2018). In addition, LAB can highlight numerous production advantages concerning other organisms in terms of high growth rate, ability to use different carbon sources, microaerophilic/anaerobic characteristics and tolerance to various stress conditions.

Their use in the food and non-food sector gives them a unique role in the perspective of the biobased economy. Indeed, industrial biotechnology is based on the possibility to develop efficient and economic microbial-cell processes, is considered a key enabling technology for the transition from fossil to the green economy (Win et al., 2018).

Biotechnological process optimization and the industrial exploitation of LAB can include strain selection, proper balancing of supply and demand reactions and modeling techniques for biological interpretation and prediction. The latter can consist of more traditional approaches (*i.e.* stoichiometric models, kinetic models for metabolic control analysis and the maximization of product accumulation, etc.) and/or recent genome-scale modeling for functional-genomics data with the aim of improving knowledge and industrial applications (Teusink & Smid, 2006).

The specific biotechnological process features depend on the type of application. In any case, the selected LAB strains must be cultivated and produced under the most stringent conditions. On the other hand, the low-cost industrial growth substrates or waste materials became a priority within the bioeconomy concept. In this regard, metabolic system engineering can improve the development of microbial cell factories that can efficiently produce a myriad of chemicals and materials, including biofuels, bulk and fine chemicals, polymers, amino acids, natural products, and drugs. Genome editing tools are becoming increasingly crusial for understanding metabolisms and molecular mechanisms, identifying targets and discovering new cell properties and applications, offering the possibility to make tailored design strains with desired properties (Börner et al., 2019). Despite their providing the opportunity to develop new performing industrial strains, genome editing tools for LAB are limited compared to other microbial species. This is primarily due to consumers' concerns regarding genetically modified organisms (GMOs) in food and restrictive food legislation. Current legislation prohibits GMOs in food production and fermentation, and probiotic applications. However, GMOs are allowed in some emerging production platforms, *i.e.* ingredients, chemicals and enzymes in order to reach economically feasible production levels and to expand the number of employed strains, and produced compounds (Börner et al., 2019). For these reasons, in the food sector, strain improvements continue to be mainly obtained traditionally with time-consuming untargeted natural strategies such as random mutagenesis, adaptive evolution, dominant selection and even natural transduction and conjugation systems. In particular, laborious random mutagenesis methods based on selection pressure have been widely applied for strain improvements in food applications, as these strains are considered non-GMO (Ayivi et al., 2020).

On the other hand, nowadays, access to microbial and genetic diversity is limited by the Nagoya Protocol (Nagoya Protocol to the Convention on Biological Diversity has created legal barriers to the access and use of genetic resources such as LAB) and, mainly, by the lack of its unambiguous interpretations (Johansen, 2017). This leads to an ever-increasing impoverishment of microbial biodiversity, becoming a current challenge in strain study, selection and production (Börner et al., 2019).

In any case, few industrial biotechnological processes are extensively applied, involving a limited number of LAB strains. In fact, LAB interactions and adaptation with the environmental niches (*i.e.* nutrient-rich ecosystems) imply gene loss and gain through horizontal gene transfer, leading to vast intra-specific biodiversity. These genetic differences are reflected in wide phenotypic variability even among strains, which show peculiar metabolic characteristics and stress-related behaviors (Wu et al., 2017). These peculiarities have been exploited as a vital possibility for product innovation, diversification, and functional improvement in the food sector. On the other hand, such great strain of biodiversity could represent an obstacle to the optimization of industrial processes andthe standardization of the production of compounds with high added value. In this perspective, a more profound knowledge of several molecular mechanistic insights which limit the exploitation of metabolic LAB potential is needed (Börner et al., 2019; Teusink et al., 2011). Most definitely, the gap between cellular processes and population dynamics in communities still needs to be bridged. For further LAB applications, early steps in the direction of metatranscriptomics and metabolomics are highly relevant.

It is interesting to note that numerous key metabolisms and functions, even those of industrial importance such as citrate metabolism or bacteriophage resistance, are encoded on plasmids and conjugative transposons. This fact requires continuous selective pressure in cultivation processes and specific replication modes in order to ensure that these critical functions are not lost to steady genetic drift during replication (Ayivi et al., 2020).

Concerning the industrial production of valuable metabolites, the industry has to face well-known problems of non-controlled growth of undesirable microorganisms or contamination, such as the development of ethanol during lactic acid fermentation (Win et al., 2018). Among the most important gaps in LAB industrial application and use are scaling-up issues. It is well known that cellular behaviors demonstrated *in vitro* and on a laboratory scale, including efficiencies and optimizations of metabolisms and production of compounds, are chalenging to apply in a simple, straightforward manner in industrial biotechnological processes. For example, the cultivation media are different, due to the use of low-cost sources in processes, which can affect and shift metabolome production. Moreover, for some LAB strain applications in products, i.e. for bioprotective cultures, there is the necessary to introduce a further production step during the manufacturing, changing the process plan and highlighting the need for additional training for specialized workers. In addition, the environmental factors and the need for industrial processes standardization necessarily involve adaptations that could affect the final results, limiting the actual application to well-known and established procedures and strains (Balciunas et al., 2013).

General Food Law regulation ensures a high level of protection of human life and consumers' interests in relation to food. However, the use of LAB in food is not harmonized by European food law. The EU laws that could be applicable for the utilization of new strains of LAB in foods are related to novel foods and novel food ingredients; the contained use of genetically modified micro-organisms, food additives, flavourings for use in foods, food supplements, food additives other than colours and sweeteners and microorganisms as additives in animal feeding stuffs. Similarly, the USA has no specific regulation for the use of LAB as food culture. According to USA legislation, a new strain of microorganism for use in food can either be classified as an additive or as a GRAS substance (generally recognized as safe) (Wessels et al., 2004).

8 Conclusion

LAB can inhibit foodborne pathogens and prolong the shelf life of foods. In recent years, researchers have continued to search for alternative natural preservatives that can replace chemical preservatives that are currently used in food and to work on identifying potential species for a healthier diet and lifestyle. Growing consumer awareness of nutrition and the continuing trend toward natural and healthy products have resulted in an increase in the popularity of LAB as a focus of research. Exploring the biodiversity of lactic acid microflora in different food sources, the isolation, identification, and characterization of LAB is a new approach to forming a variety of starter communities to create innovative nutritional matrices for functional fermented dairy foods. Future perspectives on the study of LAB may be related to the expansion of our knowledge in the fields of genetics and genetic engineering. Genetic science may help to improve existing strains and develop new strains with characteristics designed for specific purposes.

Authorship statement

Conception and design of study: Fatih Özoğul, Salam A. Ibrahim.

Acquisition of data: Tuba Esatbeyoglu, Vida Simat, Monica Trif, Giulia Tabanelli;

Drafting the manuscript: Tina Kostka, Chiara Montanari, Hafize Fidan, Tuba Esatbeyoglu, Vida Simat, Monica Trif, Giulia Tabanelli; Fatih Özoğul, Salam A. Ibrahim.

Writing of the original draft: Tina Kostka, Chiara Montanari, Hafize Fidan, Tuba Esatbeyoglu, Vida Simat, Monica Trif, Giulia Tabanelli.

Revising the manuscript critically for important intellectual content: Salam Ibrahim, Fatih Özoğul.

Approval of the version of the manuscript to be published (the names of all authors must be listed): Hafize Fidan, Tuba Esatbeyoglu, Vida Simat, Monica Trif, Giulia Tabanelli; Tina Kostka, Chiara Montanari, Fatih Özoğul, Salam A. Ibrahim.

Q4 Uncited references

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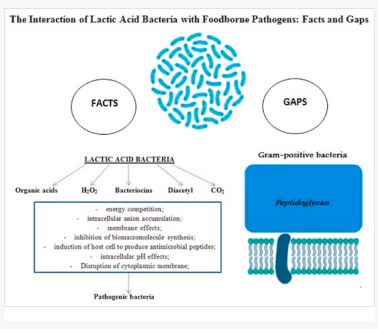

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