Multi-Product Lactic Acid Bacteria Fermentations: A Review

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Abstract: Industrial biotechnology is a continuously expanding field focused on the application of
microorganisms to produce chemicals using renewable sources as substrates. Currently, an increasing
interest in new versatile processes, able to utilize a variety of substrates to obtain diverse products, can
be observed. A robust microbial strain is critical in the creation of such processes. Lactic acid bacteria
(LAB) are used to produce a wide variety of chemicals with high commercial interest. Lactic acid (LA)
is the most predominant industrial product obtained from LAB fermentations, and its production is
forecasted to rise as the result of the increasing demand of polylactic acid. Hence, the creation of
new ways to revalorize LA production processes is of high interest and could further enhance its
economic value. Therefore, this review explores some co-products of LA fermentations, derived from
LAB, with special focus on bacteriocins, lipoteichoic acid, and probiotics. Finally, a multi-product
process involving LA and the other compounds of interest is proposed.

Keywords: LAB metabolites; probiotics; lactic acid; lipoteichoic acid; bacteriocins; biomass

1. Introduction

During the last decades, the interest in the development and utilization of more sustainable
energy and chemical resources increased due to worldwide concerns regarding fossil-fuel depletion
and environmental protection [1]. Since the middle of the 19th century, the petrochemical industry is
responsible for meeting the world's chemical and energy needs. Nevertheless, the finite nature of oil, its
price volatility, and the environmental impact of its utilization are some of the reasons that encouraged
research into alternative ways of meeting the energy and chemical demands of a continuously growing
population. Industrial biotechnology is an expanding field, with special focus on the application of
microorganisms to produce energy and chemicals using renewable resources as substrates.

Currently, there are several well-established single product bioprocesses which show economic
and environmental feasibility. However, multi-product routes, through the valorization of residues and

by-products, were proposed to improve industrial single-product biotechnological processes [2]. One example is the use of cellulose and hemicellulose from sugarcane bagasse (a residue obtained during the bioethanol production and usually used for energy generation) for the production of value-added chemicals [3]. Likewise, glycerol, a by-product of the biodiesel industry with low value in the market, is targeted as a molecule of interest in fermentation processes. Such multi-product processes, based on the conversion of renewable materials into biobased products, are known as biorefineries [4].

The study, development, and application of robust microbial strains, able to utilize a variety of substrates and to produce a wide range of products, is considered a milestone in the development of biorefineries [4]. Lactic acid bacteria (LAB) are a diverse group with recognized potential for the development of integrated biorefineries [5]. LAB are non-sporulating, non-motile, acid-tolerant, non-respiring but aerotolerant, catalase-negative, Gram-positive cocci or rods. They are characterized by the production of lactic acid (LA) as the major end metabolic product of carbohydrate fermentation [6–9]. Given the lack of a functional respiratory system, LAB obtain energy through substrate-level phosphorylation following two metabolic pathways for hexose fermentation, i.e., homofermentative and heterofermentative. As shown in Figure 1, the first pathway is based on glycolysis with the production of mainly LA, whereas the second one, known as the pentose phosphate pathway, is characterized for the production of CO_2 and ethanol, or acetate in addition to LA [6].
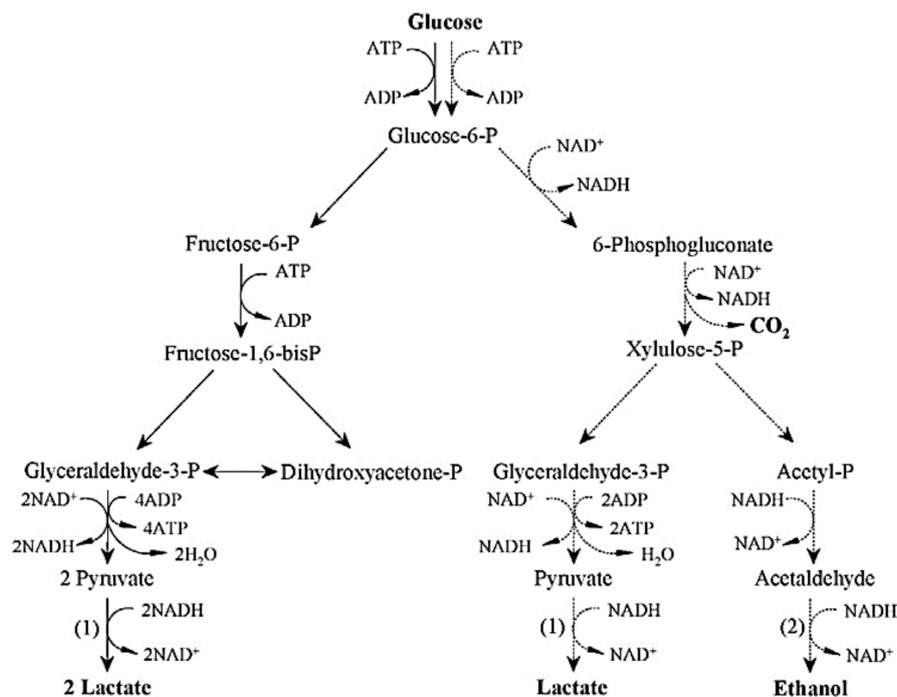

Figure 1. Metabolic pathways of homofermentative (solid line) and heterofermentative (dotted line) lactic acid bacteria: P, phosphate; ADP, adenosine 5′-diphosphate; ATP, adenosine 5′-triphosphate; NAD^+, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide (reduced form); (1), lactate dehydrogenase; (2), alcohol dehydrogenase (from Reference [8], licensed under CC BY-NC 4.0 at https://www.ftb.com.hr/80-volume-44-issue-no-2/445-biotechnological-production-of-lactic-acid-and-its-recent-applications).

Most LAB are part of the phylum Firmicutes, class Bacilli, and order Lactobacillales. The order Lactobacillales includes six families, i.e., Aerococcaceae, Carnobacteriaceae, Enterococcaceae, Lactobacillaceae, Leuconostocaceae, and Streptococcaceae, over 30 genera, and more than 300 species, a number that continues rising as novel species are discovered [10,11]. The genus *Bifidobacterium* (family Bifidobacteriaceae) is also included in the LAB group, although it belongs to the phylum Actinobacteria [6]. LAB identification is based on the criteria originally stated by Orla-Jensen in 1919 [12], which includes morphology, mode of glucose fermentation, growth temperature ranges, and

sugar utilization patterns [6], in addition to phylogenetic analysis based on 16S ribosomal RNA (rRNA) gene sequences [8]. Moreover, because some LAB species share high sequence similarities within the groups, some housekeeping genes are used as alternative markers. Currently, whole-genome sequencing is a common tool for LAB identification in the laboratory [6,8]. Species identification, using sequencing, provides essential information to conduct genome editing of food-grade LAB, i.e., using clustered regularly interspaced short palindromic repeats (CRISPR) tools [13,14]. Potential applications of these technologies include the development of therapeutic probiotics and strains with resistance against viruses [14,15].

Lactic acid bacteria are ubiquitous and widespread in nature, found in a variety of nutrient-rich habitats such as animals, food, feed, humans, plants, and soil [10,16]. Isolation of LAB from composts, fermented foods, gastrointestinal and vaginal tracts, plant surfaces, and silages, to name a few, was reported [8]. Owing to their versatile metabolism and their ability to synthesize a wide range of beneficial metabolites in addition to LA, LAB are extensively used in biotechnology, food, and therapeutic products. Some of the applications of LAB include their use as additional hurdles for spoilage and pathogenic microorganisms, antifungal and anti-mycotoxigenic agents, bacteriocin producers, nutraceutical producers, probiotics and starter cultures, among others [6,10,16–19]. After safety assessment, the United States (US) Food and Drug Administration (FDA) and the European Food Safety Agency (EFSA) included numerous LAB species and food additives derived from them on the generally recognized as safe (GRAS) inventory or accordingly granted the qualified presumption of safety (QPS) status [6,20].

This review aims to highlight the different industrial uses of LAB, from probiotics to their use as biofactories of metabolites of interest. Furthermore, it investigates the potential of homofermentative LAB for simultaneously producing several products of interest. Finally, a multi-product biorefinery process is proposed.

2. Potential Uses of Lactic Acid Bacteria

Lactic acid bacteria are mainly used in fermentation systems which may be performed in solid (SSF) or liquid states (SLF). SLF is the most studied and industrially implemented approach, which targets the isolation of organic acids (mainly lactic acid), ethanol, bioactive peptides, among others. After fermentation, isolation and purification steps are needed to extract these compounds from the supernatant or the biomass phase. Nevertheless, in addition to the supernatant products, some LAB biomass, traditionally used in single-product fermentation processes, may also have probiotic potential. Thus, their isolation and further use, considering a multi-product process approach, could add value to the product. Figure 2 summarizes some of the most relevant compounds linked to LAB that are further discussed in this review.

Among LAB metabolites, LA and bacteriocins are examples of extracellular bacterial products that are continuously produced during growth and remain in the fermented broth. By the end of the fermentation, biomass is normally discarded; however, recently, the interest in biomass as an added-value product gained attention. Biomass is used as a protein source for the supplementation of by-products utilized in green processes; however, if the bacterial genus used is recognized as a probiotic, applications in the food industry may also be developed. Furthermore, the cell wall of LAB consists of a thick multilayered sacculus made of peptidoglycan, teichoic and LTAs, cell-wall polysaccharides, and cell surface proteins, which are also compounds with great potential for biotechnological applications [21]. With an appropriate methodology, each of these components can be separated and purified, and many applications in the food and pharmaceutical industries may be found, e.g., LTA may be used for the treatment or prevention of oral infectious diseases or as an anti-inflammatory agent [22–24]. Therefore, the multiple metabolic pathways of LAB may be an advantage for the development of more efficient and sustainable multi-product processes.
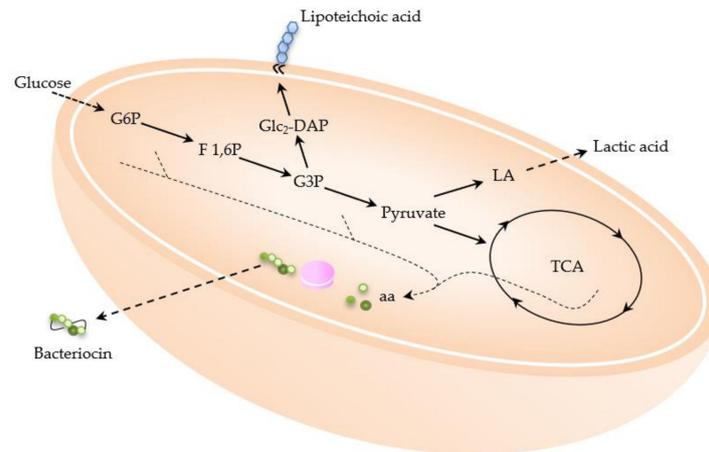
Figure 2. Illustration of the co-production of compounds in lactic acid bacteria (LAB). Extracellular products such as lactic acid (LA) and bacteriocins are synthetized and excreted from the cell, whereas lipoteichoic acid (LTA) accumulates in the cell walls of the microorganism.

2.1. Products Present in Supernatant

While growing, microorganisms produce and secrete different metabolites to their surrounding environment. These molecules, which are excreted to the supernatant during fermentation, provide information regarding changes in microbial metabolism and can be purified for certain purposes. Extracellular metabolites are mainly produced as by-products of microbial metabolic activities, and their production is influenced by environmental conditions such as temperature, pH, nutrients, and others [25]. LAB require relatively simple substrates in order to excrete, for instance, lactic acid or bacteriocins, as described in Sections 2.1.1 and 2.1.2. Unlike intracellular metabolites, which require cell disruption in order to be quantified and used, the separation of products present in the supernatant can be easily achieved via simple techniques such as centrifugation and filtration.

2.1.1. Lactic Acid

LA (2-hydroxypropanoic acid) is a chiral molecule with two optical enantiomers, L-(+) and D-(−), which can be produced via either chemical synthesis or microbial fermentation. Nevertheless, the vast majority of LA in the world is produced via biotechnological routes (via homo- and heterofermentative LAB). Furthermore, some LAB species can synthesize only one of the two enantiomers, i.e., L-(+) and D-(−), which allows the utilization of the product for some specialized applications. Most of the biotechnological LA production targets the L-(+) enantiomer, partly because the D-(−) cannot be metabolized by animal cells, which restricts its utilization in some cases, e.g., the food industry. Additionally, the production of polylactic acid, which increased the interest in LA and is now a market driver in its production [26], requires high enantiomeric purities [27].

Due to its technical simplicity, LA is traditionally produced in batch processes; nonetheless, other cultivation strategies such as fed-batch were also investigated [28]. Application of fed-batch conditions offers several advantages such as improving the productivity and reducing substrate inhibition issues [28]. Recently, it was stated that continuous fermentation of LA is most economically viable, and favoring this process in the future is highly recommended [29].

High titers of L-LA were achieved in fed-batch processes: 215.3 g·L^{-1} of 100% optically pure L-LA was produced from glucose using a genetically modified *Lactobacillus paracasei* strain reaching a productivity of 1.79 g·L^{-1}·h^{-1} [28]. A fed-batch fermentation, combined with the increase in temperature during the process, enabled *L. rhamnosus* to produce 210 g·L^{-1} L-LA from defatted rice bran with a productivity of 2.56 g·L^{-1}·h^{-1}. Nevertheless, the optical purity of the product was not stated in the study [30]. *Enterococcus mundtii* was tested in several artificial sugars and sugar mixtures of glucose, xylose, and cellobiose [31–33]. The best titer in these studies was reported from a fed-batch

fermentation with a cellobiose–xylose mixture, reaching 163 g·L^{-1} L-(+)-LA of >99% optical purity in 240 h [33]. L-(+)-LA titers of 182, 134.9, and 93 g·L^{-1} were achieved with *E. faecalis* in batch fermentations utilizing glucose, sugar molasses, and oak wood chips, respectively [34–36]. Overall productivities using glucose, sugar molasses, and oak wood chips were 5.0, 4.3, and 1.7 g·L^{-1}·h^{-1}, respectively. The optical purities for the LA obtained through the sugar molasses and oak wood fermentations were >98% and 96%, respectively.

Batch fermentation studies using *E. faecalis* also focused on scale-up, starting from working volumes of 3 L, going up to 5.2 m^3 by utilizing waste plywood chips as a substrate. At a 3-L scale process, 102.4 g·L^{-1} of > 99% pure L-(+)-LA was produced, with a productivity of 1.28 g·L^{-1}·h^{-1}. On the other hand, at 5.2-m^3 scale, only 91.5 g·L^{-1} of LA was obtained, with a productivity of 0.88 g·L^{-1}·h^{-1}. Additionally, a longer lag phase was observed due to the differences in the oxygen levels of both bioreactors tested [37]. Wee et al. [38] conducted a 200-L pilot-scale batch using corn steep liquor as a nitrogen source and glucose as a the carbon substrate. In this study, *Lactobacillus* species RKY2 grown in a glucose concentrations of up to 125 g·L^{-1} led to a maximum L-(+)-LA-titer of 115.1 g·L^{-1} and a productivity of 1.1 g·L^{-1}·h^{-1}, albeit with an optical purity of 70% L-(+)-LA [38].

Regarding the production of D-(−)-LA, 102.3 g·L^{-1} and 77.8 g·L^{-1} of >99% optical purity was obtained while conducting simultaneous saccharification and fermentation processes with lignocellulosic substrates. In these studies, *L. plantarum* reached a productivity of 0.7 g·L^{-1}·h^{-1} in delignified kraft pulp, whereas *Pediococcus acidilactici* was able to produce 1.0 g·L^{-1}·h^{-1} in corn stover hydrolysate [39,40].

Numerous investigations focused on transferring suitable lactate dehydrogenase (LDH) genes from LAB to yeast species. The acid tolerance of yeast enables it to grow at lower pH values of 4–5. This condition not only reduces the input of neutralization agents, but also allows the utilization of a wider range of substrates [41]. For example, the combination of D-LDH genes from *Leuconostoc mesenteroides* with *Saccharomyces cerevisiae* resulted in titers as high as 112 g·L^{-1} of D-(−)-LA in a fed-batch process at a productivity of 2.2 g·L^{-1}·h^{-1} [42–44].

Continuous fermentation, with the implementation of cell recycle, offers an interesting approach for industrial-scale LA production; this option increases the overall operation time and the productivity by enabling high cell densities [45]. By employing *E. faecalis* in cell recycle continuous fermentation, an L-(+)-LA titer of 90 g·L^{-1} and a productivity of 3.72 g·L^{-1}·h^{-1} were achieved using glucose as a carbon source. The dilution rate was set at 0.04 h^{-1} and residual sugars in the bioreactor were <5 g·L^{-1}; however, the optical purity of the product was not specified [46]. Cell recycle fermentation with *E. mundtii* led to a titer of 41 g·L^{-1} optically pure L-(+)-LA (> 99.9%) from xylose, reaching a productivity of 6.15 g·L^{-1}·h^{-1} at a dilution rate of 0.155 h^{-1}. Residual xylose (11.1 g·L^{-1}) remained in the process, as well as several by-products including acetic and formic acids and ethanol, which amounted to 3 g·L^{-1} [47]. A high productivity of 57 g·L^{-1}·h^{-1} and a titer of 92 g·L^{-1} of L-(+)-LA from glucose were obtained after fermentation with *L. rhamnosus* by connecting two bioreactors, with membrane cell recycle, in series. This system was run at an overall dilution rate of 0.62 g·L^{-1}·h^{-1} and residual sugars were reduced to <3 g·L^{-1}, but the optical purity of the acid was not analyzed [48]. Furthermore, lignocellulosic substrates like corn cob hydrolysates and oak wood chips were utilized for continuous fermentation employing *L. casei* and *Lactobacillus* sp. RKY2. Titers of 108.9 g·L^{-1} and 42 g·L^{-1} at productivities of 13.1 g·L^{-1}·h^{-1} and 6.7 g·L^{-1}·h^{-1}, respectively, were achieved in these studies; only the latter reported the L-(+)-LA optical purity (70%) [49,50].

Concerning LAB, several studies focused on the co-production of other metabolites alongside LA. For instance, *Streptococcus* species coproduced hyaluronic acid or biogas; however, in both cases, downstream aspects of the process were not considered [51,52]. More typically, processes aim to produce LA while concurrently trying to achieve high biomass concentration, which can be used as a high-quality feed or probiotic food supplement [53–57].

2.1.2. Bacteriocins

Bacteriocins are small, ribosomally synthesized peptides with antimicrobial properties. Normally produced by LAB, these compounds are active against other Gram-positive bacteria or closely related microorganisms. Given their antimicrobial properties, some bacteriocins such as nisin and pediocin are used as preservatives in food products in order to inhibit the growth of spoilage and pathogenic microorganisms. Additionally, bacteriocins are believed to contribute to the competitiveness of the producer cells, which is an important feature for some LAB used as starter cultures in fermented foods [58]. The general antimicrobial mechanism of bacteriocins is based on the disruption of the cell membrane via either pore formation or a "detergent effect", as in the case of nisin [59].

Bacteriocins are typically low-weight, cationic, and hydrophobic molecules composed of 20 to 60 amino-acid residues. They are normally synthesized along with a leader sequence that is cleaved during maturation and then released from the cell [59]. Based on their general structure and properties, bacteriocins can be classified into three different categories:

- Class I (lantibiotics): peptides containing lanthionine (a non-canonical amino acid). These can be elongated with a net positive charge (sub-class A, e.g., nisin), or globular with negative or no charge (sub-class B, e.g., mersacidin).
- Class II: heat-stable peptides, not containing lanthionine. Their sub-classes depend manly on the activity (sub-class A, e.g., pediocin; sub-class B, e.g., lactococcin, plantaricin; sub-class C, e.g., acidocin).
- Class III: large, heat-labile peptides, not very well characterized. They are lytic proteins often classified as murein-hydrolases (e.g., helveticin).

Despite the variety of antimicrobial peptides produced by LAB, only nisin and pediocin are commercially available, mainly used as food additives, especially in dairy products [58]. Nevertheless, due to the increase in antibiotic-resistant strains and the growing demand for minimally processed foods and clean labels, the research and development of novel antimicrobial peptides is one of the main interests within the LAB biotechnological sector. Even though new bacteriocins or bacteriocin-like peptides from LAB are discovered every year, challenges for further commercial application of these compounds still hinder their utilization. Before considering the industrial production of bacteriocins, studies to develop optimized processes for bacteriocin synthesis and the subsequent purification of the compounds are still necessary.

Regarding bacteriocin production, most studies combined bacterial growth and antimicrobial production. So far, the most relevant factors reported are related to the fermentation conditions, e.g., media composition, acidity levels, and incubation temperature. Some studies additionally reported microbial modeling and optimization processes to define the best conditions for bacteriocin synthesis (Table 1).

Table 1. Culture conditions necessary to attain high bacteriocin titers from *Lactobacillus* according to scientific literature [a].

Microorganism	Optimized Bacteriocin Level (AU·mL^{-1} × 10^3)	Media	Relevant Media Component [b]	pH [c]	T (°C)	Other Considerations [d]	Reference
L. lactis subsp. *lactis*	131	M17 broth	Lactose (3.0%)	6.0	30	Early stationary phase	[60]
L. amylovorus	25.6	Sourdough simulation medium	NaCl (10 g·L^{-1})	5.4	37	NR	[61]
L. amylovorus	25.6	Modified MRS	Glucose (11 g·L^{-1}), nitrogen mixture (25 g·L^{-1})	5.0	37	Continuous fed-batch fermentation	[62]
L. lactis sbsp. lactis	15.4	Optimized medium	Various ingredients	5.5	30	Max activity after 7 h	[63]
L. acidophilus	12.8	MRS broth	Glucose (20 g·L^{-1})	6.5	37	100 rpm	[64]
L. plantarum	12.8	MRS broth	Tryptone (10 g·L^{-1}), meat extract (5 g·L^{-1}), yeast extract (5 g·L^{-1}), maltose (20 g·L^{-1}), mannose (20 g·L^{-1})	5.5–6.5	30	Max activity after 14 h	[64,65]
L. pentosus	6.4	MRS	Tryptone (12.5 g·L^{-1}), meat extract (7.5 g·L^{-1}), maltose (20 g·L^{-1}), glucose (10–20 g·L^{-1}), no glycerol	n.r.	30	NR	[66]
L. sakei sbsp. sakei	10.9	MRS broth	Glucose (5.5 g·L^{-1}) and Tween-80 (10.5 μL·mL^{-1})	6.0	30	Media supplemented with Tween-20, sodium citrate, KCl, and cysteine	[67]
Ln. mesenteroides	10.2	MRS	Glucose (4.5%), peptone (8%), yeast extract (1.5%)	5.5	25	NR	[67]
L. plantarum	9.0	MRS	KH$_2$PO$_4$ (2, 5, and 10 g·L^{-1})	n.r.	30		[64,65]
L. brevis	6.4	MRS	Yeast extract (2–3%), NaCl (1–2%), glucose (1%), Tween-80 (0.5%)	n.c.	30	Final pH between 3.86 and 4.04	[68]
L. amylovorus	6.4	MRS	Glucose (20 g·L^{-1})	n.r.	37	NR	[69]
L. plantarum	6.4	MRS	Meat extract (1.5%), yeast extract (1%), biotin (0.01 mg·L^{-1})	6.5	30	NR	[70]
L. plantarum	6.4	MRS	Meat and yeast extract (20 g·L^{-1}), maltose (3.0%), no glycerol	6.5	30	NR	[64,65]
L. acidophilus	6.4	MRS	Glucose (20 g·L^{-1})	6.0	37	100 rpm	[71]
L. amylovorus	5.5	Sourdough simulation medium	Yeast extract (12 g·L^{-1}), tryptone (10 g·L^{-1})	5.4	37	NR	[72]
L. lactis	2.1	Cultural medium	Soybean peptone (4.49 g·L^{-1}), KH$_2$PO$_4$ (28.42 g·L^{-1})	6.8	30	Shaking at 180 rpm	[73]

[a] Bacteriocin activity values reported after testing the conditions individually or in combination (according to the reference). [b] Ingredients added to the basic formulation of each culture media. [c] pH levels at the beginning of the process. In some cases, acidity levels increased by the end of fermentation. [d] NR: no other relevant factors were reported.

Moreover, bacteriocins are a group of molecules that are normally secreted into the medium. Due to the complexity of the chemical structures, their purification is often based on the affinity to organic solvents. For the isolation of each specific bacteriocin, parameters such as solubility and stability at a given salt concentration and pH should be taken into consideration. An organic extraction can be efficiently incorporated into the LA downstream process due to the poor solubility of LA in organic solvents.

2.2. Use of LAB-Biomass

After the production of extracellular metabolites, the whole cell can be used as a product (probiotics), with an easy application since no extraction is required. Contrary to biomass, intracellular metabolites require extraction and purification methods to disrupt the mechanical barrier and to obtain the compound of interest. This is usually achieved using extracting solvents and separation techniques, which result in the extraction of both small and large molecules into the extraction solution [74].

2.2.1. Probiotics

Some LAB were characterized for their probiotic potential. This term refers to "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [75]. An increased interest in the use of these microorganisms, to treat specific diseases or their associated symptoms, prompted the execution of numerous comprehensive studies. Probiotics are generally added to foods as supplements and provide benefits to consumers, such as the maintenance of a healthy intestinal microbiota, lower cholesterol levels, and regulation of the immune response [76,77]. They are mainly used to treat digestive disorders and gastrointestinal diseases, as well as skin, mouth, urinary tract, and respiratory diseases [77–82].

Most of the probiotic species commercially available belong to the *Lactobacillus, Enterococcus, Streptococcus,* and *Bifidobacterium* genera [78,83–86]. Other genera such as *Roseburia* spp., *Akkermansia* spp., *Propionibacterium* spp., and *Faecalibacterium* spp. show promising characteristics and are currently under evaluation [87]. It is worth noting that most of the information related to probiotic characterization is derived from in vitro cell culture studies or in vivo testing using models, and this information must be corroborated in order to use the results at an industrial scale [87,88]. In recent years, there was growing interest in the characterization of new LAB isolates from different sources to use them as probiotics or for other applications [89]. Yet, in parallel to isolation and characterization efforts, identification at a species level (and, in some cases, at a strain level) is necessary for commercial purposes.

The most common identification method is based on the sequence of the conserved region of the 16S rRNA gene; normally, this is used to define the phylogeny of the isolates [90,91]. When several strains are studied, other molecular tools can be used for differentiation and selection of the isolates, e.g., rep-PCR DNA fingerprinting, pulsed field gel electrophoresis (PFGE), denaturing gel gradient electrophoresis (DGGE), randomly amplified polymorphic DNA (RAPD), and, more recently, whole-genome sequencing.

Probiotic evaluation is based on the ability of the strain to survive the gastrointestinal tract conditions, such as low pH and lysozyme resistance [92,93]. Other characteristics such as bile resistance, antibiotic susceptibility, and the ability to adhere to the intestinal mucosa, human epithelial cells, or different cell lines are also used to analyze new probiotic isolates [93–95].

Under normal conditions, probiotics produce metabolites with antimicrobial activity such as exopolysaccharides, biosurfactants, bacteriocins, and organic acids. Moreover, theses microorganisms use an agglomeration mechanism that facilitates the excretion of pathogens from the digestive system. Antagonism is also associated with the production of lactic and acetic acids during carbohydrate metabolism, which favors a lower pH of the medium and inhibits the growth of some pathogenic microorganisms [96–98]. Therefore, antagonism toward pathogenic bacteria is also a desirable characteristic in order to be considered as a probiotic.

Regarding the immunological response, probiotics may improve it, stimulating host cell antibody secretion. Increased immune response can be evaluated through the co-culture of probiotics with immune system cells, which allows the detection and quantification of cytokines; these compounds are indicative of an inflammatory process [99,100]. Through in vivo studies, promising results concerning diseases associated with the immune system were reported, e.g., inflammatory bowel diseases [101] and symptoms caused by allergies [102].

There is an increased interest in understanding how probiotics interact with the host. Currently, many studies are focused on the modulation of the immune response, production of organic acids and antimicrobial compounds, interaction with host resident microbiota, improvement of the integrity of the intestinal barrier, and production of secondary metabolites beneficial to the host [87]. However, it is important to evaluate potential probiotic microorganisms to confirm their benefits to human health and to demonstrate their correct use.

2.2.2. Lipoteichoic Acid (LTA)

Microbial plasma membranes are surrounded by a wall which allows the classification of bacteria as Gram-positive and Gram-negative. The cell wall of Gram-positive bacteria and the outer membrane of Gram-negative bacteria contain anionic lipid molecules such as LTA and lipopolysaccharide (LPS), respectively [103,104]. LTA molecules are composed of a glycolipid and hydrophilic polymer of glycerophosphate covalently linked [104–106]. LTA was firstly isolated from *L. arabinosus* in the 1960s. Since then, different studies reported LTA structural and functional variations according to the genera and species of bacteria [107,108]. At the cellular level, LTA function is associated with the regulation of cell-wall autolytic enzymes during cell division, which is important for cell growth and proliferation [109]. At an industrial level, LTA shows a variety of potential applications including the enrichment of food matrices and the development of new pharmaceutical products.

Several studies showed that LTA possesses anti-biofilm properties with the potential to treat or prevent oral infectious diseases. Moreover, LTA also showed anti-inflammatory activity for the treatment of colitis and immunomodulation properties [22–24]. Weill et al. [110] performed in vivo assays in mice and proved that oral administration of pure LTA from probiotic *L. rhamnosus* GG (ATCC 53103) can modulate the immune-suppressive effect of ultraviolet radiation and skin tumor development. Nevertheless, Brauweiler et al. reported that LTA from *Staphylococcus aureus* promotes keratinocyte proliferation and inhibits the expression of skin barrier proteins [111]. The wide variety of biological effects shown by LTA from different bacteria highlights the need for a better understanding of the mechanisms implicated on its biological response and the chemical composition of the LTA extracted from different sources.

The first reports regarding the recovery of LTA were published in 1975. The extractions were performed using organic solvents at high temperatures [112]. Years later, Morath et al. [113] reported a modification based on the substitution of chromatography technique for extraction with organic solvents in order to increase that yield of purification. However, those two downstream techniques are not environmentally friendly; therefore, alternative technologies, such as membrane separation, should be evaluated for purifying LTA. This is one of the main opportunities within the research and development of novel recovery processes for this compound.

2.3. Other Compounds with Industrial Potential Produced by LAB

As mentioned before, LAB is one of the most extended groups of prokaryotes used within the industry mainly due to the biotechnological production of LA and its use as a probiotic. LAB is a group with great potential for the production of fine chemicals due to its capacity to synthesize a large number of bioactive molecules, from which many biological activities were reported [112]. Furthermore, current advances in synthetic biology tools facilitated the development of novel strains able to produce a vast range of molecules such as flavors, antimicrobials, pharmaceuticals, texturizing compounds, vitamins, sweeteners, and nutraceuticals, among others (Table 2) [114]. From an industrial

point of view, *Streptococcaceae* and *Lactobacillaceae* represent the most important taxa since they include the highest number of commercialized LAB [115].

Except for the industrial production of probiotics, cell biomass is normally treated as a by-product in most biotechnological processes. Even in the case where cells are used as catalysts, these are eventually discarded. However, LAB cells contain different compounds with commercial value, such as LTA or conjugated linoleic acid (CLA). CLA possesses great potential as a pharmaceutical product, and it can be produced by LAB via linoleic acid isomerization or from castor oil via ricinoleic acid dehydration. Currently, CLA is produced through the chemical isomerization of linoleic acid, which results in the production of undesired isomers. LAB produces the CLA isomers (*cis*-9, *trans*-11; *trans*-9, *trans*-11; *trans*-9, *cis*-11) at different ratios, but strains that produce specific isomers were already identified [116,117]. Up to 70% of CLA is accumulated intracellularly or associated with cells; this means that LTA and CLA would be separated in the early stages of the downstream process where cells are discarded, while the supernatant follows the pipeline of purification.

In the case of LA recovery and purification after cell separation, the supernatant is normally filtrated to eliminate cell debris and macromolecules. After this step, organic acids such as azelaic acid (AA) and caproic acid (CA) can be separated from the flow through an organic extraction. AA is a C7 saturated dicarboxylic acid with antibacterial properties; meanwhile, CA is a C6 medium-chain triglyceride used within the food, drug, and cosmetic industry. In both cases, there are reports of liquid–liquid extraction methods with organic solvents used to recover these compounds [118,119].

Table 2. Secondary metabolites produced by LAB compatible with a multi-product bioprocess.

Metabolite	Titer	Microorganism	Location within The Fermentation	Biological Activity	Downstream	Reference
2,3 butanediol	32 g/L	*Lactococcus lactis*	Supernatant	Bulk chemical in plastic industry	Distillation, stream stripping, pervaporation	[120]
2-pyrrolidone-5-carboxylic acid (Pyroglutamic acid)	-	*Lactobacillus* spp. *Pediococcus* spp.	Supernatant	Antimicrobial	Ethanol precipitation, gel filtration, and anion exchange	[121]
Azelaic acid	2.71 mg/L	*Leuconostoc citreum* L123	Supernatant	Antifungal	Organic extraction	[122]
Bacteriocins	0.72 g/L	*Staphylococcus gallinarum* and *S. epidermidis*	Supernatant	Antimicrobial	Salting-out, solvent extraction, ultrafiltration, adsorption–desorption, ion exchange, and size exclusion chromatography	[123,124]
Caproic acid	102 mg/L	*Lactobacillus sanfrancisco* CB1	Supernatant	Antimicrobial, Flavor, and fuel precursor	Organic extraction	[125]
Conjugated linoleic acid	40 g/L	*Bifidobacterium* spp., *Propionibacterium freudenreichii*, *Lactobacillus plantarum* AKU 1009a	Intracellular or cell-associated	Reduces carcinogenesis, atherosclerosis, and body fat	Intracellular (or associated with cells) and extracellular; urea treatment after organic extraction	[116,117]
Cyclic dipeptides	-	*Lactobacillus* spp., *Leuconostoc* spp., *Weissella* spp., and *Lactococcus lactis*	Supernatant	Antiviral, antifungal	Selective precipitation (ethanol, trichloroacetic acid, or ammonium sulfate); ultra and nano-filtration; chromatographic methods.	[126–128]
Diacetyl and acetoin	DC 3.5 mg/L AMC 2.6 g/L	*Leuconostoc sp.*, *Streptococcus diacerylactis*	Supernatant	Flavor and fragrance	Distillation at 86–87 °C and reactive distillation	[129,130]
Exopoly-saccharides	5.12 g/L	*Lactobacillus acidophilus*	Supernatant	Antioxidant, antibacterial, antiulcer, antitumor, immunostimulatory	Ethanol precipitation	[131]
Lipoteichoic acid	-	*Staphylococcus aureus* *Lactobacillus rhamnosus* GG	Cell-associated	Immunomodulator	Organic extraction, hydrophobic interaction, chromatography	[110,111]
Mevalonic acid Mevalonolactone	-	*Lactobacillus plantarum* VTT E-78076	Supernatant	Antifungal	Ultra and nano-filtration	[132]
Phenyl lactic and *p*-hydroxyphenyl acetic acid	-	*Lactobacillus plantarum* strain 21B	Supernatant	Antifungal	Ultra and nano-filtration	[133]
Reuterin (3-hydroxypropionaldehyde)	8 mg/L	*Lactobacillus reuteri*	Supernatant	Antimicrobial	Alcoholic extraction, organic extraction, size filtration, and ion exchange; distillation	[133,134]
Sweeteners (mannitol, tagatose, sorbitol, trehalose)	-		Supernatant	Food industry	Ultra and nano-filtration, chromatographic methods	[135]
Vitamins (B-group)	-		Supernatant	Food supplement	Ultra and nano-filtration, chromatographic methods	[136,137]

During fermentation, exopolysaccharides (EPS) are liberated. These compounds are branched polymers of sugars (or derivatives) with commercial value due to their properties as food texturizers and their health-promoting attributes [80,81,138]. EPS precipitate via the addition of ethanol, but the use of this solvent is not compatible with the LA downstream process since concentration of this solvent may increase total operational volumes. Nevertheless, during filtration and ultrafiltration steps, LA remains in the permeate and EPS are retained in a solution with a lower volume. At this point, EPS purification via ethanol precipitation would be possible [139]. Depending on their properties, some cyclic dipeptides could be purified following the same approach [128], as well as 2-pyrrolidone-5-carboxylic acid (used as a humectant for dry skin and hair products) [121]. Other polar molecules such as sugars, small organic acids, and vitamins follow the same purification path as LA, and chromatographic methods would be necessary to separate them [132,135,136].

The final step in a LA downstream process is distillation, which is basically used to eliminate water from the final LA solution. Volatile compounds produced by LAB, e.g., reuterin and diacetyl (DC), can be recovered via distillation at 78–82 and 86–87 °C, respectively. Reuterin is a potent antimicrobial, and DC is used as a food and beverage supplement due to its characteristic butter flavor. Acetoin, the precursor of DC, can be recovered as well after an enzymatic transformation into DC. In this sense, the addition of a reactive distillation step would be useful in order to recover both compounds and to eliminate acetoin from the supernatant.

As mentioned before, there are several options in which an LA production/purification process can be combined with the recovery of other high-value compounds that are normally discarded within the downstream process. Key points or challenges remain in the combination of the fermentation and downstream process in such a way that production of all the compounds is sustainable.

3. Perspectives of Multi-Product Processes

Many research efforts focused on the development of green processes orientated toward the production of organic chemicals via biorefinery or white biotechnology by using carbohydrate sources such as corn syrup [1,140–142]. However, alternative energy sources, e.g., agro-industrial by-products and other solid food waste, were extensively evaluated for the production of these compounds, which are normally used in the automobile, textile, pharmaceutical, beverage and food, plastic, and many more industries [1,140–144]. Such processes are possible because agro-industrial by-products not only serve as a carbohydrate source but also provide extra nutrients, i.e., amino acids, vitamins, and minerals. One of the most important reasons for using by-products is that these materials do not compete for arable land with grain crops cultivated for human feed [145]. As mentioned before, some metabolites obtained from green processes are lactic, succinic, and 2,3-butanediollactic acids, fructo-oligosaccharides, bioethanol, biodiesel, bioactive peptides, enzymes, volatile compounds, and many more [1,140,141]. In parallel, current rigorous regulations regarding the application of by-products together with the demand for renewable compounds and fuels are forcing the manufacturing industry toward more cost-effective processes while meeting customer demand [142].

Regardless of the microorganism used, white biotechnological processes are traditionally developed and optimized based on a specific-metabolite pathway involving selected starter cultures or microbial consortia [140]. Although this approach proved to be very successful in the production of specific metabolites such as ʟ-(+)-LA, researchers constantly search for bacterial mechanisms focused on the use of potential by-products to simultaneously produce more than one bio-product, while enhancing the effectiveness of the process [146]. An example of a multi-product process was recently reported by Nguyen et al. [146]; they proposed an integrated process for economical high-yield production of ᴅ-mannose and bioethanol from a coffee residue. This process involves pretreatment, enzymatic hydrolysis, fermentation, recuperation, and purification steps which can be performed using environmentally friendly technologies [146].

From a technological point of view, efforts focused on the production of metabolites may employ the so-called "reverse food engineering" strategy, comprising at least five main steps: (i) isolation of LAB

species, (ii) DNA screening of LAB for the ability to release the metabolites of interest, (iii) exploitation of the best metabolite´s producer strain for innovation in multi-product processes, (iv) development of extraction, separation, and purification process of each metabolite, and (v) an industry interested in the implementation of the process once the economic feasibility is proven [140]. Furthermore, the best conditions to produce one metabolite may not be necessarily the best environment for the synthesis of another metabolite; therefore, the overall effectiveness of the process may be compromised. When all these steps are clear, it is necessary to construct a cell factory for an efficient refining platform to produce a variety of natural products from bacteria. Therefore, many studies must be done to define the conditions allowing a balanced multi-product process.

In the case of LA, a potential valorization of the process could be achieved via the utilization of different streams obtained during the downstream process (Figure 3).
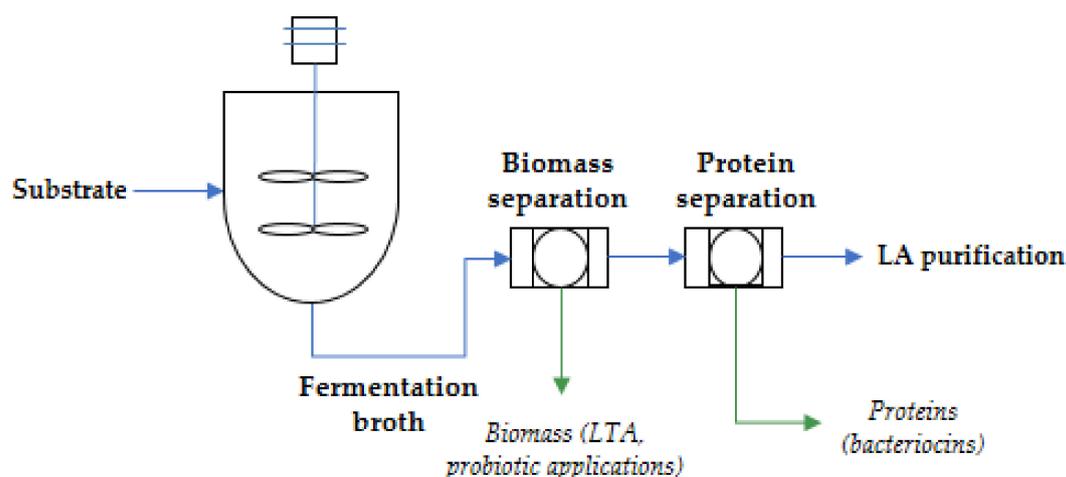

Figure 3. Potential process flow diagram for of a multi-product LAB based process (adapted from Reference [147] licensed under CC BY-NC 4.0 available at https://doi.org/10.1016/j.jclepro.2019.119165).

4. Conclusions

Recently, circular bioeconomy emerged, and it is expected to continually evolve, driven by sustainability challenges, e.g., expanding population, resource depletion, and climate change [148]. Its concurrence with technological processes, in addition to economic and environmental assessments, strongly motivates the industry to consider bio-based chemical production as an attractive area for investment. In concordance with this, biorefineries should integrate processes to facilitate the complete fractionation and the valorization of all biomass components [148,149]. The creation of multi-product integrated processes is a key aspect to favor the research, development, and industrial implementation.

Lactic acid bacteria are proposed as some of the most promising microorganisms for the transformation of biomass into valuable industrial products. LA is a very versatile biotechnological molecule which plays an important role as an intermediate metabolite to produce many products of interest [150]. In addition to LA, several products with interesting characteristics can be obtained from LAB fermentation such as bacteriocins, probiotics, and LTA. However, the titers for these secondary products are not yet optimized. Nevertheless, they hold potential and market significance, which could enhance the value of traditional LA fermentation. Further investigation toward a successful co-production of LA and other metabolites of interest could in fact pave the way for the establishment of sustainable and more efficient multi-product bioprocesses.

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