Review

Lactic Acid for Green Chemical Industry: Recent Advances in and Future Prospects for Production Technology, Recovery, and Applications

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Abstract: Lactic acid, an organic acid produced by numerous microorganisms, has many applications in the food, chemical, pharmaceutical, and polymer industries, with novel applications being developed particularly in the chemical industry. The lactic acid market has steadily grown with the introduction of novel and environmentally friendly products. Therefore, developing novel technologies for lactic acid production, with improved yield and reduced production costs, has become a major research goal. Utilization of inexpensive and renewable biomass is a major strategy for economically producing lactic acid. However, most lactic acid bacteria cannot directly utilize lignocellulosic biomass and require hydrolysis, which is costly. Immobilization techniques for large-scale production can enhance fermentation yield. Moreover, novel techniques, such as cell recycling systems and simultaneous saccharification, will enable microorganisms to produce lactic acid with increased concentration, yield, and productivity. Recently, genetic and metabolic engineering methods have been used for key solving problems, such as product inhibition, by-product formation, and suboptimal culture conditions, and for the effective use of cheap substrates. This review presents comprehensive insights into the most recent advances in the biological production of lactic acid from different substrates, bioprocess techniques for yield improvement, lactic acid purification, and applications of lactic acid for human welfare.

Keywords: biorefinery; lactic acid; fermentation; lignocellulose; engineered microorganisms; recovery; applications

1. Introduction

The escalating global energy demand due to constant population growth and urbanization has led to worsening environmental problems. Depletion of crude oil reserves creates a shortage in supply and increases the price for petroleum-based chemicals. These circumstances have necessitated the search for alternative and novel techniques for producing fuels and chemical products using environmentally safe and green technologies. Commercially valuable products produced from renewable resources using microbial biotechnology are attractive alternatives to conventional products in terms of environmental safety, sustainability, and circular economy [1].

Lactic acid (LA) was discovered in acid milk in 1780 by Scheele. It can be produced commercially via both chemical synthesis and biological production processes. Chemical synthesis yields a racemic mixture of D/L-LA, whereas biological production can provide optically pure D- or L-LA depending on the selection of appropriate microorganisms. LA can be biologically produced by several groups of microbes, including bacteria, yeasts,

and algae. Furthermore, fermentative LA production offers benefits such as renewable substrate utilization, environmentally safe conditions, and lower energy demand [2].

The global LA market was valued at USD 3.2 billion in 2021 and is predicted to reach USD 6.9 billion by 2030 with 8.91% growth annually [3]. The demand for LA is expected to surge in the near future because of the increasing demand for fermented foods such as yogurt, canned vegetables, and butter in India, China, the USA, and Germany and the applications of LA in the cosmetics and personal care industry owing to its antimicrobial and moisturizing properties. In addition, production processes are trying to utilize LA in the development of bioplastics and biochemicals from sustainable feedstock. The price of products generated through fermentation technology mainly depends on the price of raw materials, such as carbon and nitrogen sources. Recently, the enhanced price of corn and tapioca have directly impacted the price of LA. Consequently, industries are switching their focus towards alternative and more economic resources and substrates for the effective production of LA from starchy, lignocellulosic, and green microalgae [4–6]. The challenges in using renewable resources, such as residues from other industries and agricultural crops, are purification, uneven biomass composition, and seasonal availability. These properties cause uncertainties with regard to process upscaling and the feasibility of using waste-derived LA for polymer synthesis. For ideal industrialization, plastic production using poly(lactic acid) (PLA) requires a specific ratio of pure L- or D-lactides to produce useful fibers and films [2]. Another advantage of pure LA and its salt forms (calcium, sodium, and potassium) is that they have been approved as a Generally Recognized as Safe (GRAS) food additive by the US Food and Drug Administration (FDA) [7]. The overall aim of this review is to emphasize recent advances in the biological production, purification, applications, and future prospects of LA.

2. Lactic Acid Production Technologies

2.1. Chemical Synthesis

LA can be synthesized via the lactonitrile route, and it is a by-product of acrylonitrile technology; this process was discovered by Wislicenus in 1863 [8]. In brief, lactonitrile was first produced by the addition of hydrogen cyanide to liquid acetaldehyde in the presence of a basic catalyst under high pressure. Methyl lactate was subsequently produced by hydrolysis with sulfuric acid and esterification with methanol. Finally, the purified LA was recovered by separating methanol through distillation. Certain companies, such as Monsanto (St. Louis, MO, USA), Sterling Chemicals (Houston, TX, USA), and Musahino Chemicals (Tokyo, Japan), have produced good amounts of LA from chemical processes [9].

In competition with the biological production process, a chemocatalytic process has recently been developed for producing LA from lignocellulosic biomass. This process offers prospects for improving the process capability by optimizing the catalysts and the operating conditions. Moreover, chemocatalysis can be used for directly converting biomass (except monosaccharides or oligosaccharides) into the required chemicals in a one-pot process using multifunctional catalytic systems. In recent years, considerable attention has been focused on developing chemocatalytic methods for the production of building-block chemicals directly from biomass [10–13]. The chemical process for LA synthesis is expensive, and it depends on fossil fuel-derived by-products from other industries [14]. Hence, the dependence on expensive raw materials and product impurities using biological synthesis needs to be bypassed.

2.2. Biological Synthesis

Biological synthesis of LA is usually a two-step process, where the first step is LA fermentation and the second step is product recovery and/or purification. Presently, approximately 90% of LA is produced through the fermentation process. LA fermentation requires the use of suitable microorganisms, substrates, and purification techniques. Several researchers have been working on the development of economically viable processes for the biological production of LA.

2.2.1. Lactic Acid-Producing Microorganisms

Bacteria and fungi are the most widely used groups for LA production [15]. Lactic acid bacteria (LAB) are predominant among the bacterial families and named on the basis of their ability to produce LA as the major and sole product of sugar fermentation. Among the fungal families, *Rhizopus* species such as *R. oryzae* and *R. arrhizus* have been exploited for direct aerobic fermentation of starchy substrates into LA. Other bacteria that naturally produce similar yields of LA include *Escherichia coli*, *Corynebacterium glutamicum*, and *Bacillus* strains. The microorganisms used for LA production are listed in Table 1. The selection of microorganisms mainly depends on the type of substrate used in fermentation, as the substrate influences the metabolism of microorganisms [16].

Table 1. Lactic acid-producing microorganisms along with their substrates.

Microorganism	Substrate	Reference
Lactobacillus delbrueckii sp. *bulgaricus*	Corn stover	[17]
Lactobacillus delbrueckii	Orange waste enzymatic hydrolysates	[18]
Lactobacillus delbrueckii	Orange peel wastes hydrolysates	[19,20]
Lactobacillus bulgaricus CGMCC 1.6970	Cheese whey powder	[21]
Lactobacillus casei Shirota	Mixed food waste, bakery waste	[22]
Lactobacillus casei	Sugarcane bagasse	[23]
Lactobacillus rhamnosus B103	Dairy industry waste	[24]
Lactobacillus rhamnosus ATCC 7469	Recycled paper sludge	[25]
Lactobacillus rhamnosus	Solid carob waste	[26]
Lactobacillus rhamnosus PCM 489	Cheese industry—whey	[27]
Lactobacillus plantarum	Brown rice	[28]
Lactobacillus plantarum	Hydrolysate of microalga *Chlorella vulgaris*	[29]
Lactobacillus paracasei	Molasses-enriched potato stillage	[30]
Lactobacillus pentosus CECT4023T	Gardening lignocellulosic residues	[31]
Saccharomyces cerevisiae	Food waste biomass	[32]
Rhizopus microsporus	Liquefied cassava starch	[33]
Rhizopus oryzae	Animal feeds from *Sophora flavescens* residues	[34]

Although fungi and bacteria produce LA, *Lactobacillus* spp. are highly preferable for industrial purposes. LAB are usually Gram-positive, non-spore forming, facultative anaerobic microorganisms that produce LA as a primary fermentation metabolite. They belong to the order Lactobacillales, which contains six families with 38 genera, including *Lactobacillus*, *Pediococcus*, *Enterococcus*, *Leuconostoc*, *Streptococcus*, and *Lactococcus*. LAB have a genome size of only 2–3 Mbp. They are highly tolerant to acidic conditions, can survive in a high temperature range, and can easily modify the selective production of LA isomers [35]. Moreover, these microorganisms are considered GRAS; no reports of adverse effects have been reported among workers or consumers [2]. They are known to produce high titers and 100% optically pure LA (up to 215 g/L). LAB have the ability of hydrolysis of starch and protein and produce aromatic products. Requirements of complex nutrients and mesophilic nature are the only challenges in using LAB and *Lactobacillus* spp. for LA fermentation. Apart from this, only a few species are known to produce cellulases and utilize lignocelluloses directly for LA production. These challenges can be overcome through genetic engineering because LAB are genetically very amicable organisms [36]. Compared to the LAB, selection of *Bacillus* strains has some advantages, such as utilization of inexpensive nutrients for their growth and LA production, significant production of LA at high pH (6–6.5), and ability to produce LA in thermophilic conditions (50–55 °C). They have the ability of complete utilization of lignocellulose hydrolysates with their pentose phosphate pathway and glycolysis, and most of them are known to produce only L-LA with high yield and productivity [35].

Sufficient reports have been published on LA production by filamentous fungi such as *Rhizopus*, which utilizes glucose aerobically to produce LA. The commercial process requires agitation and aeration [37]. *Rhizopus* species, such as *R. oryzae* and *R. arrhizus*, have

been studied extensively and recognized as potential candidates for LA production. LA fermentation by fungi has some advantages: (i) it can produce LA using both surface and submerged cultures, and the fungal biomass can be easily separated from the fermentation broth; (ii) it can produce LA directly from starch because of its amylolytic activity; (iii) it selectively produces L(+)-LA isomers; and (iv) owing to simple and cheap downstream processes, fungal biomass harvested from LA fermentation can be used in the purification of contaminated effluents, for fungal chitosan production, and as animal feed supplements. Despite these advantages, LA production from *Rhizopus* strains faces some challenges. They require vigorous aeration; the process exhibits low maximum yields (80 g/L) with a production rate below 3 g/L·h because of the low reaction rate caused by mass transfer limitations [37,38]. They cannot grow quickly and sometimes inhibit growth at the low pH of 4.5. The formation of by-products, such as fumaric acid and ethanol, is another reason for the low yield of LA [39]. *Rhizopus* strains, along with the substrate utilized for lactic acid, are listed in Table 1.

2.2.2. Biochemistry of Lactic Acid Production

LAB belong to one of the largest and most highly diverse genera, and they are classified into two groups according to their product formation pathways: homofermentative and heterofermentative. Homofermentative LAB exclusively convert glucose to LA as the sole product. Theoretically, in homolactic fermentation, two moles of LA are produced from each mole glucose consumed. Homofermentative LAB usually metabolize glucose via the Embden–Meyerhof pathway (glycolysis) (Figure 1). Examples of homofermentative bacteria are *L. acidophilus*, *L. amylophilus*, *L. bulgaricus*, *L. helveticus*, and *L. salivarius* [40,41]. In contrast, heterofermentative LAB catabolize glucose into ethanol, CO_2, and/or acetic acid along with LA. The theoretical yield of LA is only 0.50 g/g substrate consumed. Examples of heterofermentative LAB are *L. brevis*, *L. fermentum*, *L. parabuchneri*, and *L. reuteri* [40,41]. Only homofermentative LAB are preferred for the industrial production of LA [42].
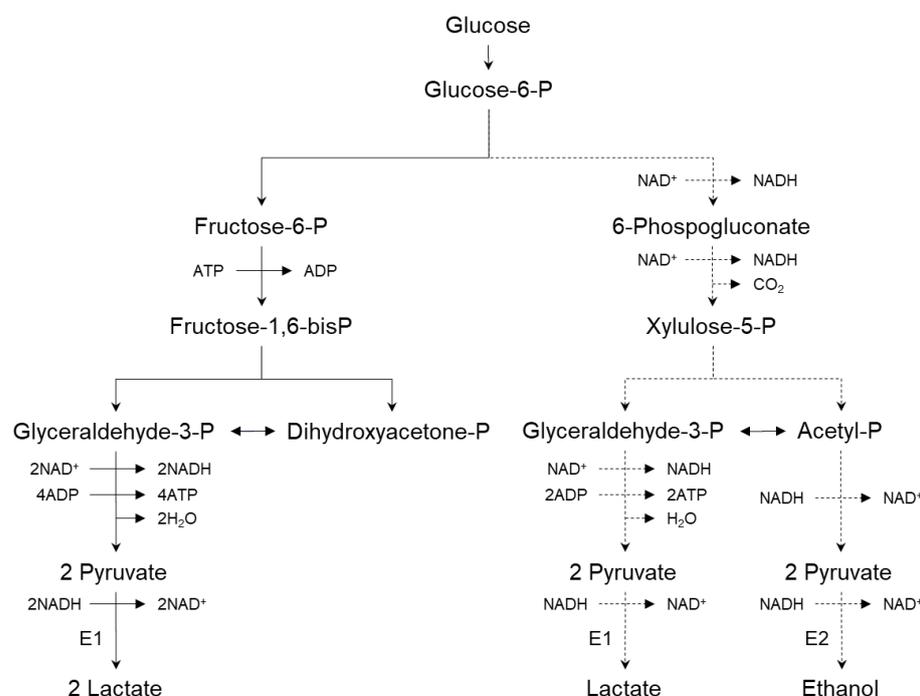

Figure 1. Metabolic pathways of homofermentative (solid line) and heterofermentative (dotted line) lactic acid bacteria. P, phosphate; ADP, adenosine 5′-diphosphate; ATP, adenosine 5′-triphosphate; NAD^+, nicotinamide adenine dinucleotide (oxidized form); NADH, nicotinamide adenine dinucleotide (reduced form); E1, lactate dehydrogenase; E2, alcohol dehydrogenase.

Other organisms such as *L. alimentarius*, *L. rhamnosus*, *L. pentosus*, and *L. xylosus* can produce LA not only from glucose but also from other hexoses and pentoses [43–45]. The production cost of LA can be decreased by utilizing inexpensive and abundantly available renewable materials, such as lignocellulose, as substrates in the production of LA [46].

L. xylosus and *L. rhamnosus* have been used for xylose and glucose mixture fermentation and production of acidic hemicellulosic hydrolysates of wood, respectively [45,47]. Ou et al. [48] reported that the highest levels of LA were obtained from xylose and glucose fermentation by *Bacillus coagulans*. Wang et al. [49] utilized *R. oryzae* to produce LA (83 g/L) from a mixture of glucose and xylose. In addition to the mixed substrates, a mixed culture of LAB was investigated for the efficient and simultaneous fermentation of hexoses. This strategy can be used for producing LA from lignocellulose-derived sugars [50]. Another important metabolic characteristic of LAB is the production of stereospecific lactic acid (D or L) through chemical synthesis, unlike racemic mixtures. The presence of lactate dehydrogenase, which possesses stereospecific NAD^+-dependent enzymatic activity, determines the stereospecificity of LA [51]. In these two groups, *L. amylophilus*, *L. casei*, *L. brevis*, *L. buchneri*, *L. delbrueckii*, *L. rhamnosus*, *L. lactis*, and *Streptococcus* sp. are L(+)-LA producers, whereas *L. coryniformis* produces D(-)-LA, and *L. helveticus*, *L. plantarum*, and *L. pentosus* are mixed producers [52,53]. Production of only the L(+)-LA isomer is desired because D(-)-LA cannot be metabolized by humans, and excessive intake may result in acidosis. Medical applications require L(+)-LA, and L(+)-LA isomers are the best choice for PLA synthesis [46,54].

2.2.3. Factors Affecting Lactic Acid Production

LAB are fastidious organisms that require a complex medium for growth. Many factors, such as carbon and nitrogen sources, minerals, vitamins, pH, temperature, inoculum, agitation, and incubation period, affect LA fermentation.

Carbon source is the main factor that affects LAB growth and LA production. It is present in the culture medium in the form of sugars and amino acids [50]. Pure glucose was the preferred carbon source for LA production. However, high initial concentrations inhibit growth and, in turn, decrease the product yield of certain species such as *L. delbrueckii* and *L. bulgaricus* [55,56]. *L. casei* has a good tolerance to carbon sources, and it can withstand up to 100 g/L sucrose [57]. Other carbon sources, such as xylose, inhibited growth and productivity at concentrations above 20 g/L for *L. brevis* and *L. pentosus*. However, lactose did not show any inhibition above 110 g/L [58]. Xylose inhibition appears to be stronger than that of glucose [59]. The fed-batch process is one of the most suitable methods for minimizing this inhibition because the substrate can be added to the fermentation medium periodically at low concentrations. The fed-batch process was proved to be superior with respect to the final LA concentration (210 g/L), yield (0.97 g/g), and productivity (2.2 g/L·h) when compared with the batch fermentation process [60,61].

Nitrogen, a building block of living organisms, is essential for both anabolic and catabolic processes. It is required for the synthesis of amino acids, purines, pyrimidines, co-factors, and other nitrogen-based substances [62]. It is present in the form of amino acids, peptides, and inorganic compounds that can be added to the culture medium, such as peptone, yeast extract, urea, or ammonium sulfate [63]. The ratio of nitrogen to carbon sources is a main factor affecting the conversion of sugar into LA. This situation may be overcome by adding complex nitrogen sources to the fermentation medium. Yeast extract was the preferred nitrogen source. Peptone and meat extracts have also been used in several studies [64]. However, this addition greatly increases the raw material costs. For this reason, considerable effort has been focused on finding alternative nitrogen sources that minimize costs without loss of product yield. Mineral elements (Mg, Mn, and Fe), which are present in the medium in the form of salts ($MgSO_4$, $MnSO_4$, and $FeSO_4$), and vitamins (mainly belonging to the B group) present in yeast extract are essential elements that function as co-factors in many enzymatic reactions [57]. The ratio between carbon and

nitrogen (C/N) is very important for LA production. The optimal C/N ratio is essential for high yielding of LA and the adequate ratio is from 3 to 7 [65–67].

A pH between 5.0 and 7.0 is favorable for LA fermentation. The pH of the medium decreased with LA production, which inhibited both growth and fermentation. To avoid this, the addition of basic compounds such as calcium carbonate at the beginning of batch fermentation can maintain the medium pH at approximately 6.0 by neutralizing the produced LA. Hetényi et al. [68] reported that among ammonium hydroxide, sodium hydroxide, dimethylamine, trimethylamine, and calcium carbonate, trimethylamine showed the best neutralizing capabilities and ammonium hydroxide stood second, considering suitability from the industrial perspective. The continuous inline release of ammonium hydroxide by the hydrolysis of urea was investigated to maintain the pH during fermentation [69]. Isolation or use of mutant strains that can tolerate acidic pH is the best possible method to overcome product inhibition. In addition, the selection of acid-tolerant strains would help reduce the addition of buffering agents, reduce the cost, and improve the recovery of free LA from the fermentation broth and pollution problems [70].

All microorganisms grow rapidly and produce a high amount of product at an optimum temperature, which mainly depends on the species and strain, as well as on the fermentation conditions. When the temperature of the medium is above or below the optimum temperature, the growth and yield are reduced, and the organisms may die [71,72]. Roy et al. [73] reported that for *L. helveticus*, the optimum temperature range for growth was 42–45 °C; they observed a high specific growth rate of 0.639 h^{-1} at a temperature of 42 °C. Simulated studies by Peleg [74] revealed that the bacterial growth rate increased by approximately 2-fold when the operating temperature was increased from 15 °C to 45 °C. Temperature affects the rate of biochemical reactions, activity of extracellular enzymes, generation time, and the metabolite formation rate of microorganisms. Qin et al. [75] studied the effect of temperature on the growth and LA production when *L. casei* G-03 was cultured in a 7 L bioreactor, and they found that the maximum specific growth rate (0.27 h^{-1}) and L-LA concentration (160.2 g/l) were obtained at 41 °C. Therefore, the fermentation temperature should be maintained as constant as possible because bacteria grow optimally within a narrow temperature range, and they are adversely affected by sudden temperature fluctuations. The effect of temperature was very strong in the presence of LA and acetic acid compared to that of temperature alone. Hence, at higher temperatures, microorganisms are damaged rapidly because of the higher production rate of pyruvate, which in turn is converted into LA; temperature and LA exhibit a synergistic effect.

The selection of the optimum inoculum size and age is vital for the quality of the final product. The effect of the inoculum size of *L. amylovorous* NRRL B-4542 was studied under submerged fermentation, and a linear increase in LA production was observed as inoculum size was increased from 1% to 5%; thereafter, a clear decline was noticed [76]. Appropriate inoculum size is an important factor for achieving better product yield and productivity. At a small inoculum size, the substrate is not completely utilized and remains as a residual compound, which extends the incubation time. In contrast, a large inoculum size will lead to competitive growth of the microorganisms over a limited substrate amount. Thus, the amount and age of inoculum are important factors in achieving high LA productivity.

Appropriate incubation time is also an important parameter in LA fermentation. Most LA fermentations using different *Lactobacillus* cultures were conducted for 48–72 h for efficient LA production [77–79]. The effect of incubation time on LA production by *L. amylovorous* NRRL B-4542 has been studied; the growth of biomass was increased up to 25 h and further showed LA production up to 30 h. Subsequently, no increase was observed in either growth or LA, and the growth remained almost the same up to 48 h. This may be due to exhaustion of the substrate in the fermentation medium and product inhibition. In contrast, Reddy et al. [46] reported a very short incubation time for LA production from fermentation using hydrol. They observed that *Enterococcus faecalis* RKY1 completely consumed 50 g/L hydrol within 5 h and produced 47 g/L LA with a very high productivity of 9.44 g/L·h. From the literature, it can be concluded that the incubation time varies from

one organism to another and mainly depends on the characteristics of LAB, carbon source, and environmental conditions. Bacterial growth and production of lactic acid are mainly dependent on the presence of nutrients and the produced product concentration. After the logarithmic phase, the nutrient limitation and high product concentration inhibit both the growth and further product formation [67].

2.2.4. Substrates for Lactic Acid Production

LA fermentation is affected by several parameters, one of the most significant being the cost of the raw materials. The sustainability of LA production from fermentation depends on the type of substrate. In many previous investigations, commercial technologies have utilized crop-based substrates such as sugarcane juice, beet juice, molasses, and corn starch for LA production. As the cost of raw materials can be as high as 40% of the LA cost, researchers have focused on identifying novel, economical, and renewable materials [46,80]. Among the many biomaterials evaluated, lignocellulosic materials are recognized as attractive. Agricultural waste from wheat or rice straw, corn stalks, soybean residues, sugarcane bagasse, industrial waste from pulp and paper industries, forestry residues, and municipal solid waste are sources of abundant available feedstock, and they do not compete with food crops [81]. The worldwide annual availability of lignocellulosic biomass has been estimated to be more than 1.0×10^{10} MT. Thus, production of value-added products from lignocellulose is proposed as a potential alternative to petroleum-based resources in terms of environmental preservation, sustainability, and circular economy. Most importantly, the challenges in using biomass material as feedstock, such as impurity removal, heterogeneity of the biomass, and utilization of remaining residues, are seldom addressed, which leaves uncertainties regarding process upscaling and the feasibility of using waste-derived LA for PLA synthesis. The amount of PLA produced from LA is still lower than the total amount of petrochemical materials used for plastic production [82].

Glucose

Glucose is the most preferred carbon source for LA fermentation. Sugar produced from sugarcane or sugar beets is a main feedstock for LA production. Pure glucose-based LA will have high demand in the future because its usage is increasing in the manufacturing of bioplastics and biochemicals. For instance, the Institute for Bioplastics and Biocomposites (IfBB; Hannover, Germany) and Wageningen University & Research Centre (WUR; Wageningen, Netherlands) compared and analyzed the data for crop yields, the feedstock for which is efficient for producing biomaterials such as bioethanol, PLA, and biopolyethylene (bio-PE). Carbon sources used in the current industrial production of LA are carbohydrates such as glucose, sucrose, lactose, starch, maltose, molasses, whey, and barley malt [83]. The use of sugars is not profitable because they remain superior substrates owing to certain constraints such as: i) unavailability of potential amylolytic strains with high yield efficiency for LA fermentation and ii) unavailability of organisms for utilizing alternative crude agricultural raw materials that are abundantly available, inexpensive, and renewable and that enable high-efficiency production.

Starch

After glucose, starch is the second-most preferred substrate for LA fermentation. Various starchy materials such as corn, maize, rice, rye, wheat, potato, barley, and cassava have been studied for LA production [84]. Conversion of starchy materials to glucose is mandatory for the production of LA, except when the LAB exhibit amylolytic activity, which enables direct production of LA from starchy materials. The preparation of glucose from starchy materials requires two additional steps during the fermentation process: liquefaction by thermostable α-amylase and saccharification by α-amylase and amyloglucosidase. The glucose released by enzymatic treatment can be used directly as a carbon source for LA fermentation [85]. Starchy substrates work well, and they are sustainable substrates for LA production, especially when associated with amylolytic LAB (ALAB) [86].

Additionally, the use of starch avoids substrates that are generally affected by high glucose levels. ALAB convert starch directly into LA during a single-step fermentation. ALAB primarily occur in food fermentation, especially in cereal-based fermented products, and have been isolated from traditional cereal- or cassava-based fermented foods [87–89]. Because of their α-amylase activity, some ALAB strains can partially hydrolyze raw starch [90], and ALAB can ferment different types of starchy materials such as corn [91], potato [92], or cassava [93] and starchy substrates [86,94,95]. However, these materials are used for human and animal feeding. The competition between the LA industry and the food sector is the same as that demonstrated for the biofuel sector. Further information on ALAB and direct starch hydrolysis was previously reviewed by Reddy et al. [96].

The filamentous fungus *R. oryzae* is frequently utilized for the direct conversion of starchy materials and solid-state fermentation for the production of L-LA. *R. oryzae* and *R. arrhizus* can aerobically convert starch to LA [97]. *R. arrhizus* 36,017 and *R. oryzae* 2062 produce LA in a single-stage simultaneous saccharification and fermentation (SSF) process using potato, corn, wheat, and pineapple waste streams as production media. *R. arrhizus* has been shown to produce a high LA yield up to 0.94–0.97 g/g of starch or sugars, while *R. oryzae* generated an LA yield of 0.65–0.76 g/g over 36–48 h of fermentation. Supplementation with 2 g/L ammonium sulfate, yeast extract, and peptone increased the LA yield by 8–15% [98]. The production of LA has been enhanced using potato pulp pretreated with pectinase. However, in most studies on fermentation using *Rhizopus* strains, starchy materials were converted to LA in an SSF process [99–105].

Lignocellulose

Lignocellulosic materials are natural, inexpensive, and abundantly available as agricultural waste (wheat straw, rice straw, corn stalks, soybean residues, and sugarcane bagasse), industrial waste (pulp, paper industry, and food processing), forestry residues, and municipal solid waste; thus, the use of these materials does not involve competition with the human food industry [81]. The conversion of these potential feedstock materials into high-value-added products is projected to be an appropriate substitute for petroleum-based products in terms of environmental preservation, sustainability, and circular economy [82]. Lignocellulose is composed of three major polymers: cellulose (linear polymer of D-glucose), hemicellulose (heteropolysaccharide with xylose, glucose, mannose, galactose, and arabinose monomers), and lignin (polymer of three closely related phenylpropane moieties: guaiacyl, syringyl, and hydroxybenzaldehyde). Among them, cellulose is the backbone and is surrounded by hemicellulose and lignin.

The major hurdle for the utilization of lignocellulose is that many microorganisms cannot utilize it directly for metabolism and product production. It is essential to convert polymeric lignocellulosic biomass into a simple and digestible monomeric form by appropriate pretreatments to release lignin and hemicellulose for better enzyme accessibility and enzyme hydrolysis, which results in the release of glucose and xylose molecules. Through efficient pretreatment and hydrolysis, the major economic and technical challenges of lignocellulosic materials can be overcome [82]. Pretreatment methods have been developed over many years, and they can be grouped into three types: (i) physical methods by irradiation, chopping, and milling; (ii) chemical methods using oxidizing agents, acid, alkaline, organosolvents, ionic liquids (ILs), steam explosion, or hot water with or without catalysts; and (iii) biological methods using lignolytic white rot fungi [106]. The most popular technologies are dilute acid and alkali, steam explosion, and ammonia fiber expansion (AFEX), which can remove a large amount of lignin; however, they break hydrogen linkages in the crystalline moieties of cellulose [107], which affects the efficiency of further hydrolysis by cellulase enzymes, resulting in low conversion because of the presence of residual hemicellulose and lignin [108]. Cellulase loading can overcome the problem of low conversion. In addition, harsh pretreatment conditions such as high pressure and high temperature cause sugar degradation and inhibitor formation [109]. Considering these challenges, the development of a robust pretreatment method is necessary for ef-

ficient production of fermentation products. During pretreatment, hemicellulose is the most susceptible material in lignocellulosic biomass, and its selective removal is crucial for the efficient and economical processing of lignocelluloses. This process can be achieved using organosolvent fractionation; organic or aqueous–organic solvent systems have been used with and without catalysts at 100–250 °C [110,111]. Pretreatment with acid catalysts containing mineral acids (such as hydrochloric acid, sulfuric acid, and phosphoric acid) and organic acids (such as formic acids, oxalic acid, and salicylic acid) can efficiently remove hemicellulose, whereas organic solvents assist in solubilizing lignin from lignocellulose. This process can also be conducted at room temperature and atmospheric pressure by increasing the acid concentration [112]. Three types of solvents are commonly used in organosolvent pretreatment: (i) alcohols with low boiling point (methanol and ethanol), (ii) alcohols with high boiling point (glycerol, ethylene glycol, and tetrahydrofurfuryl alcohol), and (iii) others such as dimethylformamide, dimethyl sulfoxide, phenols, ketones, and ethers [113,114].

ILs are organic solvents that exist as ion pairs. Some are liquids, and some are solids at room temperature with melting temperatures below 100 °C. ILs are highly persistent, polar, and thermally stable single-component ingredients [115,116]. The most popular ILs are imidazole salts such as 1-allyl-3-methylimidazolium chloride (AmimCl) and 1-butyl-3-methylimidazolium chloride (BmimCl), which are used for cellulose dissolution [110]. It is probable that the mechanism of cellulose dissolution involves the alteration of lignocellulose crosslinking by hydrogen bonds, which results in an increase in biomass digestibility. Sun et al. [117] investigated an integrated one-pot process for the production of fermentation products from lignocellulosic biomass, where the process of cellulose hydrolysis was optimized because of the following problems associated with ILs: enzyme inhibition, structural modification, and deactivation.

Biological biomass pretreatment methods mainly utilize wood-decomposing fungi or their enzymes. These fungi produce enzymes that can depolymerize or cleave lignin, cellulose, and hemicellulose. In this process, no chemicals are used; hence, it does not release toxic compounds into the environment, and it is safe. Microbes such as brown, white, and soft rot fungi have been used for degrading lignin and hemicelluloses from lignocellulosic biomass [118]. Research has been conducted on the evaluation of biological pretreatment of structural alterations and enzymatic hydrolysis after biological pretreatment. The efficiency of biological pretreatment and degradation of lignin depends on the efficiency of the lignolytic enzymes (lignin peroxidase, manganese peroxidase, and laccase produced by the microbes). As no harsh chemicals or conditions are used, the by-products released in this process are not harmful, and they do not inhibit the subsequent hydrolysis and fermentation processes [119].

Cellulose and hemicellulose separated from lignocellulosic biomass by pretreatment need to be hydrolyzed to release fermentable hexoses and pentoses, which can then be fermented into various products such as ethanol and LA. Through this saccharification process, cellulose is broken down into glucose, and hemicellulose is disintegrated into five different sugars, i.e., arabinose, galactose, glucose, mannose, and xylose, and other components, such as acetic, glucuronic, and ferulic acids [119].

Generally, cellulose is in crystalline form, and it requires conditions such as high temperatures and high acid concentrations to liberate glucose from these tightly associated chains. When heated to high temperatures with dilute sulfuric acid, long cellulose chains can be broken down into shorter groups of glucose molecules, which can then be degraded to hydroxymethyl furfural [116]. Furthermore, the cellulose hydrolysis rate increased with the temperature compared to the glucose degradation rate, which resulted in increased yields at a high temperature and acid concentration. In addition, a very short reaction time of approximately 6 s at 250 °C with 1% sulfuric acid released the maximum amount of glucose from the lignocellulose. Although this is an effective method, dilute sulfuric acid hydrolysis is expensive, representing approximately one-third of the total cost of producing ethanol and other fermentation products [120]. The corrosive nature of acids requires the

use of expensive and hard materials in reactors. In acid hydrolysis, by-products such as furfurals, lignin fragments, and other solubilized compounds such as acetic acid must be removed to avoid their inhibition during fermentation by other expensive processes.

Enzymatic hydrolysis is a promising and highly fermentable sugar-yielding method for pretreatment of lignocellulose by depolymerizing the insoluble fraction [121]. Two different types of enzymes, cellulases and hemicellulases, are required for complete hydrolysis of cellulose and hemicellulose into fermentable sugars. For effective hydrolysis, a combination of these two enzymes is required for efficient hemicellulose hydrolysis, thus increasing the access of cellulose to cellulase, which decreases the time and process costs [122]. The rate of cellulose hydrolysis mainly depends on the degree of polymerization [107]. Efficient and complete hydrolysis of cellulose requires the synergistic action of three classes of cellulolytic enzymes: endo-β-1,4-glucanases (EG; EC 3.2.1.3), exo-β-1,4-glucanases or cellobiohydrolases (CBH; EC 3.2.1.91), and β-glucosidases or cellobiases (β-G; EC 3.2.1.21). EG randomly hydrolyzes accessible intramolecular β-1,4-glucosidic linkages of cellulose chains and inserts a water molecule into the β-1,4 linkage, creating a new reducing and non-reducing chain end pair. CBH splits the cellulose chains at the ends of the polymer, releasing soluble cellobiose or glucose. β-G completes hydrolysis by splitting cellobiose into two glucose molecules [123], thus avoiding end-product inhibition [124]. These three types of cellulases, auxiliary or "helper" enzymes that work on hemicellulose and lignin, are important for hydrolysis as they improve the accessibility of the cellulases to the cellulose. Xylans are chemically more complex than cellulose, and their hydrolysis requires several different enzymes such as endo-1,4-β-xylanase, β-xylosidase, β-glucuronidase, β-L-arabinofuranosidase, and acetylxylan esterase [125]. Mannanase and mannosidase break the glucomannan polymer backbone [124]. Due to the lower crystallinity of xylan than cellulose, xylan is more easily accessible to all enzymes required for xylan hydrolysis [126]. The hydrolytic activity of an enzyme mixture depends on the properties of the individual enzymes and their ratio in the multienzyme mixture [127].

Whey

Whey is a major by-product of the dairy industry and is a potent and suitable source for LA production with 5% lactose, 1% protein, 0.4% fat, and some minerals. It causes severe disposal problems because of its high BOD content (40,000–60,000 ppm) [128]. Theoretically, 4 moles of LA should be produced from 1 mole of lactose through a homofermentative pathway after the cleavage of lactose to 1 mole of glucose and 1 mole of galactose. In whey fermentation using *L. casei* NRRL B441, a productivity of 3.97 g/dm^3·h was obtained at pH 5.5. The productivity achieved using whey is very high compared to that using analytical lactose and glucose [57]. Roukas and Kotzekidou [129] reported LA production from deproteinized whey by mixed cultures of free and co-immobilized *L. casei* and *L. lactis* cells using fed-batch culture. Additionally, the effect of process conditions on LA production from whey has been studied [130,131]. The value addition of whey and its bioutilization for LA production have been well reviewed by Panesar and Kennedy [132].

The global yogurt market has grown rapidly over the last decade, creating a large amount of damaged or expired yogurt as waste. It is a potential raw material in the dairy industry because it contains more fermentable sugars than whey. *L. casei* ATCC 393 has been reported to exhibit high LA production with yogurt whey, that is, 25.9 g/L of LA (at a yield of 0.9 g/g and productivity of 0.76 g/L·h) from 44% of total sugars in a batch fermentation process [133]. However, mixed sugar utilization of lactose, glucose, and sucrose is a major problem that must be addressed for the effective utilization of yogurt whey.

Food Waste

Food waste provides copious raw materials for fermentation and other value-added processes. It is generated in huge amounts from food processing units and by the end consumer (1.3 billon MT) annually [134]. It has high amounts of carbohydrates, proteins, and minerals, and it is suitable for LA production. Several studies have been conducted

on the utilization of food waste such as kitchen residues/refuse, mixes of cooked rice, vegetables, meat, and bean curd [135], and rice, noodles, meat, and vegetables [22,136]. Residual vegetable and fruit wastes are generated in large amounts; these include carrot peel, cabbage, potato peel, banana peel, apple peel, and orange peel, baked fish, rice, and used tea leaves [137,138]. Waste generated from coffee processing units (coffee mucilage and coffee pulp) has been used for producing LA with high productivity (4.02 g/L·h) [139]. Kwan et al. [22] developed an LA production process from food waste via solid-state fermentation using a fungal hydrolysis technique. In addition to prevention and reduction through education and policy, advanced technology plays an important role in facilitating recycling in food waste management. Food waste biorefinery is a potential method for converting different types of food waste into value-added products through fermentation and the extraction of nutrients, which enables the development of a sustainable bioeconomy.

Glycerol

Glycerol is produced as a by-product of biodiesel production using edible and inedible vegetable oils and algal oils. It is generally produced at a ratio of 1:10 (glycerol:biodiesel) [140]. Therefore, effective utilization of glycerol as a cheap substrate would solve both economic and environmental challenges. Certain microorganisms such as *Klebsiella*, *Clostridium*, *Achromobacter*, and *Lactobacillus* can produce LA from glycerol. The main disadvantage of these organisms is their low yield and productivity [141–143]. Wild-type *Escherichia coli* usually produces very low concentrations of LA under anaerobic and microaerobic conditions through heterofermentation [144]. However, Hong et al. [145] reported the production of a high concentration of LA from glycerol, using *E. coli* AC-521: 56.8 g/L and 85.8 g/L using *E. coli* AC-521 in batch and fed-batch fermentations, respectively. In recent years, engineered *E. coli* has been utilized for LA production from glycerol [140,146,147]. Higher concentrations of D-LA up to 111.5 g/L [146,148] and 50 g/L [149] were achieved through fed-batch fermentation by engineered *E. coli*.

Algae

Algal biomass contains high levels of carbohydrates and proteins and no lignin-like lignocellulose [5,150]. Nguyen et al. [5] reported the composition of *Hydrodictyon reticulum*, which contains 62.9% polysaccharides and 10% proteins. Available polysaccharides can be converted to fermentable sugars, such as glucose and mannose, with fewer inhibitory compounds. The use of microalgae and cyanobacteria for LA production could decrease feedstock costs because of their ability to harness energy from sunlight to fix CO_2 [64,151].

2.2.5. Neutralizing Agents Used in Lactic Acid Fermentation

In LA fermentation, the produced LA decreases the pH of the medium from the set point owing to acidification of the medium. To balance the medium pH, NH_3, NH_4OH, KOH, NaOH, $NaHCO_3$, $Ca(OH)_2$, or $CaCO_3$ is used as a neutralizing agent in LA fermentation [152]. Among the above compounds, the addition of $Ca(OH)_2$ or $CaCO_3$ is advantageous; it can precipitate LA as calcium lactate, which helps reduce the negative effects of LA on growth and production [152]. Nevertheless, the use of these compounds shows very slow neutralization capacity and narrow regulation [152]. During recovery and purification, concentrated acid (H_2SO_4) is essential for releasing LA from its calcium salt and generating calcium sulfate (gypsum) as a by-product [153]. Ammonia and its hydroxides are the most commonly used neutralizing agents after calcium substances in LA fermentation because of their easy pH regulation, positive effect on cell growth as an extra nitrogen source, and the fact the compounds obtained after recovery of LA can be used as a fertilizer with good market value. However, high concentrations of ammonia substances cause toxicity towards microbial growth by increasing osmotic stress in the form of ammonium lactate, and purification of LA present in the form of ammonium lactate from the fermentation broth is difficult and time consuming. Similar to ammonia, sodium in-

hibits LA production when used as a neutralizing agent [154]. Therefore, it can be deduced that LA production might be relevant to the ionic strength of the fermentation broth.

It has been reported that some of the neutralizing agents used in LA fermentation interfere with product separation and purification processes. Hence, one should keep this in mind during selection of neutralizing agents. Purification of LA is relatively easier when using $NaHCO_3$ instead of $CaCO_3$, because of the higher solubility of sodium lactate than calcium lactate. However, $CaCO_3$ helps in slightly higher productivity when compared to $NaHCO_3$. Hence, the highly soluble $NaHCO_3$, $NaOH$, NH_3 might be the first choice for process designers whenever recovery is important and it could reduce the cost of the final production cost of LA [84].

2.2.6. Lactic Acid Fermentation Technologies

Batch fermentation is the most popular fermentation process and is regularly used for LA production. This process is referred to as a closed system because all carbon and nitrogen sources and other medium components are added before initiating fermentation, and nothing is done during fermentation, except for the addition of neutralizing agents for pH control. According to a previous report [155], LA production kinetics during batch fermentation showed that the final concentration of the product increased with substrate concentration up to a high level, that is, 192 g/L LA from 200 g/L by *L. paracasei* subsp. *paracasei* CHB2121. In addition to the final product yield, LA production through batch fermentation has other benefits such as ease of operation, absence of contamination, and a well-studied process. The highest final concentration of product is possible in batch mode; however, the major limitation of batch fermentation is catabolite repression of high substrate and low productivity due to low cell density, limited nutrients, and substrate at the final phases and/or product inhibition. Researchers have made several improvements in batch fermentation modes, such as separate hydrolysis and fermentation (SHF), simultaneous saccharification and fermentation (SSF), mixed culture fermentation, immobilized cell stirred tank fermentation (CSTR), and open batch fermentation for increased productivity and economic viability.

SHF is a conventional process used for the production of LA from starch and lignocellulosic resources. This process provides the advantage of optimizing enzymatic hydrolysis and fermentation steps separately. Inhibition of carbohydrate hydrolases, amylase, cellulose, xylanase, and β-glucosidase activities by the released sugars, mainly maltose, cellobiose, and glucose, is the main drawback of high yields [156]. High concentrations of glucose inhibit the catalytic reactions of cellulase. Cellobiose also inhibits the cellulase activity. This will increase the time of completion of hydrolysis by reducing the rate of the reaction [157–159].

Unlike SHF, SHF combines enzymatic hydrolysis and fermentation in one step. This can minimize the product inhibition of enzymes, as microorganisms immediately consume the released sugars. It can also facilitate the production of cellulase and fermentation of hemicellulose hydrolysis products. This process has several advantages over SHF, such as increased LA yield, decreased enzyme loading, decreased contamination, and lower capital costs. The disadvantages are differences between the optimum temperatures for enzyme hydrolysis and fermentation and inhibition of cellulase by the produced ethanol [120,160].

Compared with SHF, SSF can reduce the complexity of the SHF procedure and facilitate economically feasible production of LA from lignocellulosic biomass by merging the process steps and avoiding end-product inhibition of enzymes. SSF can avoid glucose catabolite repression, thus improving LA production from starch-related substrates. Nakano et al. [161] reported a higher LA production from broken rice by *L. delbrueckii* JCM 1106. In addition, SSF can increase productivity by reducing the time required for separate hydrolysis in the SHF method. Marques et al. [162] reported a higher LA yield of 0.97 g/g using SSF than that obtained using SHF (0.81 g/g) from recycled paper sludge with *L. rhamnosus* ATCC 7469. In contrast to the above advantages, a long-standing constraint of SSF is that low product yields are obtained with high-solids loading of biomass owing to the difference

in optimum conditions for hydrolysis and fermentation. Wu and Lee [163] suggested a modified SSF process, non-isothermal simultaneous saccharification and fermentation (NSSF), to overcome the issues arising from the difference in optimum temperature and other conditions; in this process, hydrolysis and fermentation occur simultaneously but in two separate reactors, each operated at its own optimum temperature. Compared to SSF, NSSF increased the yield and productivity with a reduced overall enzyme loading of 30–40%, which increased the capital cost for extra equipment. An important problem in using SSF or NSSF at the industrial level is to study and obtain a point of convergence for both hydrolysis and fermentation. The primary advantage of SSF is that it can avoid inhibition due to high glucose concentrations.

Simultaneous saccharification and co-fermentation (SSCF) is considered an improved process compared to SSF. SSCF involves enzymatic hydrolysis of cellulose and hemicellulose and fermentation of both hydrolysis products in the same fermenter with one microorganism [164,165]. Compared to SSF, the cost of the SSCF process is low. SSCF offers several other advantages, such as continuous extraction of end products produced during hydrolysis, which avoids the inhibition of cellulase and β-glucosidase activities and enhances the rate of fermentation products compared to the SHF and SSF. It can be carried out with high water-insoluble solids (WISs) for higher product titers [160,166,167]. SSCF can also be run in a fed-batch fashion for escaping the primary glucose utilization rather than xylose [168]. It requires a microorganism that can simultaneously ferment both glucose and xylose without any by-products. In a previous study using the SSCF process, >90% LA was produced by *L. pentosus* ATCC 8041 using pretreated corn stover as the substrate and the commercial cellulase Spezyme-CP for hydrolysis. The low yields of LA were attributed to acetic acid production as a by-product through the utilization of xylose and arabinose. Another disadvantage of SSCF is its low final LA concentration owing to product inhibition [169]. Hence, this process requires metabolically engineered microorganisms that can strongly co-ferment pentose without by-products [170].

The fed-batch process is a modified batch fermentation process, where the substrate is fed in a controlled manner, either continuously or periodically, without product removal. It is also known as a semi-closed fermentation process because the fermentation broth is not removed during fermentation. A periodic supply of nutrients allows longer logarithmic and stationary phases of microbes and, in turn, improves the product concentration. The fed-batch method can be classified into the fixed-volume fed-batch method (addition of a very highly concentrated medium) and variable-volume fed-batch method (addition of the same or low-concentration medium). It is highly advantageous over batch fermentation; through this process, high substrate inhibition can be avoided because of the Crabtree effect and catabolite repression [171]. However, it does not address severe product inhibition resulting from the accumulation of high amounts of LA. Additionally, it is difficult to study the effects of several factors in a fed-batch system, which is important for optimizing the fermentation process and enhancing product concentration.

Intermittent, continuous, and exponential feeding are common feeding strategies. The pulse-feeding strategy is an improved variation; it is less complex and less labor intensive, and it enables high LA production [172,173]. Bai et al. [60] reported that it achieved 60% higher product yield, 180 g/L LA through exponential feeding of nutrient solution (glucose 850 g/L and yeast extract 1%), compared with batch fermentation and 210 g/L LA (0.97 g/g with 2.2 g/L·h) by continuous feeding and pH-controlled fed-batch fermentation by *L. lactis* BME5-18M. Repeated fed-batch cultivation significantly improved LA production by 16–20% when compared to normal fed-batch cultivation, and further LA production was enhanced by pH control [174].

A fed-forward controlled fed-batch fermentation process was used for enhancing the production of LA from Arabic date juice [175]. *E. mundtii* QU25 was used for fermenting a glucose/xylose mixture to L-LA; it produced 129 g/L LA with 5.60 g/L·h productivity by fed-batch fermentation. Hu et al. [176] developed a fed-batch SSF process for LA production using NaOH and cellulase-pretreated stover supplemented with 10 g/L yeast

extract in a 5 L bioreactor under non-sterile conditions. In a pulse-feeding fed-batch process with six pulsed additions of recycled paper sludge (40 g at each 5 h), 108.2 g/L L-LA was produced [25]. They studied SSF in fed-batch processes for the production of LA from recycled paper sludge and improved the kinetics of *L. rhamnosus*. Pejin et al. [177] utilized brewer's spent grain (BSG) hydrolysates for L-LA fermentation by *L. rhamnosus* ATCC 7469 through fed-batch fermentation; this process achieved 20.7% higher productivity than batch fermentation. A fed-batch process with one-step integrated fermentation strategy using *R. oryzae* efficiently improved L-LA production to 162 g/L and productivity to 6.23 g/L·h [178]. Coelho et al. [179] achieved 206.81 g/L LA with the highest productivity of 5.3 g/L·h by exponential feeding using 900 g/L granulated sugar solution and 1% yeast extract at 50 °C and pH 6.5 for 39 h. Exponential fed-batch fermentation showed a 133.22% improvement compared with simple batch fermentation. This study presented the highest LA productivity by thermotolerant *Bacillus* sp. and reported a novel and high-efficiency purification technology using inexpensive materials, celite, and charcoal. Brock et al. [180] reported 221 g/L LA with 1.55 g/L·h productivity and 96% yield using chemically hydrolyzed rapeseed meal and minimal supplementation through fed-batch fermentation. Genetically engineered *E. coli* HBUT-D15 was evaluated at a semi-industrial scale (30 m^3) in fed-batch fermentation with 160 g/L of glucose; it produced 146–150 g/L D-LA with a 3.95–4.29 g/L·h productivity, 91–94% yield, and 99.8% purity. These results are comparable to those of current industrial scale L-LA fermentation [178].

An automatic fed-batch process with alkaline wheat straw as a feeding substance for dual benefits as a carbon source and a neutralizing agent was developed. A constant residual glucose concentration showed better performance than maintaining microbial activity [181]. Integrated glucose feedback-controlled fed-batch fermentation produced superior results to pulse feeding and feeding at a constant rate, and *L. rhamnosus* LA-04-1 produced 170 g/L of L-LA [181]. SSF fed-batch fermentation can be run in a single reactor, and it reduces equipment and labor costs. By SSF fed-batch fermentation using *L. rhamnosus*, Romaní et al. [182] obtained 37.8 g of LA with 0.87 g/L·h of productivity from cellulase-treated cellulosic biosludge. Wang et al. [183] reported highly efficient single-pulse and multipulse feeding SSF fed-batch fermentation for enhanced D-LA production from peanut meal and glucose as substrates, producing 207 g/L and 226 g/L D-LA, respectively. Ou et al. [48] obtained 80 g/L LA using *B. coagulans* 36D1 from cellulose through multipulse feeding SSF fed-batch fermentation. Jerusalem artichoke tubers were evaluated for LA production using two different cultures of *A. niger* SL-09 and *Lactobacillus* sp. G-02 in fed-batch SSF; it produced 120.5 g/L LA in 36 h [184]. Here, *A. niger* SL-09 facilitated the production of inulinase and invertase. Although the fed-batch process is an industrially preferred fermentation as it allows higher LA concentration up to 226 g/L, the productivity is relatively low (<4.7 g/L·h) [183,185]. Methods for increasing the LA concentration and productivity are required for efficient and economical LA fermentation.

LA production is a growth-associated fermentation process, and LAB obtained energy from the LA production pathways. Sharma and Mishra [186] fitted the modified Gompertz equation to the logarithm of cell concentration to determine the maximum specific growth rates, lag phase, and maximum cell numbers of *L. plantarum* in various media. Three types of fermentation can be distinguished: growth-associated product formation, mixed growth-associated product formation, and non-growth-associated product formation [187]. Many researchers used the mixed growth-associated product formation for LA production kinetics which suggests that the product formation rate depends on growth rate and cell concentration. The kinetics model for LA production on beet molasses using *L. delbrueckii* was proposed by Monteagudo et al. [188]. According to this equation, the LA formation rate will become zero when LA concentration approaches its maximum concentration [189]. In contrast to batch and fed-batch fermentation, cell growth can be maintained at a constant rate during continuous fermentation. In continuous culture processes, chemostat (by the adjustment of medium components) and turbidostat (by the adjustment of culture turbidity) methods can be used for maintaining the cultures in the logarithmic growth phase.

Chemostat fermentation is a classic continuous fermentation system in which fresh medium with a growth-limiting substrate is fed to the fermenter to maintain a constant growth rate. In turbidostat fermentation, a constant cell growth is maintained via spectrometric observation of culture optical density [190]. Tashiro et al. [191] achieved 18 g/L·h LA productivity using *L. delbrueckii* subsp. *lactis* QU41 through continuous fermentation; this value was 35-fold higher than that achieved with batch mode. Extensive research data are available in the literature, and the establishment of a continuous LA process in industry has rarely been reported [192]. Gao and Ho [193] conducted comparison studies for batch, fed-batch, and continuous cultures using *B. subtillis* MUR1; a big difference was not observed between batch and continuous fermentations (16.1 g/L·h and 17.1 g/L·h). The main difference between the fed-batch and continuous processes was that the maximum productivity was maintained for only 1 h in the fed-batch process. Lee et al. [194] compared continuous and batch fermentation modes using *E. faecalis* RKY1 with yeast extract-supplemented glucose as a substrate. The results showed that the productivities were almost the same, even though yeast extract supplementation in the continuous mode was reduced by 77% compared to that in the batch mode.

Unlike batch fermentation, continuous fermentation does not need to stop for activities such as harvesting, cleaning, sterilization, and refilling, and it allows constant productivity without a decrease during the lag phase [190,194]. The dilution rate is an important factor in obtaining maximum productivity and has been well investigated. An increase or decrease in dilution rate affects efflux and causes a decrease in LA concentration by leaving unutilized carbon sources and cells from the fermenter. Substrate and product inhibition problems are fewer in continuous systems; however, the productivity of the product is affected by the production in the case of LA fermentation. Maintaining the fermenter under mild basic conditions continuously increases the operational cost. Therefore, microbial strains that can work in high substrate and LA concentrations are required. These problems can be solved using advanced fermentation technologies such as high cell density (HCD) fermentation.

Repeated-batch fermentation is a popular LA production strategy that involves the use of microorganisms as inoculum after completion of the first cycle for the next cycle. Here, a part or all of the free or immobilized cells from a previous cycle can be used in the next cycle; it has several advantages over conventional systems, including reduction in time, cost for inoculum and preparation, and labor and high LA productivity [7,195]. Except for the inoculum, the substrate concentration and other fermentation parameters were maintained constant. This often results in increased LA productivity during the initial run. This may be due to the acclimatization of cells to the fermentation process and the development of resistance towards the substrate and product [196].

Different methods have been employed for the reuse of bacteria (centrifugation, immobilized cells, use of hollow fibers, and partial reuse of culture) and fungi (filtration or mycelial pellet precipitation) in repeated-batch fermentation processes. Repeated-batch and fed-batch processes reduce fermentation time and improve LA productivity.

Kim et al. [197] reported that repeated-batch cheese whey LA fermentation by *Lactobacillus* sp. RKY2 exhibited 6.2 times higher productivity (6.34 g/L·h) than batch fermentation. Wee et al. [198] achieved 2.7 times higher productivity (4.0 g/L·h) with repeated-batch fermentation using *E. faecalis* RKY1 than with batch fermentation using wood hydrolysate and corn steep liquor. Wang et al. [199] reported a maximum L-LA production of 102 g/L with 0.942 g/g and a productivity of 2.90 g/L·h using the hydrolysate of sweet sorghum juice. Furthermore, they reduced the cost of the production process by substituting the yeast extract and salts with corn steep powder. In contrast, Tosungnoen et al. [200] reported a decreased LA yield from the first batch to the 5th batch (28.71 to 20.29 g/L) using SSF of synthetic cassava starch wastewater (SCW) by *L. plantarum* MSUL702 under non-sterile conditions and at room temperature. These results could be attributed to the lower cell concentrations and product inhibition in SCW. In a comparative study, Abdel-Rahman et al. [175] reported a production of 82.4 g/L LA with 0.858 g/g and productivity of 2.0 g/L·h with a 100 g/L glucose medium in a batch fermentation

system. LA productivity was enhanced by up to 5.5-fold in 11 runs of open repeated-batch or fed-batch fermentation by reusing the inoculum from the previous batch. A comparative study conducted using an alkaliphilic LAB, *E. hirae* BoM 1–2, demonstrated a dramatic increase in LA productivity up to 39.9 g/L·h (18-fold compared to the first run) using 40 g/L glucose compared with a very low productivity of 1.07 g/L·h with batch fermentation. LA-producing fungi have also been investigated in repeated-batch fermentation for L-LA production [103,201,202].

Cell immobilization is a preferred technique for improving cell concentration in fermentation processes. In LA fermentation, immobilization of LAB permits the utilization of cells for several cycles (reutilization/recycling), which results in reduction of product/substrate inhibition, achievement of greater volumetric productivities, and reduction of contamination risks [203]. LA fermentation with immobilized LAB can reduce the production cost by combining fermentation and separation processes and can achieve LA production by stationary phase cells for extended periods. Adsorption, entrapment, encapsulation, covalent bonding, and cell–cell crosslinking are well-known methods used for cell immobilization [187]. The immobilization matrix should be inert, stable, cheap, and available in all seasons. The selection of this matrix is important for achieving stable and enhanced LA production. The immobilization matrix mainly depends on the type of microorganism and the fermentation conditions. A large list of natural materials, such as agar, carrageenan, alginate, cellulose, and its derivatives, and synthetic materials, such as polyester, polyacrylamide, polyurethane, and polystyrene, have been utilized for microbial cell immobilization [30,203].

Among the methods of cell immobilization, adsorption is the most popular and commonly preferred because it is easy and simple to prepare. Including its ease, it has little effect on the morphology during attachment to the surface of the adsorbent. Microbial cells can be attached to a porous or non-porous matrix. Adsorption of cells to the carrier occurs by physical (van der Waals) or electrostatic forces and hydrogen bonding. Adsorption is more appropriate than other immobilization techniques for the immobilization of viable cells. Adsorption of microbial cells onto the support is primarily dependent on its chemical nature and age [30]. Desorption of cells from the adsorbent and low efficiency are major drawbacks of this method. Very strong covalent binding can be achieved using chemicals; however, aggressive chemicals damage the cells, and they are not preferred for this technique [203]. Various natural and synthetic materials have been evaluated as adsorbents. Another common cell immobilization technique used for LA production is entrapment. Cells are physically entrapped inside a matrix, and the bonds involved may be covalent or non-covalent. Matrix materials used for entrapment are water soluble, and entrapment occurs by mixing the polymers with a cell suspension by dripping into a precipitate-forming solution or by thermal polymerization. Leakage and pore diffusion are major limitations of this technique.

During encapsulation, microbial cells are enclosed in a semi-permeable membrane capsule by membrane filters, entrapped in a microcapsule, or immobilized onto the interaction surface of two immiscible liquids [204]. Some microbial cells can self-aggregate and form larger units, which are used for forming flocs that adhere in clumps and sediment rapidly. Cell aggregation occurs naturally in molds and fungi. Fungal cells can aggregate naturally and form pellets during submerged fermentation; artificial aggregating or crosslinking agents are available, which can be used for achieving aggregation of cells that cannot aggregate themselves [204]. Fruit pieces have been utilized as food-grade immobilization matrices for food-grade LA production and for achieving enhanced aroma and consumer acceptance [204]. Recent reports on immobilization of LAB for LA production are listed in Table 2. Immobilization has been utilized for enhancing the production of LA by high cell density fermentation processes, such as packed-bed reactors (PBRs), continuous-flow stirred tank reactors (CSTRs), fibrous-bed reactors, fluidized-bed reactors (FBRs), and membrane cell-recycling fermentation [205,206]. The characteristics and advantages of this high cell density fermentation process are presented in Table 3.

Table 2. List of recent reports on immobilization methods and their lactic acid yield.

Immobilization Method/Material	Microorganism	Substrate	Lactic Acid (g/L)	Productivity (g/L·h)	Reference
Loofah sponge	*Rhizopus oryzae* PTCC 5263	Soluble potato starch	5	-	[207]
Alginate beads	*Lactobacillus rhamnosus*	Carob waste juice	22	1.22	[26]
Poly(vinyl alcohol)/ calcium alginate (PVA/Ca-alginate) matrix	*Lactobacillus rhamnosus* ATCC7469			0.8	[208]
Zeolite	*Lactobacillus rhamnosus* ATCC 7469	Liquid distillery stillage	42.19	1.69	[209]
Sodium alginate	*Enterococcus faecalis*	Salted cheese whey	36.95	-	[210]
Chitosan-modified polypropylene	*Lactobacillus casei*	Synthetic media	20.4	-	[211]
Asterisk-shaped fibrous matrices in a honeycomb configuration	*Rhizopus oryzae*		49.5	0.57	[212]

Table 3. Lactic acid fermentation using the advanced bioreactors with high cell density.

Type of Bioreactor	Fermentation Method	Microorganism	Lactic Acid (g/l)	Productivity (g/L·h)	Reference
PBR	Fed-batch	*L. lactis*-11	115.0	2.3	[213]
	Batch	*L. lactis* IO-1	29.78	2.2	[214]
	Recycled batch	*L. lactis* IO-1	23.0	2.4	[214]
	Continuous	*L. lactis* IO-1	8.9	4.5	[214]
	Continuous	*L. bulgaricus*	n.p.	1.5	[215]
CSTR	Batch	*L. casei, L. lactis*	22.5	0.9	[131]
	Repeated batch	*L. casei, L. lactis*	46.0	1.9	[131]
	Continuous	*L. helveticus*	n.p.	28.5	[216]
	Continuous	*L. casei* MTCC 1423	106	5.9	[217]
	Repeated batch	*R. oryzae*	n.p.	3.8	[202]
FBR	Batch	*R. oryzae* NRRL395	75.2	1.05	[218]
	Fed-batch	*R. oryzae*	90.0	2.5	[103]
	Fed-batch	*S. inulinus* Y2-8	218	1.65	[219]
	Continuous	*R. oryzae* NRRL395	72.4	0.7	[218]
	Repeated batch	*R. oryzae*	137	2.1	[220]
	Continuous	*R. oryzae*	n.p.	11	[221]
	Continuous	*L. bulgaricus*	0.45	n.p.	[222]
MCRR	Continuous	*L. delbrueckii* NCIM-2025	250	12.4	[223]
	Continuous	*A. succinogenes*	183.4	1.5	[224]
	Continuous	*E. faecalis* RKY1	90.0	3.72	[194]
	Repeated batch	*E. faecalis* RKY1	95.5	6.4	[46]
	Continuous	*E. mundtii* QU 25	41.0	6.2	[175]
	Fed-batch	*L. rhamnosus* ATCC 7469	58.0	6.9	[25]

PBR, packed-bed reactor; CSTR, continuous stirred tank reactor; FBR, fluidized-bed reactor; MCRR, membrane cell-recycling reactor; n.p., not provided.

2.2.7. Genetic Engineering in Lactic Acid Production

Although researchers have developed advanced processes for improved LA production, multiple challenges need to be overcome for sustainable and economical production chains. In this regard, robust organisms are needed that can produce pure LA isomers from inexpensive substrates with high production capabilities (yield (%), titer (g/L), and productivity (g/L·h)). This can only be attained through genetically altered microorganisms (through mutation, heterologous expression, and directed evolution technologies) in addition to the above-described process technologies. The available genome sequences

of industrially important strains provide advances in the genetic modification of LAB for many industrial and commercial applications. These studies provide a rapid and better understanding of the molecular pathways used for substrate utilization, product and by-product generation, and stress conditions.

Lactobacillus strains have great feasibility for adaptation to new environmental conditions, and they are easy to genetically modify because several *Lactobacillus* species are available; additionally, approximately 40 LAB strain genome sequences have been determined, and sequencing of another 100 LAB genomes is currently underway [225]. Many genetic engineering tools, including gene expression vectors, are available for LAB and are known to be potential biorefineries, as established by the effective production of many compounds [226,227]. Various chromosomal integration systems for LAB have been developed and have been continuously optimized since the 1980s [220]. In recent years, several reports have been published on genetically modified microorganisms, and some examples of genetically modified microorganisms that produce LA are listed in Table 4. At present, researchers are investigating the incorporation of heterologous genes responsible for specific LA isomers and the expression of LDH enzymes in non-native LA producers to achieve high LA concentration and productivity. Recent investigations have suggested that yeasts play a significant role in the development of new and robust organisms for LA production. However, pH tolerance and acid stress/product inhibition are important challenges for large-scale production. The expression of LA production enzymes in yeast and other fungi provides a potential advantage in overcoming the above-mentioned challenges. The metabolic functions of many LAB have been investigated using transcriptomic, proteomic, and/or metabolomic approaches, and the information obtained will contribute to the development of metabolically engineered LAB [225,228,229].

Table 4. Genetically modified microorganisms used for lactic acid fermentation.

Microorganism	Modification	Substrate	Lactic Acid (g/L)	Reference
Bacillus sp. N16-5	L-Lactate dehydrogenase gene (*ldhL*) was knocked out, and the D-lactate dehydrogenase gene (*ldhD*) from *L. delbrueckii* was introduced to construct a D-lactate producer. Exopolysaccharide biosynthesis (*epsD*) was subsequently disrupted.	Glucose/peanut meal	142.1	[230]
Bacillus coagulans	Deletion of native L-lactate dehydrogenase gene (*ldhL*) and acetolactate synthase gene (*alsS*) to impede anaerobic growth, and suppressor mutants that restored growth.	Glucose/LB medium	99.8	[231]
Bacillus coagulans	Deletion of native L-lactate dehydrogenase gene (*ldhL*) and acetolactate synthase gene (*alsS*) to impede anaerobic growth, and suppressor mutants that restored growth.	Sorghum juice, corn steep liquor	124.4	[232]
Corynebacterium glutamicum	Overexpression of the phosphofructokinase encoding gene.	Glucose/mineral salt medium	195.0	[233]
Escherichia coli HBUT-D	The *E. coli* strain HBUT-D (Δ*pflB* Δ*frdABCD* Δ*adhE* Δ*pta* Δ*aldA* Δ*cscR*) engineered from *E. coli* W (ATCC 9637) for D-lactic acid production.	Glucose/NBS medium/yeast extract	127.0	[234]
Escherichia coli BLac-2106	Elimination of *mgsA* and enhanced expression of *glpD-glpK* in the glycerol catabolism and of a heterologous gene encoding D-lactate dehydrogenase.	Glucose/mineral salt medium	105	[235]
Escherichia coli JH15	Replaced the recombinant L-lactate dehydrogenase gene (*ldhL*) with a D-lactate dehydrogenase gene (*ldhA*).	Glucose/xylose	83.0	[236]
Klebsiella oxytoca KMS002	Deletion of alcohol dehydrogenase gene, *adhE*, and the phospho-transacetylase/acetate kinase A genes, *pta-ackA*.	Maltodextrin derived from cassava	33.6	[237]
Lactobacillus plantarum	Deletion of L-lactate dehydrogenase gene (*ldhl1*), expression of alpha-amylase (*AmyA*) from *Streptococcus bovi*.	Raw corn starch	72.8	[238]
Lactobacillus plantarum	Introduced xylose-assimilating *xylAB* operon from *L. pentosus* (PXylAB) and phosphoketolase 1 gene (*xpk1*) was replaced with the transketolase gene (*tkt*) from *L. lactis*, and the phosphoketolase 2 (*xpk2*) gene was deleted.	SSF/delignified hardwood pulp	102.5	[239]
Pediococcus acidilactici ZP26	Disruption of *ldhD* or *ldh* gene.	Corn stover/peptone, yeast extract	77.8	[240]
Saccharomyces cerevisiae OC 2	Deletion of pyruvate decarboxylase 1 and introduction of two copies of D-LDH gene.	YPD medium/peptone, yeast extract/glucose	61.5	[241]
Saccharomyces cerevisiae JHY5330	Overexpression of D-lactate dehydrogenase gene (*ldhA*, LEUM_1756) of *Leuconostoc mesenteroides* ATCC 8293.	YPD medium/peptone, yeast extract/glucose	112.0	[242]
Kluyveromyces marxianus	L-lactate dehydrogenase (LDH) expression of *Staphylococcus epidermidis*, *Lactobacillus acidophilus*, and *Bos taurus*.	Glucose	24.0	[243]
Synechocystis sp. PCC6803	Increased expression level of lactate dehydrogenase (LDH), co-expression of a heterologous pyruvate kinase, knockdown of phosphoenolpyruvate carboxylase.	CO_2	12.9	[244]

Acid tolerance of *L. pentosus* ATCC 8041 was improved by error-prone amplification of its genomic DNA using random primers and *Taq* DNA polymerase [245]. Through whole-genome shuffling, the advantages of two different types of organisms can be obtained by allowing DNA shuffling and recursive genomic recombination within the population to provide desirable phenotypes. Wang et al. [246] improved both acid tolerance and volumetric productivity. They achieved a high volumetric productivity of 5.77 g/L·h from 10% glucose, which was 2.6-fold higher than that achieved with the wild organism.

In addition to end-product inhibition and acid stress, substrate cost is an important factor in LA production. Starch and lignocellulose materials are cheap and abundantly available; however, their conversion into fermentable sugars is tedious and cost-oriented. Direct production of LA from starch and lignocellulose materials through consolidated bioprocessing is very helpful for economical production processes. Mazzoli et al. [229] described the genetic engineering aspects of LA production using recombinant LAB that can utilize starch, cellulose, and hemicellulose.

In genome editing with CRISPR/Cas, the clustered regularly interspaced short palindromic repeats/associated genes (CRISPR) system provides new advancements for all microbial-related areas. This method offers evidence of previous phage/strain interactions and unlocks methods for improving phage resistance of all industrially important strains, including *Lactobacillus* sp. and yeast [226]. Type II CRISPR has revolutionized the idea of genetic engineering because of the genome editing capability of the programmable, precise, portable, and efficient Cas9 signature nuclease. CRISPR-based technologies have opened new opportunities for the development of next-generation food microorganisms and probiotics with enhanced functionality and safety. Hidalgo-Cantabrana et al. [247] reported the possibility of using CRISPR-based technologies in LAB. Genetic engineering is a crucial tool for efficiently obtaining LAB in a short duration and accomplishing targeted bioprocesses for LA production.

3. Recovery Processes of Lactic Acid

After the fermentation process is completed, the process of harvesting the cells and recovering the products from the fermentation broth is known as downstream processing. In the case of LA recovery, a considerable amount of information in the form of a research investigation is available to identify an effective purification method. Although several methods are available, four different separation and purification methods, precipitation, solvent extraction, adsorption, and membrane separation, have been extensively investigated for LA recovery from fermentation broth.

Precipitation is the most common and conventional method. In this method, calcium hydroxide or calcium carbonate is added to the medium before fermentation to neutralize the acid produced. This process generates a calcium salt of the acid, calcium lactate, which is treated with concentrated sulfuric acid to precipitate calcium sulfate (gypsum). In the next step, the gypsum is filtered, and the filtrate, containing free LA, is evaporated to obtain pure LA. In this method, one can achieve only 22–44% pure LA, which can be utilized for technical purposes. Purity can be increased by esterification of technical-grade LA with methanol or ethanol [14]. Utilization of zinc sulfate or zinc carbonate increases the purity, and zinc lactate is precipitated as zinc sulfide with hydrogen sulfide. Zinc salt is the most preferable for this process because it exhibits better crystallization properties than any other lactate [248]. Limited information is available on industrial processes for LA recovery. Ecochem Inc. (League City, TX, USA) developed a process that produces ammonium salt instead of calcium salt as a by-product of recovery. Cargill (Minneapolis, MN, USA) has reported an alternative method, in which sodium carbonate was used as a neutralizing agent and sodium lactate was extracted with a tertiary amine solvent mixture under CO_2. The amine LA was reverse-extracted with hot water to produce high-purity LA [14].

Solvent extraction is an alternative and efficient recovery method, in which solutes are recovered from the liquid mixture liquids by transferring solute(s) to an extracting solvent through an immiscible phase. The main factors affecting the extraction are the

distribution coefficients, selection of a specific solvent for extraction, and easy separation of the liquid phase [249]. An ideal solvent must have high specificity, stability, referability, low toxicity, low corrosiveness, and low viscosity. Extractants are classified into three types. Hydrocarbons, such as octanol and methyl isobutyl ketone (MIBK), are widely used for LA extraction. The main disadvantage of hydrocarbons is their low distribution coefficient. Ethyl ether has the highest selectivity, followed by ethyl acetate, hexanol, isoamyl alcohol, and furfural. Phosphorus-bonded solvents such as tributyl phosphate are used for LA extraction; however, they do not provide efficient extraction because of their low distribution coefficient. High-molecular-weight aliphatic amines such as dodecyl amine are very efficient for LA extraction because of their high distribution coefficient.

In recent years, functionalized compounds have been developed for improving the extraction efficiency [250]. The prepared nitrogen-based functional molecules, such as silica compounds with double bonds between nitrogen and carbon, exhibited the highest distribution coefficients for LA extraction. Although solvent extraction is popular, it requires more area to exchange the solute from the fermentation broth. The high cost and toxicity of the solvents towards microorganisms limit their use in in situ extraction processes.

Membrane-based separation processes provide more flexibility in the scale of production, depending on market demand. Owing to their high selectivity, these membranes can guarantee efficient separation and purification. Membrane separation can be combined with currently used fermenters, permitting simultaneous production and purification in a single piece of equipment. This reduces the need for separate purification installations and results in a simple design with reduced capital costs. Here, no phase change is involved, which reduces energy consumption [155]. Membranes that can play an effective role in the separation of this process are microfiltration, ultrafiltration, nanofiltration, reverse osmosis, and electrodialysis membranes. The process is an environmentally benign, simple, economically viable, and continuous manufacturing scheme capable of producing monomer-grade LA with high productivity. Microbial cells and proteins can quickly foul all membranes; however, the extent of fouling may be far less during microfiltration. However, membranes used in certain modules may be operated for a long time without significant fouling [14].

Distillation is the oldest and primary process in chemical industries, and separation occurs according to the differences in the boiling points of the component. However, the conventional distillation process under ordinary heat and pressure is inefficient for separating LA from the crude acidified broth [84]. Hybrid distillation methods, such as reactive distillation and molecular distillation, have been developed as alternatives to conventional processes, where they combine absorption, extraction, reaction, and other purification methods. In reactive distillation, crude LA is first converted to esters and then hydrolyzed to obtain a pure product. In principle, molecular distillation separates products by diffusional mass transfer of homogeneous liquid mixtures with low volatility, high molecular mass, and thermal sensitivity. In this special type of evaporation, gaseous molecules do not return to the liquid phase (no vapor–liquid equilibrium), and it is achieved by installing a hot evaporation surface and cold condensation surface side by side [84]. In recent years, multiple investigations have been reported on the recovery of highly pure L-LA (95–97% purity and 70–85% yield) through molecular distillation [251–253].

4. Applications of Lactic Acid

LA is a GRAS chemical with several potential applications in various industries such as the chemical, food, pharmaceutical, and cosmetic industries. Prospective applications of LA are shown in Figure 2.
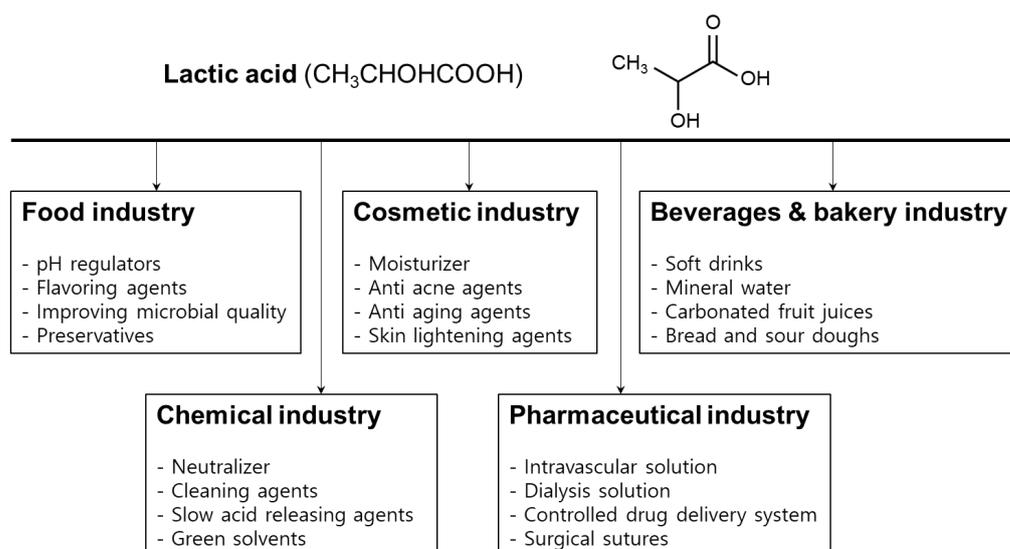
Lactic acid (CH₃CHOHCOOH)

Food industry

- pH regulators
- Flavoring agents
- Improving microbial quality
- Preservatives

Cosmetic industry

- Moisturizer
- Anti acne agents
- Anti aging agents
- Skin lightening agents

Beverages & bakery industry

- Soft drinks
- Mineral water
- Carbonated fruit juices
- Bread and sour doughs

Chemical industry

- Neutralizer
- Cleaning agents
- Slow acid releasing agents
- Green solvents

Pharmaceutical industry

- Intravascular solution
- Dialysis solution
- Controlled drug delivery system
- Surgical sutures

Figure 2. Prospective applications of lactic acid in different industries.

Due to its numerous functions, LA is extensively used in all areas of the food industry. Approximately 85% of LA produced is utilized in the food and food-related sectors. LA occurs naturally in many food products and acts as an acidulant, flavor, preservative, and pH regulator for a long period. It is additionally used in combination with acetic acid for improving bactericidal activity. Calcium lactate, a calcium salt of LA, has greater solubility than the corresponding salt of citric acid, and this solubility decreases the turbidity caused by calcium. Owing to the mild acidic taste of LA, it is also used as an acidulant in salads and dressings, baked goods, pickled vegetables, and beverages. Calcium lactate has high salt capability and has been used for fruit and vegetable canning. LA also plays a major role in mineral fortification of food products. In the meat industry, LA is predominantly used for inhibiting food pathogens and increasing the shelf life of meat. The addition of lactic acid reduces water activity and improves the shelf life against the food-borne pathogen *C. botulinum*.

In confectioneries, LA is used for balancing the flavor and pH of the cooked mix. As it is a better acidulant than citric acid, it is mainly utilized as an acidulant in the confectionery industry. Its use decreases the inversion of sugars during hard boiling. Compared with citric acid, which provides an initial burst of flavor and tanginess, LA imparts a mellower and lasting sourness and better enhances the flavor. It is used in high boiled sweets (such as bonbons) for preparing perfectly clear sweets with less sugar inversion and low air trapping.

LA is used as an acidulant and pH regulator in soft drinks and fruit juices. Its usage enhances the natural flavor and taste and imparts a lingering taste to the beverages. Therefore, LA is preferred over citric acid for the production of soft drinks, mineral water, and carbonated fruit juices. In beer and wine, LA is used for adjusting the pH and enhancing shelf life by killing unwanted microorganisms.

LA is used in the preparation of certain types of breads, sourdoughs, and fermented dough. Its application improves the loaf of bread, and LA fermentation enhances crust color. Supplementation with LA increases the shelf life of bakery products as it inhibits the development of rope and molds. Sodium and calcium stearoyl lactates are employed as emulsifiers in the baking industry because they improve the product quality and shorten the baking process. These stearoyl lactates are good conditioners and emulsifiers for yeast-leavened bakery products. Additionally, they are used for butter stability and replacement of egg albumin.

LA is generally used as a moisturizer, pH regulator, and skin lightening agent, and it exerts an antimicrobial effect. LA has a water-retaining capacity; hence, it is widely used in cosmetic creams. LA inhibits skin darkening by inhibiting tyrosinase activity. It is used as

an alternative to glycolic acid, an antiaging compound, which softens lines and reduces sun damage. LA increases sensitivity to UV; hence, precautions need to be taken during supplementation in cosmetic creams.

LA has been included in the US DOE's list of top 15 chemicals because of its numerous applications. It can be used for producing different products using similar technologies; hence, it is a favorite portfolio molecule. Chemically, LA is a highly oxidized molecule with high reactivity and low energy density, making it a suitable precursor for various chemicals. Dehydration of LA (combined with other reactions) produces molecules such as acetaldehyde, acrylic acid, 2,3-pentanedione, and propionic acid, whereas esterification results in the synthesis of alkyl lactates, lactide, and PLA. The reduction and oxidation of lactic acid yield 1,2-propanediol and pyruvic acid, respectively. In several reactions (Figure 3), LA esters can be used as precursors; they often deliver higher yields of the desired product. Catalytic upgrading of LA is a complex pathway. It proceeds via propionic acid and acetaldehyde to yield C_5-C_7 ketones. LA conversion products procured in the organic fraction are considerably less oxidized, and they have higher caloric values. Therefore, they are suitable for use as fuel.

LA is employed in various pharmaceutical formulations, especially in topical ointments, lotions, antiacne solutions, humectants, parental solutions, dialysis applications, and anticaries agents. Additionally, LA is used as an electrolyte in many intravenous fluids for restoring body fluids and in electrolyte solutions and as a dialysis solution in conventional artificial kidney machines. Furthermore, LA is widely used in various mineral preparations such as tablets, prostheses, and surgical sutures. The calcium salt of LA is extensively used for calcium deficiency and as an anticaries agent in dental treatment. Drugs with an LA base exhibit antitumor and antimicrobial activities. LA is used in preparations of sanitizers and for the treatment of dermatological problems such as warts [254].

Another important application of LA in the chemical industry is in the production of polylactic acid (PLA), a base compound for biodegradable plastics. Optically pure LA can be polymerized into high-molecular-mass PLA through a series of reactions, including polycondensation, depolymerization, and ring-opening polymerization. PLA has a wide range of uses such as protective clothing, food packaging, mulch film, trash bags, rigid containers, shrink wrap, and short shelf-life trays [255,256]. In agriculture, PLA is used as a carrier for herbicides and pesticides released into the soil. This is very useful for controlled release of pesticides, depending on the severity of infestation and plant stage [257,258].
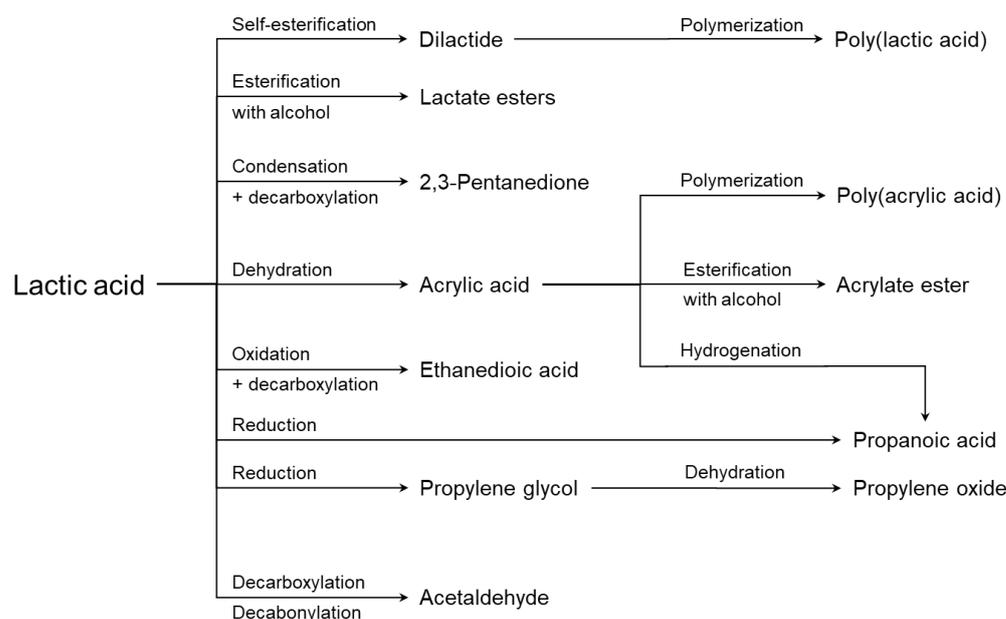

Figure 3. Lactic acid as a precursor molecule for the synthesis of industrially important chemicals.

Low-molecular-weight PLA is used for the preparation of microspheres, microcapsules, pellets, or tablets for controlled drug release systems. In this procedure, drugs are prepared in a polymeric device (PLA), and drug release is regulated by either diffusion through the polymer barrier or erosion of the polymer matrix [259]. The natural degrading property of PLA is advantageous over other polymers such as polyethylene and silicon rubber, as they require surgical recovery. PLA introduced into the body is easily degraded by non-enzymatic hydrolysis to LA, which can be metabolized by the human body [254,260].

L-LA is used as an acidulant in leather tanning industries and for pH adjustment in hardening baths for cellophanes used in food packaging, terminating agents for phenol formaldehyde resins, alkyl resin modifiers, solder flux, lithographic and textile printing developers, adhesive formulations, electroplating and electropolishing baths, and detergent builders. It is additionally used as an adhesive for the lamination and extraction of gelatin from fish waste [261].

Due to its descaling properties, LA is used as a decalcifier in toilets and bathrooms. Lactate esters, such as ethyl or methyl lactate, are used for degreasing. LA is used in the Ni plating process because of its unique complexing constant for Ni. LA is used as a neutralizer in the production of certain types of surfactants used in special detergents and personal care products [262]. Recently, PLA has been used as an easy material to print. PLA's popularity in 3D printing stems from its incredible printability and versatility. Especially in recent years, PLA has become more and more widespread in the biomedical field such in as scaffolds for tissue engineering [263].

5. Future Prospects

The novel and commercially implemented usage of LA as a green solvent and as a monomer in biodegradable polyesters necessitates the availability of cheaper LA. In particular, for PLA, both the L and D enantiomeric forms should be equally available at low prices. Furthermore, LA can be easily converted into useful intermediates such as acrylic acid, propylene glycol, and 2,3-pentanedione, and it even holds promise in catalytic upgrading to higher-carbon-number molecules and fuel precursors through heterogeneous catalysis, indicating further novel applications. Fermentation is an appropriate method for large-scale LA production; however, sustainability issues with regard to feedstock cost, separation, purification, and gypsum co-production rise with increasing demand. Nevertheless, LA produced by the fermentation process is not very profitable because of the high cost of hydrolytic enzymes for the saccharification of cellulose and hemicellulose and the separation process. To address this problem, more efficient microbes that utilize lignocellulosic biomass need to be applied and viable separation technologies need to be developed for increasing the potential of LA. To enable such developments, more advanced genome editing tools need to be developed for a wider range of LAB strains. This includes making more strains genetically accessible for transformation and establishing recombineering and CRISPR/Cas-based methods, including multiplex genome editing and silencing. The ever-increasing interest in LAB and advances in genome editing and biotechnological developments will undoubtedly provide breakthrough solutions for innovations in the wide and ever-expanding applications of LAB.

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