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Review

Engineered Microbial Cell Factories for Sustainable Production of L-Lactic Acid: A Critical Review

Tiantian Liu [1,2], Xianhao Xu [1,2], Yanfeng Liu [1,2], Jianghua Li [1,2], Guocheng Du [1,2], Xueqin Lv [1,2,*] and Long Liu [1,2]

[1] Key Laboratory of Carbohydrate Chemistry and Biotechnology, Ministry of Education, Jiangnan University, Wuxi 214122, China; liutiantian@jiangnan.edu.cn (T.L.); xianhaoxu@jiangnan.edu.cn (X.X.); yanfengliu@jiangnan.edu.cn (Y.L.); lijianghua@jiangnan.edu.cn (J.L.); gcdu@jiangnan.edu.cn (G.D.); longliu@jiangnan.edu.cn (L.L.)

[2] Science Center for Future Foods, Jiangnan University, Wuxi 214122, China

* Correspondence: lvxueqin@jiangnan.edu.cn; Tel./Fax: +86-0510-85918312

Abstract: With the increasing demand for the biodegradable polymer material polylactic acid and its advantage of being metabolized by the human body, L-lactic acid (L-LA) is becoming increasingly attractive in environmental protection and food industry applications. However, the supply of L-LA is not satisfied, and the price is still high. Compared to enzymatic and chemical synthesis methods, L-LA production by microbial fermentation has the advantages of low cost, large yield, simple operation, and environmental protection. This review summarizes the advances in engineering microbial cell factories to produce L-LA. First, the synthetic pathways and microorganisms for L-LA production are outlined. Then, the metabolic engineering strategies for constructing cell factories to overproduce L-LA are summarized and fermentation modes for L-LA production are also given. Finally, the challenges and prospects of the microbial production of L-LA are discussed. This review provides theoretical guidance for researchers engaged in L-LA production.

Keywords: L-lactic acid; microbial fermentation; metabolic engineering; process optimization

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1. Introduction

Lactic acid (Lac; $CH_3CHCOOH$), one of the three major organic acids, exists in nature in three forms due to its optical isomerism: D-Lac, L-Lac, and DL-Lac [1]. Lac is widely used in food, medicine, cosmetics, tobacco and chemical industries [2]. Since humans and animals can only metabolize L-lac enzymes, D-lac cannot be absorbed. The excessive intake of D-lac or DL-lac will lead to the accumulation of D-lac in blood, which may cause fatigue, metabolic disorders, and even acidosis [3]. The World Health Organization advocates the use of L-lac as a food additive and oral medicine. L-Lac (L-LA) is used in the food industry as a sourness agent, preservative, and food fortifier [4]. L-LA also enhances human physiology and improves immunity in medicine [5]. In recent years, a variety of L-LA-derived products have been put on the market for the medical industry, such as surgical sutures, drug-controlled release preparations, and fracture internal fixation materials [6,7]. L-LA has also made important contributions to the field of environmental protection, as it can be used in the production of the green solvent L-methyl lactate, L-ethyl lactate, and the biodegradable plastic polylactic acid (PLA) [8,9]. With increasingly serious environmental problems, the demand for degradable plastics is increasing at a compound annual growth rate of 33% [10]. In addition, the precursors of PLA synthesis must be Lac monomers with high optical purity. Therefore, it is of great significance to improve the production capacity and reduce the production costs of L-LA.

The production strategies of L-LA include chemical synthesis, enzyme transformation, and microbial fermentation. The Monsanto Company of the United States first developed the chemical synthesis approach to synthesize L-LA using acetaldehyde and hydrocyanic

acid as substrates [11]. However, this production pipeline generates serious pollution, high costs, and it is difficult to synthesize L-LA by a single configuration. Meanwhile, there are many inevitable by-products and residual harmful intermediates which can pose serious safety risks if consumed by humans. L-LA production by enzymatic catalysis takes pyruvate (Pyr) or 2-chloropropionic acid as a substrate, catalyzed by high-specific lactate dehydrogenase (LDH) or L-2-halogenate enzyme. In this way, single optical rotation L-LA could be obtained. However, due to the complex transformation conditions, enzymatic catalysis has the disadvantages of low yield and high costs, and therefore is rarely used in industrial applications [12]. Compared to chemical and enzymatic synthesis, L-LA bioproduction by microbial fermentation meets the needs of industrial mass production and reduces the production costs due to cheap biomass resources. Furthermore, L-LA production with high optical purity can be realized using engineered microorganisms. Therefore, microbial fermentation has become the main route for L-LA production.

At present, the global L-LA market demand is increasing by 10% annually, and the production of L-LA by microorganisms has become the mainstream. How to produce high-quality L-LA under the premise of environmental protection and economic growth remains a topic of concern. In recent years, many microbial fermentation methods for L-LA production have emerged, but a relevant review of these is lacking. This review thus aims to summarize the recent advances in L-LA bioproduction, mainly focusing on the synthetic pathways and microorganisms for L-LA production, metabolic engineering strategies for constructing cell factories to overproduce L-LA, and fermentation modes for L-LA production. This review also discusses the challenges for L-LA production and will hopefully guide biological engineers working in L-LA production and applications.

2. Synthetic Pathways and Microorganisms for L-LA Production

2.1. Biosynthetic Pathway of L-LA

Different microorganisms have different enzyme systems, which means that they have different Lac fermentation mechanisms. The L-LA anabolic pathway can be divided into four types as follows.

2.1.1. Homolactic Fermentation

Homotype Lac fermentation refers to glucose (Glu) assimilation by microorganisms through the Embden–Meyerhof–Parnas (EMP) pathway (Figure 1A). Glu is degraded into Pyr through the EMP pathway, and Pyr is reduced to Lac under the catalysis of LDH. Then, 1 mol Glu can generate 2 mol Lac, and its theoretical conversion rate is 100%. However, owing to a series of other physiological activities in microorganisms during fermentation, the actual conversion rate of homotype fermentation is considered >80% [11]. *Streptococcus*, *Diplococcus*, *Small coccus* and a part of *Lactobacillus* all belong to this fermentation type. The general reaction formula is as follows:

$$C_6H_{12}O_6 + 2\ ADP + 2\ Pi \rightarrow 2\ CH_3CH(OH)COOH + 2\ ATP \quad (1)$$

2.1.2. Heterolactic Fermentation

Some Lac bacteria (LAB) can synthesize Lac via the hexose monophosphate pathway (Figure 1B), namely heterolactic fermentation. These LAB can decompose Glu into phosphate-5-ribulose, which is converted into phosphate-5-xylulose (X5P) by epimerase and catalyzed by phosphoketolase (PK) to generate glyceraldehyde-3-phosphate (G3P) and acetyl phosphate (AP). AP is further reduced to ethanol (ET) and phosphoric acid. G3P is reduced to Lac after a series of reactions, with the accompanied generation of ET, CO_2, and ATP, so the actual conversion rate of heterolactic fermentation is only 50%. The strains that undergo heterolactic fermentation include *Candida intestinalis*, *Lactobacillus brevis*, and *Bifidobacteria*. The general reaction formula is as follows:

$$C_6H_{12}O_6 + ADP + Pi \rightarrow CH_3CH(OH)COOH + CH_3CH_2OH + CO_2 + ATP \quad (2)$$

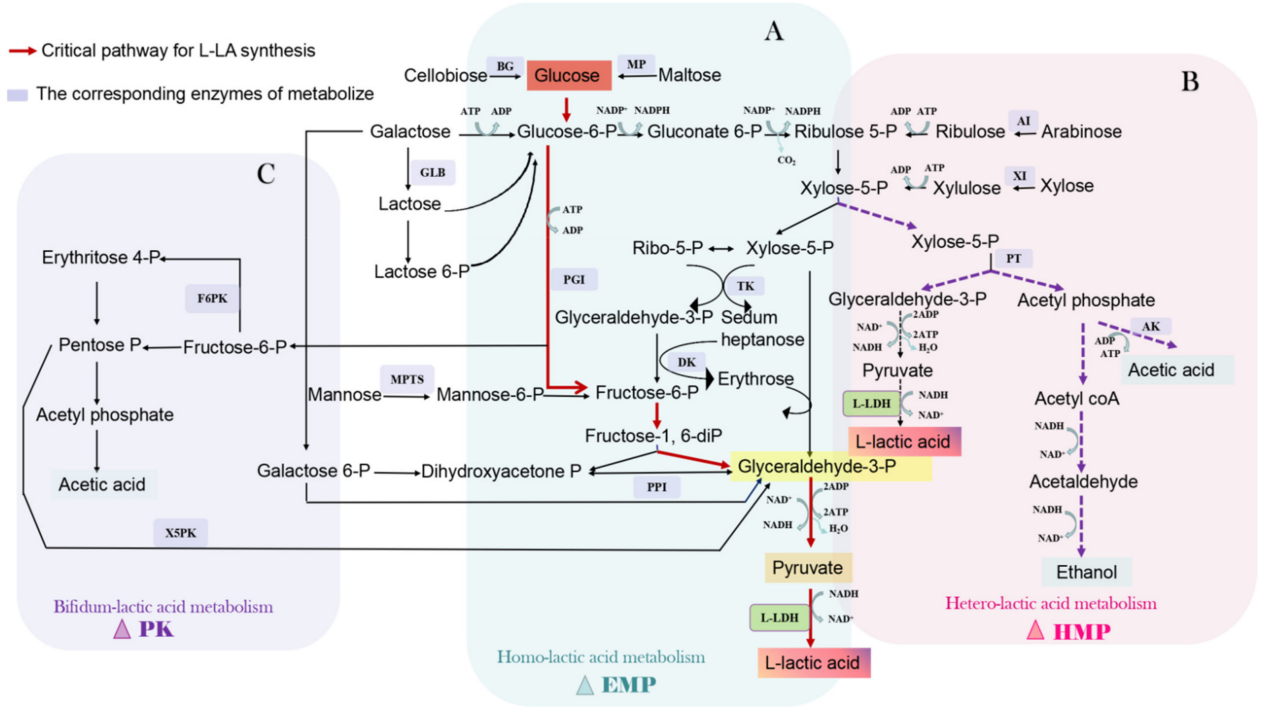

Figure 1. Biosynthesis pathway of L-LA. BG, β-1,4-glucanase; MP, maltose phosphorylase; GLB, β-galactoenzyme; AI, arabinose isomerase; XI, xylose isomerase; TK, transketolase; DK, dihydroxyacetone kinase; PT, phosphotransferase; AK, acetate kinase; PPI, propanose phosphate isomerase; PGI, phosphoglucose isomerase; MPTS, mannose phosphotransferase system; F6PK, F6P ketolyase; X5PK, xylukelose 5-phosphate ketolyase.

2.1.3. Bifidobacterium Fermentation

Bifidobacterium cannot utilize Glu via the EMP pathway because it lacks aldolase and Glu-6-phosphate dehydrogenase. Instead, Lac is produced through the PK pathway (Figure 1C), accompanied by acetic acid formation. There are two PKs involved in this pathway: (1) phospho-6-fructose ketolase, which decomposes fructose-6-phosphate (F6P) into acetic acid phosphate and erythritol-4-phosphate; and (2) phosphate-5-xylose ketolase, which decomposes X5P into G3P and AP. G3P forms Lac under the action of G3P and LDH with a conversion rate of 50%. The general reaction formula is as follows:

$$2\,C_6H_{12}O_6 \rightarrow 2\,CH_3CH(OH)COOH + 3\,CH_3OOH \quad (3)$$

2.2. Strains for L-LA Production

The natural producers of L-LA mainly include Lactobacillus [13] (e.g., Lactobacillus rhamnosus, Lactobacillus delbrueckii, and Lactobacillus casei), Rhizopus [14–16] (Rhizopus nigricans, Rhizopus oryzae, Rhizopus chinensis, etc.), Streptococcus [17], and Bacillus [18]. The production of L-LA by Lactobacillus belongs to anaerobic fermentation or facultative anaerobic fermentation, which can greatly decrease the energy consumption and facilitate continuous fermentation to reduce the production cost. The actual conversion rate of Lactobacillus homotype fermentation is above 90%. Nevertheless, Lactobacillus are chemotrophic heterotrophic microorganisms with complex nutritional conditions and which require intricate nitrogen sources and increasing costs. General Lactobacillus does not produce amylase, and cannot directly use starch to produce L-LA, which needs saccharification treatment [19]. The nutritional requirements of the L-LA fermentation of Rhizopus oryzae are elementary, and the starch can be directly utilized without saccharification. Meanwhile, Rhizopus oryzae has the advantages of a low pH tolerance, a product with high optical purity, large bacteria size, and being convenient for purifying the product. Nonetheless, the yield and conversion rate of L-LA by Rhizopus oryzae were lower than

those of lactic acid bacteria. In addition, Rhizopus oryzae requires ventilation and agitation during fermentation, thereby increasing the production costs [20]. Their fermentation conditions, LA titers, and advantages are summarized in Table 1. Among them, L. rhamnosus CGMCC No. 2183 could produce 235 g/L L-LA, the yield was 94.5–96.5%, and the optical purity was 98% [21]. Tsuneo et al. [22] used immobilized R. oryzae to produce L-LA, and the titer was 321 g/L.

Table 1. Microbial strains producing L-LA.

Strains	Fermentation Temperature (°C)	Raw Materials	L-LA (g/L)	Characteristic	Reference
LAB genera				Heterotrophic anaerobic type	
L. casei, L. plantarum	28–32	Sucrose	175.8	Facultative anaerobic; no need for ventilation; energy-saving economy; a variety of biological resources	[23]
Lactobacillus pentosus	30–32	Glu	108.1		[24]
Lactobacillus xylose	30–40	Xylose	40.3		[25]
Lactobacillus sake, Lactobacillus acidophilus, Lactobacillus amyloidus	35–38	Brewers' spent grain	22.1		[26]
Lactococcus lactis	36–45	Xylose	58.3		[27]
L. thermophilus	50–60	Glu	97.5		[28]
Rhizopus				Aerobic	
Rhizopus nigra, Aspergillus triticum, R. chinensis, Rhizopus sweet potato, R. oryzae, Rhizopus tuberosus, Rhizopus japonica, Rhizopus paucus, Rhizopus meilis	30	Paper sludge; rice straw	88.9	Abundant biomass resources	[29,30]
Streptococcus				Microanaerobic	
Streptococcus thermophilus, Streptococcus lactobacillus, Streptococcus salivary	40–45	Glu, fructose	49.9	Has a certain tolerance	[31]
Bacillus				Facultative and anaerobic	
B. coagulans	50–60	Lignocellulose	55.9	High optical purity and conversion rate	[32–35]
Thermophilic adipose bacillus	55–60	Oil palm empty fruit bunch	105.4		

High-throughput screening or adaptive evolution is usually required to obtain high-producing strains with high L-LA production, which are time-consuming and inefficient. With the advent of genetic engineering technology, microbial production is no longer limited by natural variation and screening, and genetic engineering can modify the metabolic network of the strain to efficiently increase L-LA production. The model microorganisms *Escherichia coli* and *Saccharomyces cerevisiae* are the most commonly used cell factories for L-LA production because of their clear genetic background, simple genetic manipulation methods, and easy high-density fermentation. Compared to *E. coli*, *S. cerevisiae* is more tolerant to low pH [36], making *S. cerevisiae* more suitable for organic acid production. Meanwhile, pH < 3.0 can effectively avoid bacterial contamination during the fermentation process. Therefore, S. cerevisiae has unique advantages in L-LA production. Colombié et al. [37] increased the L-LA titer to 50 g/L by integrating the *LDH* gene from *Lactobacillus plantarum* into the genome of *S. cerevisiae*. Novy et al. [38] integrated the *pfLDH* gene (encoding L-LA dehydrogenase) from *Plasmodium falciparum* into the genome of *S. cerevisiae*, yielding strain IBB14LA1-5. The L-LA productivity in strain IBB14LA1-5 could reach 1.8 g/L/h under microaerophilic conditions.

Compared to *S. cerevisiae*, *E. coli* has the advantages of fast growth, simple nutritional requirements, and a high optical purity of Lac products [39]. Therefore, many studies have focused on engineering *E. coli* for the efficient biosynthesis of L-LA. By screening the *LDH* gene from different sources, modifying the metabolic network of L-LA, and optimizing the fermentation conditions, the L-LA titer in *E. coli* could reach 142.2 g/L [40].

In addition to the selection of strains, the study on strain improvement through mutation and the construction of L-LA high-yield strains by metabolic engineering has become a research hotspot, one that is mainly focused on the following aspects.

3. Metabolic Engineering Strategies for Improving L-LA Production

3.1. Mutation Breeding

Mutagenesis technologies can be physical (infrared ray, X-ray, gamma-ray, fast neutron, ion beam, laser, ultraviolet (UV) irradiation, and ultrasonic wave) or chemical (base analogs, alkylating agents, deamination, frameshifts mutagens, hydroxylating agents, and metal salts). Le et al. [41] screened an L-LA high-yield mutant YBQH2-14 using UV mutagenesis, whose L-LA titer reached 93 g/L and the sugar conversion rate reached 77.5%. Gu et al. [42] mutated the original strain *R. oryzae* PW352 using ion beam mutagenesis and obtained a mutant strain RE3303. Its L-LA titer increased by 48.5% compared to the original strain and reached 140 g/L, and the conversion rate was 86%. Xian et al. [43] used *L. casei* ZW-63A as the original strain and obtained the mutant strain CGMCC No. 8029 using UV mutagenesis and diethyl sulfate mutagenesis. The L-LA titer in strain CGMCC No. 8029 reached 140 g/L, and the optical purity of L-LA reached 98.83%. Jiang et al. [44] performed a highly efficient heavy ion mutagenesis technique to improve the L-LA titer of the strain *Lactobacillus thermophilus* SRZ50. Based on the microtiter plate screening method, the mutant strain A69 was screened, and A69 could synthesize 114.2 g/L L-LA at 96 h in fed-batch fermentation compared to the original strain which increased by 16.2%. In summary, high-throughput screening-assisted mutation breeding is an effective strategy for obtaining high-yield LA strains.

3.2. Strain Improvement by Metabolic Engineering

3.2.1. Expression of Exogenous L-LA Dehydrogenase

Because some strains lack the L-LA biosynthetic pathway, it is necessary to express L-LA dehydrogenase heterologously in their cells. Ishida et al. [45] found that bovine-derived *LDH* was more suitable for producing L-LA in *S. cerevisiae* and integrated four or six copies of exogenous *LDH* into the genome, respectively. Their results showed that the L-LA titer was positively correlated with the copy number of *LDH*, indicating that the expression level or catalysis efficiency of *LDH* was a bottleneck for the efficient synthesis of L-LA. Kong et al. [46] found that the *LDH*s from *P. falciparum* and *Bacillus subtilis* were more efficient for L-LA production in *Kluyveromyces marxianus*. By overexpressing the proton-coupled monocarboxylate transporter from *S. cerevisiae*, native 6-phosphofructokinase, and disrupting the native putative *D-LDH*, the L-LA titer in strain *K. marxianus* increased to 103 g/L. Moreover, with the development of synthetic biology tools and strategies, some gene expression elements or methods can be applied to increase the expression level and catalysis efficiency of *LDH*. Redden et al. [47] adapted the 655 bp natural promoter PGPD into 116 bp in yeast according to the structural composition of the promoter and combined it with the 47 bp minimum terminator assembly as an expression vector, which could reduce the load regulation amount on DNA by 80–90%. Flagfeldt et al. [48] characterized the expression level of the heterologous gene *lacZ* (encodes β-half-lactosidase) in 20 different integration sites of the *S. cerevisiae* genome. The expression levels of *LacZ* in different loci were significantly different. Reider et al. [49] employed clustered regularly interspaced short palindromic repeats (CRISPR)-CRISPR-associated protein 9 (Cas9) technology to build a cloning-free toolkit in *S. cerevisiae*, including 23 Cas9-sgRNA plasmids, 37 promoters with various strengths and temporal expression profiles, and 10 protein-localization, degradation, and solubility tags.

3.2.2. Pyr Metabolic Pathway

In general, engineered strains should choose the homotype fermentation pathway to produce L-LA owing to its theoretical conversion rate of 100%. Therefore, promoting the accumulation of the precursor Pyr is a critical step in L-LA synthesis. To increase the accumulation of Pyr, it is necessary to weaken the branching pathway of the EMP pathway and reduce the generation of by-products, including ethanol and glycerin (Figure 2).

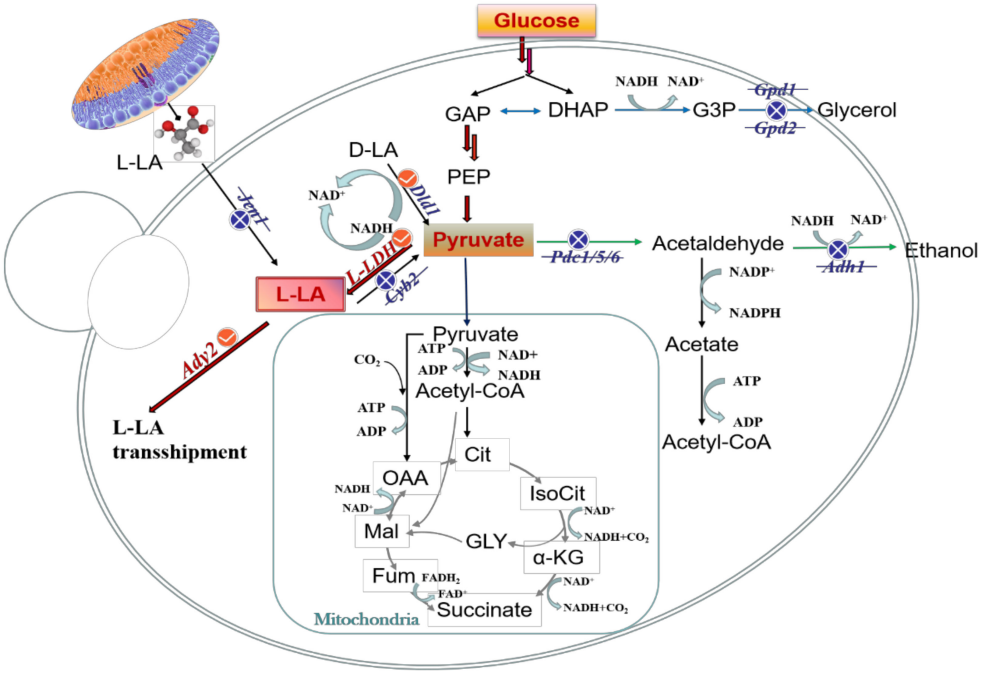

Figure 2. Metabolic regulation strategies map of L-LA. The red line is the L-LA synthesis pathway. The blue line is the by-product glycerol synthesis pathway. The green line is the by-product ethanol synthesis pathway. The blue cross line indicates the blocking pathway. The red checkmark represents the overexpression pathway. GAP, phosphoglyceraldehyde; DHAP, dihydroxyacetone phosphate; Cit, citric acid; IsoCit, isocitrate; α-KG, α-ketoglutaric acid; Fum, fumaric acid; Mal, malic acid. *Gpd1/2*, glycerol-3-phosphate dehydrogenase 1/2; L-LDH, L-lactate dehydrogenase (exogenous gene); Cyb2, lactate dehydrogenase (cytochrome); *Pdc1/5/6*, indole pyruvate decarboxylase 1/5/6; ACS, acetyl-CoA synthetase; *Jen1*, carboxyl transporter Jen1p; *Ady2*, accumulation of dyads protein 2, transporter protein required for ammonia export and acetate uptake and resistance.

The key regulatory enzyme of ethanol synthesis is Pyr decarboxylase (Pdc). *Pdc*1, *Pdc*5, and *Pdc*6 are the most frequently disrupted enzymes in L-LA production. Nobuhiro et al. [50] knocked out *Pdc*1 and inserted double copies of *LDH* into the genome of *S. cerevisiae*, resulting in an L-LA titer increase to 55.6 g/L. They further knocked out *Pdc*5, the L-LA titer increased to 82.3 g/L, and the by-product ET was completely eliminated. Alcohol dehydrogenase 1 (*Adh*1) is the isoenzyme in *S. cerevisiae* ET fermentation. Kenro et al. [51] replaced *Adh*1 with *LDH* by homologous recombination in *S. cerevisiae.* A recombinant strain AF297C with four copies of *LDH* and *Pdc*1 and Adh1 deletions was further constructed. The L-LA titer of AF297C reached 74.1 g/L, and the production of the by-product ET was reduced to 7 g/L. Mazumdar et al. [52] engineered *E. coli* to produce L-LA by replacing the native D-lactate-specific dehydrogenase with *Streptococcus bovis L-LDH*. Blocking the ET bypass pathways knocked out the ADH gene *adhA*. Then, the native aerobic *L-LDH lldD* was blocked to prevent the consumption of L-lactate. The engineered strain produced 50 g/L L-LA from 56 g/L crude glycerol at a yield of 93% of the theoretical maximum and with high optical purity (99.9%). In anaerobic fermentation, *S. cerevisiae* will consume excessive NADH through the glycerol synthesis pathway to maintain the balance of intracellular cofactors, but the synthesis and accumulation of the by-product

glycerol will lead to a decrease in the titer of the target product. To weaken competitive pathways and eliminate glycerol production, the glycerol triphosphate dehydrogenases *Gpd*1 and *Gpd*2 should be knocked out [53]. Table 2 summarizes the research status of L-LA production by genetically engineered strains and superiority strains in recent years.

Table 2. Research status of L-LA production by genetically engineered strains.

Strain	Carbon Source	Exogenous LDH Source	Genotype/Methods	L-LA (g/L)	Fermentation Time (h)	Reference
L. rhamnosus	Mixture of lignocellulosic biomass	-	SSF	61.74	44	[54]
B. coagulans	Papermill sludge	-	SCF	82.4	120	[55]
E. coli	Glu, xylose	-	Δ*ptsG*, Δ*mglB*	53.2	60	[56]
B. coagulans	Organic fraction of municipal solid waste	-	Monopolar electrodialysis membranes	61.1	36	[57]
Enterococcus faecium	GSW, corn steep liquor	-	CH_3COONa, $MgSO_4$,$MnSO_4$, K_2HPO_4, $CaCl_2$, and Tween 80	93.1	48	[58]
K. marxianus	Corncob	*P. falciparum*, *B. subtilis*	Overexpressing *PFK*, Δ*Dld1*	103.0	50	[46]
K. marxianus	Jerusalem artichoke tuber powder	*L. plantarum*	Δ*pdc1*, Δ*cyb2*, Δ*Dld1*	130.0	66	[59]
L. plantarum	Raw starch	-	Δ*ldhD*, Δ*larA-E*	87.0	72	[60]
K. marxianus	Glu	*Staphylococcus epidermidis*, *L. acidophilus*, *Bos taurus*	*LaLDH* is coexpressed with SeLDH	24.0	60	[61]
S. cerevisiae	Glu, xylose	*P. falciparum*	*LDH* insert Δ*pdc1*, Δ*pdc*5	50.0	140	[62]
Pichia pastoris	Glycerol	*B. taurus*	Expressing transporter PAS	47.0	105	[63]
S. cerevisiae	Cellobiose and xylose	*R. oryzae*	Expressing *cdt*-1, *gh1*-1, *XYL*1, *XYL*2, *XYL*3, *ldhA*	83.0	80	[64]
B. coagulans	Raw hemp hurd	-	Organosolv pretreatment and enzymatic hydrolysis	141	148	[65]
S. cerevisiae	Glu	Bovine	Δ*pdc1*, Δ*pdc*5	82.3	216	[50]
E. coli	Glu	*L. casei*, *S. bovis*, *B. coagulans*	Δ*ldh*A::*dif*l*ldD*::*Pldh-ldhBcoa*	142.2	40	[40]
B. coagulans	Glu, cane molasses	-	Cofeeding fermentation	168.3	100	[66]
R. oryzae	Glu	-	Immobilized in cubic particles	231.0	130	[22]
S. cerevisiae	Molasses, corn paste wastewater	*Lactobacillus helveticus*	*LDH* insert Δ*pdc1*	52.2	96	[67]
B. subtilis	Glu, corn syrup	-	Batch and fed-batch culture	183.2	96	[68]
S. cerevisiae	Glu	Bovine	Δ*pdc*1, regulatory cofactor	20.0	100	[69]
Candida magnolia	Glu	*R. oryzae*	pH 2.5	40.0	48	[70]
Candida utilis	Glu	*B. taurus*	Δ*pdc*1	103.3	33	[71]
Candida boidinii	Glu	Bovine	*LDH* insert Δ*pdc*1	85.9	48	[72]
L. rhamnosus	Glu	-	-	235	60	[18]
S. cerevisiae	Glu	Bovine	Δ*pdc*5, Δ*pdc*6	122.0	48	[73]

3.2.3. Cofactor Engineering Strategies

In metabolic engineering, cofactor imbalance or insufficient supply is also a key factor limiting product synthesis. The cofactor supply was mainly improved by balancing the cofactor supply and adjusting cofactor specificity [74]. Reducing the ratio of NADH/NAD^+ in the cytoplasm will facilitate the conversion of Glu into L-LA. Heux et al. [75] found that

the expression of the NADH oxidase under the control of a yeast promoter led to large decreases in the intracellular NADH concentration (five-fold) and NADH/NAD^+ ratio (six-fold). In addition, the ethanol, glycerol, succinate, and hydroxyglutarate yields were significantly reduced because of the lower NADH availability. Bhatt et al. [76] found that the mannitol added to the medium inhibited ethanol production by changing the ratio of NADH/NAD^+, thus increasing L-LA production. Cytoplasmic acetyl-CoA is a precursor of many metabolites in *S. cerevisiae*. Weakening the Pdc activity of *S. cerevisiae* will affect the supply of cytoplasm acetyl-CoA and cell growth [77]. Therefore, compensating the intermediate metabolites of acetyl-CoA could improve bacterial growth and L-LA synthesis. Lian et al. [78] introduced the exogenous synthesis pathway of acetyl-CoA to increase the acetyl-CoA content in the cytoplasm.

3.2.4. Intracellular and Extracellular Transport of L-LA

With the metabolic production of microorganisms, L-LA will be accumulated in cells. Promoting acid efflux and inhibiting acid influx can alleviate the growth inhibition caused by intracellular L-LA, thereby improving the L-LA titer. Acetate transmembrane transporter *ADY*2 and carboxylic acid transporter protein homolog *JEN*1 were the two major transporters responsible for LA assimilation in *S. cerevisiae*. Pacheco et al. [79] found that overexpressing *ADY*2 and *JEN*1 in *S. cerevisiae* increased the L-LA titer by 15%. Kok et al. discovered two novel LA transporter mutants using laboratory evolution, which could enhance the growth ability of the strain in the medium using LA as the sole carbon source. In addition, they found that the mutation sites of these two mutants are both located in the protein *ADY*2 (C755G/Leu219Val and C655G/Ala252Gly). However, the intracellular transport function of *JEN*1 was also found. Paiva et al. [80] found that when *JEN*1 was knocked out, the strain could not absorb LA, indicating that *JEN*1 was involved in the intracellular transport of LA in *S. cerevisiae*. In addition, Wakamatsu et al. [81] also confirmed that *JEN*1 was involved in the intracellular transport of LA. In the presence of Glu, the constitutive expression of *JEN*1 and *ADY*2 led to higher external LA concentrations. However, Glu deficiency would lead to the consumption of LA. Andrade et al. [82] found that excessive Glu could rapidly reduce the activity of *JEN*1, resulting in an irreversible loss of activity. Therefore, Glu concentration has a certain effect on transporters. Presently, only *JEN*1 and *ADY*2 are known as LA transporters in *S. cerevisiae*. At present, *ADY*2 is responsible for the extracellular transfer of LA, and *JEN*1 may be responsible for both intracellular and extracellular transfer according to reports, but other transporters might also be involved. The transport mechanism of L-LA still needs to be studied further.

3.2.5. Genome Editing Tools

Although many traditional metabolic engineering techniques have been applied in the construction of L-LA high-yielding strains, the efficiency of these modification methods has been low, limiting the further improvement of the L-LA titer. In recent years, many genome editing methods have been developed to efficiently modify multiple target genes in the genome, including the Cre-LoxP method, polymerase chain reaction-mediated gene traceless knockout technology, zinc finger nuclease technology (ZFNs), transcription activator effector nuclease, and CRISPR-CAS system [83]. Amanda et al. [49] constructed a cloning-free toolkit based on CRISPR-cas9 technology which could address common obstacles in metabolic engineering including select chromosome integration site, promoter strength, and protein location. Liu et al. [84] constructed an endogenous subtype II-A CRISPR-Cas system-based genome interference plasmids to exert high-efficiency markerless gene deletion, gene integration, and point mutation in *Pediococcus acidilactici*. Using this method, they found that the depletion of the native plasmids would increase cell growth, and the integration of an L-LDH gene into the genome would enhance cell growth and L-LA production.

4. Utilization of Raw Materials and Renewable Resources

Using waste and cheap raw materials including whey, molasses, starchy raw materials, and cellulose raw materials to produce L-LA not only reduces the costs, but also solves problems of waste treatment and pollution

4.1. Whey

Whey is a by-product of the dairy products processing industry. A kilogram of cheese products can produce 9 kg of whey, which is rich in nutrients, such as protein, carbohydrates, inorganic salts, and vitamins, and can promote the growth of many microorganisms [85]. Four acid-tolerant *Pedioccocus* spp. strains, previously isolated from sourdough medium, were screened for their ability to produce enantioselective lactic acid from cheese whey [86]. The results showed that the maximum L-LA production was 47.0–51.2 g/L. Turner et al. [87] expressed a cellodextrin transporter CDT-1 and a β-glucosidase GH1-1 from *Neurospora crassa* in *S. cerevisiae* to produce lactose. An LDH from *R. oryzae* was further expressed in the strain. The final strain could produce 23.77 g/L L-LA.

4.2. Molasses

Molasses is a by-product of the sugar industry, and 100 tons of sugarcane can produce 3–4 tons of molasses, and the same weight of sugar beet can produce 4–6 tons of molasses [88]. The main component of molasses is sucrose, but it also contains some Glu, fructose, and other water-soluble organic and inorganic substances. Xu et al. [67] applied a cane molasses/carbon sources cofeeding method to efficient L-LA production from cane molasses. After medium optimization, 168.3 g/L L-LA was synthesized by strain *Bacillus coagulans* H-1. Liu [89] optimized the L-LA fermentation conditions of strain *L. rhamnosus*, and 84.2 g/L L-LA was produced from sweet potato residue. Nurkhamidah et al. [90] produced 19.68 g/L L-LA from molasses using strain *L. delbrueckii* and *L. plantarum.*

4.3. Starch

Starch, including corn, corncob, sorghum, brown rice, and sweet potato, is economical for L-LA production. Trakarnpaiboon et al. [91] isolated the thermotolerant strain *Rhizopus microsporus* DMKU 33, which could produce 84 g/L L-LA from liquefied cassava starch at pH 5.5 in 3 days. L-LA production was further increased to 105 to 118 g/L with a yield of 0.93 g/g and productivity of 1.25 g/L/h in fed-batch fermentation. In addition, *R. oryzae* MTCC 8784 could produce 15.5 g/L L-LA using 30 g/L starch [92].

4.4. Other Wastes

In recent years, waste yeast from breweries [93], kitchen waste [94], distiller's grains [95], bran [96], bagasse [97], and straw [67] also have been used as raw materials for producing L-LA. Hu [98] analyzed the ability of *B. coagulans* LA204 to produce Lac from different straws and found that LA204 could effectively utilize Glu, xylose, and cellobiose generated from straw hydrolysis. Li et al. [99] reported a new strategy for the efficient production of optically pure L-LA from food waste (FW) at ambient temperature, i.e., by regulating key enzyme activity by sewage sludge supplement and intermittent alkaline fermentation. Ma et al. [100] investigated the effects of different lignocellulosic wastes on alleviating acidification in L-LA fermentation from FW. The results showed that pretreated spent mushroom substance was the best choice for FW cofermentation, and the maximum L-LA titer could reach 46.12 g/L.

To produce L-LA with cheap raw materials, mixed fermentation was also considered due to the complexity of substrate materials. As such, multiple substrates and even microbial interactions can also perform a promoting role and enhance fermentation efficiency. Mendes et al. discovered a complementary mechanism between *Lactobacillus* and *S. cerevisiae* in the mixed culture process. *S. cerevisiae* provided nutritional factors such as pyruvate, vitamins, and amino acids for *Lactobacillus*, while *Lactobacillus* provided an energy source for *S. cerevisiae* [101]. In the process of converting kitchen waste into L-LA,

open fermentation at room temperature (without disinfection and adding cultured strains) could produce a certain amount of lactic acid. Sakai et al. [102] studied the effect of pH adjustment on open fermentation to obtain a higher L-LA yield. The results revealed that lactic acid fermentation could be well sustained at pH 7.0. They subsequently discovered that constant pH control shortened the fermentation time but reduced the optical purity of L-LA. The induction of bacillus thermophilus growth and the change of pH from swing control to constant control showed the best effect, and the highest L-LA yield reached 39.2 g/L [103]. Policastro et al. [104] screened L-LA in mixed cultures by suddenly changing pH, and they found that the production of LA depended on *Bacillus* sp., *Cytobacillus* sp. and *Azospirillum* sp. by mixed microbial culture was screened by the pH oscillation biofortification technique.

5. Fermentation Modes for L-LA Production

Optimizing the L-LA fermentation process is an important method of reducing production costs. Because the strains and raw materials used for fermentation are different, the process is also varied (Figure 3). Therefore, it is crucial to choose a suitable fermentation process. To reduce the production costs of L-LA, various cheap raw materials are often used as fermentation materials. Simultaneous saccharification fermentation (SSF) could save energy and prevent the adverse effects of a high sugar concentration on fermentation strains. SSF mainly aims to produce L-LA from cellulose and starch as raw materials. In addition, in the L-LA fermentation process, the pH reduction caused by L-LA accumulation will gradually inhibit the growth of the strain. The traditional fermentation process requires the addition of neutralizing agents, making it difficult to extract L-LA in downstream processing. The methods of semicontinuous fermentation (SCF), continuous fermentation (CF), cell immobilization fermentation (CIF), and cell circular fermentation (CCF) can remove L-LA from the fermented liquid in time during the fermentation process, thereby reducing product inhibition and improving the utilization rate of raw materials and the product yield.

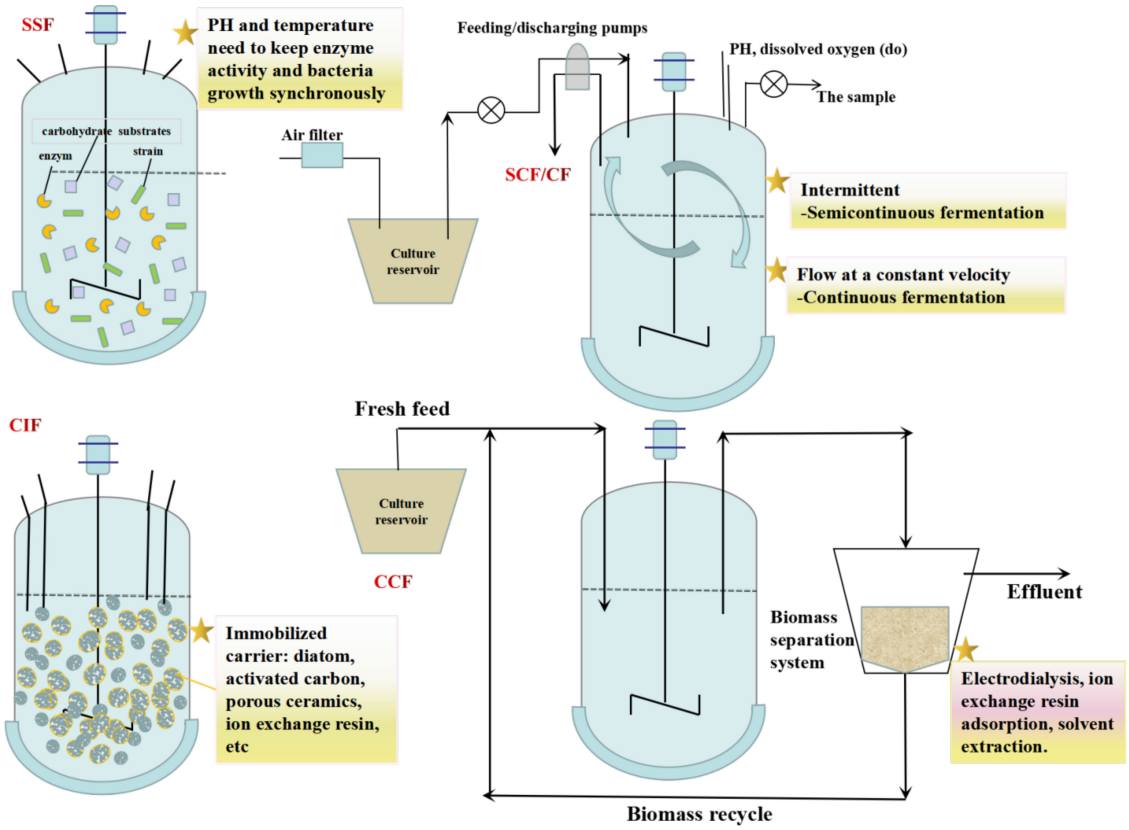

Figure 3. Fermentation modes for L-LA production.

5.1. SSF

SSF is a process in which enzymes and strains are added to the bioreactor at the same time and the enzyme-catalyzed hydrolysis of carbohydrate substrates and microbial fermentation are coupled into one step. Compared to traditional fermentation, SSF has the advantages of shortening the production cycle, saving equipment investment, improving the yield, and reducing energy consumption [105]. In recent years, SSF has been gradually used in the waste utilization fermentation process, which is helpful in increasing the yield and productivity of LA [15]. Li et al. [55] integrated the cellulase enzyme production into L-LA fermentation from papermill sludge, and the L-LA titer reached 25 g/L.

5.2. SCF/CF

Based on batch fermentation, SCF is the release of the part of the feed liquid which periodically contains products in the fermentation process and replenishes the same amount of new feed liquid. CF is the continuous release of the same amount of fermentation liquid at a certain speed to replenish the new feed liquid. Using the SCF/CF mode to produce L-LA not only makes the cell obtain a steady stream of new nutrition in the fermentation process, but also dilutes the growth-inhibiting substances generated by bacteria to ensure the high-quality growth and metabolism of bacteria. Liu [106] fermented *R. oryzae* for 15 batches using the SCF mode, and the average productivity of L-LA was 3.05 g/(L h), which was higher than that of batch fermentation (1.32 g/(L h)). Zhao et al. [107] immobilized *R. oryzae* with corncob and continuously fermented L-LA for six batches, which was 16 h shorter than the fermentation of inoculated spores. In addition, the L-LA titer reached 33.2 g/L, and the sugar conversion rate increased by 12% compared to that of pure sugar fermentation. Luongo et al. [108] investigated the fermentation performance of two reactors operating in a repeated-batch mode for semicontinuous L-LA production. The maximum L-LA concentration reached 20.1 g/L.

5.3. CIF

CIF is when cell particles or biological particles are confined to specific carriers by embedding technology which can retain their high biological activity and improve the acid production efficiency. The CIF mode can reduce the acid inhibition of the product L-LA and recycle the bacteria. Adsorption, covalent bonding, cross-linking, and embedding are the common methods for preparing immobilized cells. Radosavljevic et al. [109] studied the immobilization of *L. rhamnosus* ATCC7469 in a poly(vinyl alcohol)/calcium alginate matrix using the freezing–thawing technique for application in Lac fermentation. In batch fermentation, the immobilized biocatalyst was superior to the free cell fermentation system (by 37.1%). The highest L-LA yield and volumetric productivity of 97.6% and 0.8 g/(L h), respectively, were attained in repeated-batch fermentation. During seven consecutive batch fermentations, the biocatalyst showed high mechanical and operational stability, reaching an overall productivity of 0.78 g/(L h). Zheng et al. [110] immobilized *L. delbrueckii* on sodium alginate gel beads to produce L-LA from cellulose hydrolysate and finally obtained 48.7 g/L L-LA, and the yield of L-LA/Glu reached 95.2%.

5.4. CCF

The CCF mode uses certain separation technologies to return fermented bacteria to the bioreactor for the further utilization and discharge the aged cells in time. At present, the developed separation methods include electrodialysis, ion exchange resin adsorption, solvent extraction, and membrane fermentation. Garrett et al. [66] used the Amberlite IRA-67 ion exchange resin for building an extractive fermentation system in the fed-batch fermentation. Compared to fed-batch fermentation without the extraction fermentation system, the L-LA titer of this method could be increased by 1.31 times. Danner et al. [111] coupled a biofilm reactor and electrodialysis technology to design the membrane bioreactor (MBR)-electrodialysis system, which was used for the CF of L-LA. The system accomplished cell circulation through ultrafiltration MBR and used the unipolar electrodialysis box to

separate and purify L-LA in the fermentation broth. The remaining culture medium and fermentation substrate in the fermentation broth were reused in the fermentation tank. The L-LA titer by this system was capable of reaching 115 g/L, and this system could have run stable for a long time. After the system ran for >1000 h, there was still no cell penetration. In addition, this system has less wastewater discharge, low energy consumption, and good environmental benefits.

Nowadays, a variety of fermentation and extraction coupling technologies have emerged to overcome the shortcomings of traditional fermentation, such as product inhibition, high production costs, and the by-products produced by a neutralizer [80], representing the development directions of the L-LA fermentation industry in the future.

6. Conclusions

The microbial production of L-LA is a hot topic in global research at present. The construction of an efficient microbial cell factory for the sustainable production of L-LA is crucial for maintaining the sustainable development of the social economy. Recently, many microbial cell factories have been developed and fermentation progress have been made to efficiently synthesize L-LA. However, there are still many problems in the microbial production of L-LA, such as the imbalance of the metabolic fluxes between the cell growth and synthesis of L-LA, the high production costs in the fermentation process, and the adverse effects of a low pH caused by L-LA accumulation during fermentation.

To improve the synthesis efficiency of L-LA, we suggest that the two following aspects should be studied further. First, although enhancing Pyr accumulation can increase the L-LA titer, the production of by-products such as glycerol will also increase, resulting in the imbalance of a cofactor supply. Therefore, it is crucial to develop a global L-LA metabolism regulatory strategy through the genome-scale metabolic mode to balance the metabolic fluxes between the cell growth, cofactor supply, and L-LA synthesis. Although no metabolic model of L-LA production has been reported, there are some relevant models [112–114]. The same method can also be used as a mathematical tool for L-LA metabolism prediction and reactor optimization. Second, the L-LA accumulation will decrease the pH of the fermentation medium, further inhibiting bacterial growth. However, adding neutralizers will increase fermentation costs and introduce salt ion magazines. The high ion concentration will consume energy for cells and directly inhibit cell activity. Improving the acid resistance of cells may overcome this limitation, which can be achieved by adaptive evolution and genetic engineering [115,116].

In conclusion, microbial cell factory synthesis technology and gene dynamic regulation technology can be used to convert L-LA into low-value renewable resources for raw material production by reconstructing and engineering metabolic pathways to therefore develop the sustainable, green, and clean production of bulk chemical L-LA. The development prospects of the L-LA fermentation industry are vast, which will promote the upgrading of the food and medicine industry and represent a new horizon for the sustainable development of human society.

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