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MINI-REVIEW

Biotechnological production of enantiomerically pure *d*-lactic acid

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Abstract The fermentation process of *l*-lactic acid is well known. Little importance was attached to *d*-lactic acid, but in the past 10 years, *d*-lactic acid gained significantly in importance. *d*-Lactic acid is an interesting precursor for manufacturing heat-resistant polylactic acid (PLA) bioplastics which can be widely used, for example as packaging material, coatings, for textiles or in the automotive industry.

This review provides a comprehensive overview of the most recent developments, including a spectrum of studied microorganisms and their capabilities for the production of *d*-lactic acid. Additionally, the technological achievements in biotechnological *d*-lactic acid production including fermentation techniques like fed batch, simultaneous saccharification, and fermentation and continuous techniques are presented. Attention is also turned to suitable alternative substrates and their applicability in fermentation processes. Furthermore, advantages and disadvantages of product recovery and purification are discussed. Economic aspects of PLA are pointed out, and the present industrial producers of lactic acid are briefly introduced.

Keywords *d*-Lactic acid · Wild-type strains · Genetically engineered strains · Fermentation strategies · Renewable resources · Product recovery

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Introduction

The depleting petrochemical resources and the increasing consumption of oil-based plastics are a growing problem in our society. Thus, it is very important to develop new bio-based products and to establish alternative production processes in the industry. One of the most promising bio-based polymers is polylactic acid (PLA) which is already widely used as a packaging material.

Several forms of PLA can be synthesized by varying the ratio between the *l*- and *d*-isomer of lactic acid. Polymers made of enantiomerically pure *l*- or *d*-lactic acid are known as PLLA and PDLA, both with a melting point of 170–180 °C. The polymer achieved from the racemic mixture of lactic acid results in amorphous materials.

Enantiomerically pure PLAs, PLLA, and PDLA form a stereocomplex (scPLA) that has a melting temperature of 220–230 °C (Fig. 1, Table 1) (Ikada et al. 1987; Tsuji 2005). The reason for the improved properties of the isotactic stereocomplex PLA (scPLA) is the dense packing of the polymeric crystalline regions. The increased stability can be explained by the sum of intermolecular hydrogen bridge bonds between the methyl group and the carbonyl group of the opposite homochiral polymer chains (Zhang et al. 2005). Besides its superior thermal stability, this stereocomplex has further advantages regarding mechanical performance and hydrolysis resistance (Tsuji 2005). Due to the increased heat resistance, scPLA has the potential to replace petroleum-based packaging materials and increases the application possibilities of PLA for the electronic sector and the automotive industry (Auras et al. 2005; Garlotta 2001). The current price of PLA is 2.0–2.2 $/kg. In order to compete with petrochemical polymers, research is necessary to open up new opportunities to produce PLA more cheaply. Especially, the cost of

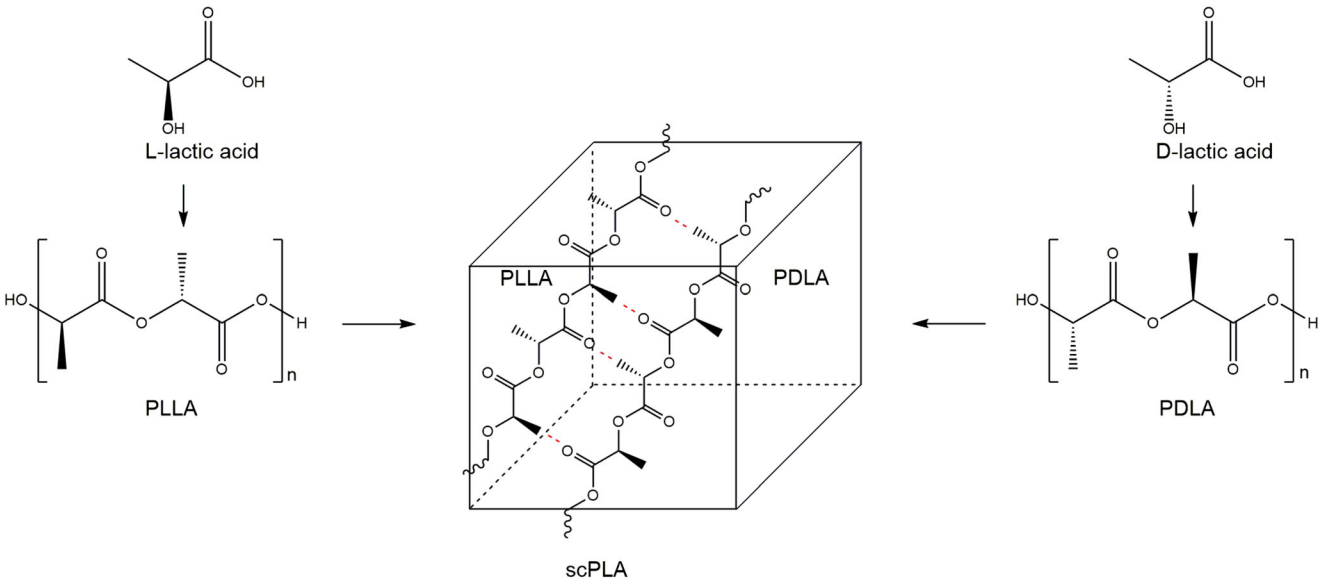

Fig. 1 Block-copolymerization of PLLA and PDLA to isotactic scPLA (*PLLA* poly-*l*-lactic acid, *PDLA* poly-*d*-lactic acid, *scPLA* stereocomplex PLA)

substrate and fermentation media must be reduced (Datta et al. 1995; E4tech 2015).

The chemical synthesis of lactic acid is based on petrochemical resources such as acetaldehyde and hydrocyanic acid and yields only in a racemic mixture of lactic acid. For this reason, 70–90 % of the yearly worldwide production of lactic acid, which amounts up to 300,000 tons, is gained by fermentation (National STEM Centre 2011; Datta et al. 1995; Ghaffar et al. 2014; Wee et al. 2006).

So far, the industrial production by fermentation is limited to *l*-lactic acid due to its application in the food industry and the predominant existence of *l*-lactic acid-producing bacteria. This fermentation process has previously been reviewed (Abdel-Rahman et al. 2013; Datta and Henry 2006; Ghaffar et al. 2014; Hofvendahl and Hahn-Hagerdal 2000; John et al. 2007; Okano et al. 2010; Vijayakumar et al. 2008; Wee et al. 2006). In contrast, little importance was attached to *d*-lactic acid, but in the past 10 years, *d*-lactic acid gained significantly in importance. Accordingly, a stable and highly productive fermentation process for *d*-lactic acid is required, and microorganisms producing enantiomerically pure *d*-lactic acid with a high selectivity are of great interest. A pilot scale demonstration of *d*-lactic acid fermentation (6 ton vessel) is described by Liu et al. using a metabolically engineered *Escherichia coli* strain (Liu et al. 2014), but only few wild-type strains, such as several *Sporolactobacillus* spp. and *Lactobacillus* spp., are able to produce *d*-lactic acid of a suitable purity and efficiency (Tashiro et al. 2011). Because the polymer properties are influenced by the enantiomerical purity of *d*-lactic acid, high enantiomerical purities of more than 99 % are preferred.

This review provides an overview of *d*-lactic acid-producing microorganisms, suitable fermentation strategies, and the use of agricultural by-products as alternative substrates. Furthermore, the product purification and recovery are presented and insights into economical and industrial aspects are delivered.

d-Lactic acid producing microorganisms

Microorganisms used for the efficient biotechnological production of *d*-lactic acid have to meet several requirements. In terms of industrial applications, it is necessary that *d*-lactic acid be produced from low-cost resources with a high yield and a high enantiomeric purity in a short fermentation time. Several factors like medium composition, growth conditions, pH, and operation mode influence the enantiomeric purity (Hofvendahl and Hahn-Hagerdal 2000).

Table 1 Thermal and mechanical properties of different PLA forms (Tsuji 2005)

	Glass transition T_g (°C)	Melting point T_m (°C)	Activation energy ΔE_{td} (kJ·mol^{-1})[a]	Tensile strength (GPa)
(*ld*)-PLA	50–60	–	–	0.04–0.05
PLLA/PDLA	50–65	170–190	87–104	0.12–2.3
scPLA	65–72	220–230	205–297	0.88

[a] Activation energy for thermal degradation estimated by thermogravimetry at 250–270 °C

The lactic acid fermentation is part of the primary metabolism and takes place with different intensity in bacteria, yeast, algae as well as in cyanobacteria.

The most used lactic acid-producing bacteria are from the genus *Lactobacillus*, *E. coli* und *Corynebacterium glutamicum*. *E. coli* and *C. glutamicum* form more organic acid by-products; therefore, only genetically modified strains are used for lactic acid production (Chang et al. 1999; Wieschalka et al. 2013). The same applies to the lactic acid production with yeast (Adachi et al. 1998). Photosynthetic microorganisms like algae and cyanobacteria produce glucose or starch from CO_2, which can be further converted to lactic acid by some strains. *Nannochlorum* sp.26A4 produced *d*-lactic acid with high enantiomerical purity and a yield of 70 % under dark anaerobic conditions (Hirayama and Ueda 2004). Although the substrate costs are eliminated, algae are rarely used in industrial processes because of the high costs caused by the need for supplemental lighting supply and the purchase of photobioreactors (Chen et al. 2011).

An overview is presented of known *d*-lactic acid-producing bacteria (*d*-LAB) and yeasts which are investigated for further biotechnological production of enantiomerically pure *d*-lactic acid. The bacteria can be distinguished into wild-type strains, mutants derived by random mutagenesis, and genetically engineered strains.

Wild-type strains and strains generated by random mutagenesis

The most studied wild-type *d*-LAB (or conservative mutants) pertains to the genus *Lactobacillus* along with studies focusing on *Sporolactobacilli* (Table 2). Both genera have a facultative anaerobic metabolism, are Gram-positive, catalase-negative, and generally recognized as safe (GRAS status). *Sporolactobacilli* are known as mesophilic *d*-LAB which grow in a temperature range of 20–45 °C whereas some *Lactobacillus delbrueckii* strains prefer temperatures between 45 and 47 °C for proliferation (Demirci and Pometto 1992; Hofvendahl and Hahn-Hagerdal 2000). Mesophilic growth temperatures increase the risk of contaminations and conflict with high optimum temperatures of most enzymes used in simultaneous saccharification and fermentation (SSF) techniques (see below).

Lactobacilli are finding broad applications in food industry and biotechnology because of their metabolic versatility, for example the utilization of various sugars such as disaccharides and pentoses as well as hexoses (Giraffa et al. 2010).

Additionally, LAB can be classified as homofermentative and heterofermentative due to their ability to metabolize sugars by different pathways (Kandler 1983).

To generate energy in the form of ATP, homofermentative LAB metabolize hexoses like glucose via the Embden-Meyerhof-Parnas (EMP) pathway (Meyerhof 1948) and pentoses via the pentose phosphate (PP) pathway (Horecker et al. 1954). The aldolase which is a key enzyme of homofermentative lactic acid fermentation divides the intermediately formed fructose-1,6-diphosphate into glyceral dehyde-3-phosphate (GAP) and dihydroxyacetone phosphate (Buyze et al. 1957). This is isomerized to GAP and finally converted to pyruvate in several steps (Fig.2 Glycolysis). Pyruvate can be subsequently converted into *d*-lactic acid by a d-lactate dehydrogenase (*d*-LDH) with a theoretical yield of 1.0 g/g hexose (2 mol/mol) (Wang et al. 2015a). Metabolizing pentoses, 3 mol of pentose generate 1 mol GAP and 2 mol fructose-6-phosphate in the PP-pathway. Fructose-6-phosphate is converted to pyruvate in several steps and lactic acid with a theoretical yield of 1.0 g/g pentose (1.67 mol/mol) (Elsden and Peel 1958).

Heterofermentative LAB uses the phosphoketolase pathway to convert pentoses and hexoses to xylulose-5-phosphate which is divided via the key enzyme phospho ketolase into GAP and acetyl phosphate (Fukui et al. 1957; Elsden and Peel 1958). Hereby, one molecule of *d*-lactic acid, acetate, or ethanol and carbon dioxide are formed (Fig. 2 Phosphoketolase pathway) (Basso et al. 2014; Zaunmuller et al. 2006). The theoretical yield of heterofermentative lactic acid production is 0.5 g/g glucose (1.0 mol/mol) and 0.6 g/g pentose (1.0 mol/mol).

The reaction of pyruvate to *l*-lactic acid is catalyzed by *l*(+)-lactate dehydrogenase (EC1.1.1.27), while the reaction of pyruvate to *d*-lactic acid is catalyzed by *d*(−)-lactate dehydrogenase (EC1.1.1.28). Most strains possess both lactate dehydrogenases, but their activity and therefore the resulting enantiomeric ratio varies between strains (Garvie 1980). According to the strain, the enantiomeric ratio can be influenced through fermentation conditions, such as pH, temperature, NaCl concentration, nutrient concentration, or gas supply (Bobillo and Marshall 1991; Yoo et al. 1996).

Compared to the phosphoketolase pathway, the glycolysis is more effective with regard to lactic acid yield as well as sugar utilization (Wang et al. 2015a). Most lactic acid bacteria metabolize hexoses homofermentatively and pentoses heterofermentatively. Abdel-Rahman et al. (2011b) depict a wild-type strain producing homofermentative *l*-lactic acid from xylose. Also a few metabolically engineered strains are able to convert pentoses using the homofermentative lactic acid production (Okano et al. 2009a; Okano et al. 2009b; Tsuge et al. 2014; Wang et al. 2011b; Wang et al. 2015a), which is favorable for the utilization of lignocellulose-containing biomass.

Table 2 gives an overview of the most promising results in *d*-lactic acid production by wild-type strains and strains generated by random mutagenesis. Wang et al. (2011a) produced in a fed batch mode 207 g/L *d*-lactic acid with a purity of 99.3 % with the wild-type strain *Sporolactobacillus*

Table 2 *d*-Lactic acid production of wild-type strains and strains generated by random mutagenesis

Microorganism	Substrate	*d*-Lactic acid [g/L]	Yield [g/g]	Productivity [g/(L h)]	Purity [%]	Cultivation time [h]	Reference
Lactobacillus coryniformis ATCC 25600	Curcuma longa	91.6	0.65	2.08	99.5	44	(Nguyen et al. 2013b)
Lactobacillus delbrueckii subsp. *Lactis* QU 41	MRS medium/glucose	87.4	1.01	0.52	99.9	168	(Tashiro et al. 2011)
Lactobacillus delbrueckii ATCC 9649 DP3[a]	YMO medium/glucose	117.0	0.76	6.50[b]	–	100	(Demirci and Pometto 1992)
Sporolactobacillus inulinus CASD[c]	Glucose/peanut meal	207.0	0.93	3.80	99.3	54	(Wang et al. 2011a)
Sporolactobacillus laevolacticus DSM 442	Glucose/cottonseed	144.4	0.96	4.13	99.3	35	(Li et al. 2013)
Sporolactobacillus sp. YBS1–5[a]	Glucose/yeast extract, corn steep liquor, wheat bran	125.0	–	1.39	99	90	(Sun et al. 2015)
Weissella sp. S26/ *Bacillus* sp.ADS3	Xylose/yeast extract, peptone	13.2	–	–	98.5	48/120	(Li et al. 2016)

[a] Strains generated by random mutagenesis

[b] Maximum volumetric productivity

[c] Strain is originally termed as *Sporolactobacillus* sp. CASD by Wang et al. (2011a) and later identified as *Sporolactobacillus inulinus* CASD by Yu et al. (2011)

inulinus CASD using glucose as carbon source and peanut meal as nitrogen source.

Li et al. (2016) produced enantiomerically pure *d*-lactic acid from xylose combining two native bacterial microorganisms. During the first cultivation step *Weissella* sp.S26 produces 13.7 g/L lactic acid including 13.2 g/L *d*-lactic acid and 8.5 g/L acetic acid using 2 % xylose as sole carbon source. In the second cultivation step, the sterilized broth was inoculated with *Bacillus* sp.ADS3. *Bacillus* sp.ADS3 is able to digest acetic acid and lactic acid. This strain preferred the digestion of acetic acid over lactic acid and *l*-lactic acid over *d*-lactic acid. Therefore, the acetic acid was completely removed from the fermentation broth with an increased enantiomerical purity of *d*-lactic acid (98.5 %).

Genetically engineered strains

d-Lactic acid production by genetically engineered microorganisms is generally based on three major strategies:

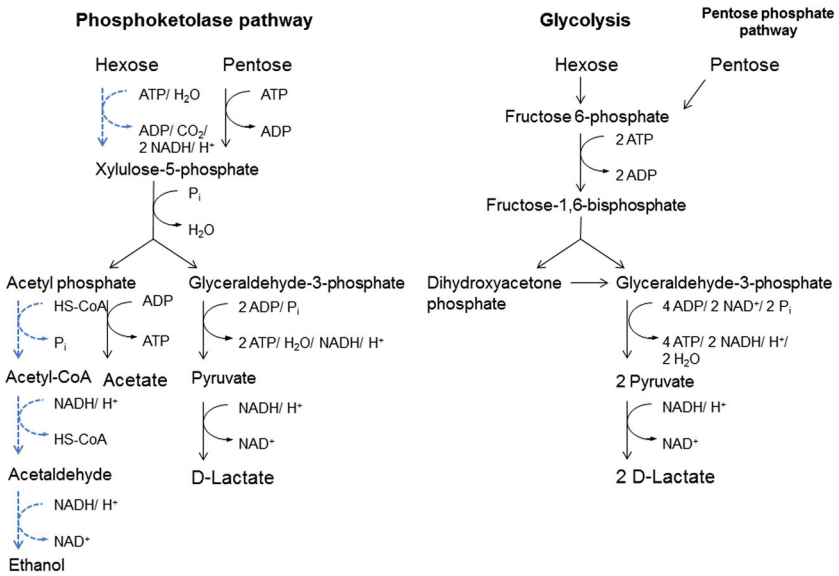

Fig. 2 Simplified illustration of the phosphoketolase pathway (*left*, *dashed arrows* represent the additional conversion of hexoses to ethanol) and the glycolysis (*right*)

1. The heterologous expression of d-LDH genes from *d*-lactic acid-producing strains in microorganisms with favorable abilities like minimal nutritional requirements or homofermentative pentose conversion. There are several attempts using the rapid growing bacteria *E. coli* and *C. glutamicum* for *d*-lactic acid production on mineral salt media (Lu et al. 2016; Zhou et al. 2016; Okino et al. 2008).
2. The deletion of competing pathways results in higher yields and productivities. A widely used modification is the deletion of l-LDH to improve the enantiomeric purity of *d*-lactic acid and the interruption of pathways leading to other mixed acid fermentation products (Jia et al. 2011; Yi et al. 2016). *Saccharomyces cerevisiae* produces large amounts of ethanol and other mixed acid fermentation products. Due to its ability to grow under acidic conditions, the amount of neutralizing agent and purification costs for *d*-lactic acid can be reduced. An efficient *d*-lactic acid production can be achieved by disrupting pathways leading to by-products (Baek et al. 2016).
3. The enablement of pentose conversion via the homofermentative pentose phosphate pathway for the efficient production of *d*-lactic acid from pentoses and lignocellulosic biomass as substrates. Zhang et al. (2016a) modified l-LDH deficient *L. plantarum* for *d*-lactic acid production from corn stover and sorghum stalks by inserting xylose assimilating genes encoding xylose isomerase and xylulokinase.

Table 3 gives an overview of the most promising results in *d*-lactic acid production by genetically modified organisms (GMOs).

Tsuge et al. (2015) produced 195 g/L *d*-lactic acid within 80 h with *C. glutamicum* holding a *d*-LDH from *L. delbrueckii*. Overexpression of glycolytic genes, in particular of phosphofructokinase, resulted in increased *d*-lactic acid production. In addition to *l*-LDH knock-out and *d*-LDH insertion, Assavasirijinda et al. (2016) disrupted the exopolysaccharide biosynthesis to obtain an increased *d*-lactic acid titer of 142 g/L by fermentation of an alkaliphilic *Bacillus* strain with NaOH as neutralizer instead of $CaCO_3$ to prevent the accumulation of $CaSO_4$.

Feng et al. (2014) genetically manipulated *Klebsiella pneumoniae* to produce *d*-lactic acid using glycerol as substrate. Overexpression of lactate dehydrogenase LdhA and knockout of genes associated with 1,3-PDO synthesis significantly improved the *d*-lactic acid production to 142.1 g/L and a productivity of 2.96 g/(L h). Inserting *d*-LDH in *E. coli*, alternative substrates such as crude glycerol can be converted to *d*-lactic acid (Ganesh et al. 2012; Mazumdar et al. 2010; Wang et al. 2015b).

Li et al. (2015) induced *d*-lactic acid production in the cyanobacterium *Synechococcus elongatus* PCC7942 by insertion of a *d*-LDH from *Lactobacillus bulgaricus*, enabling the usage of NADPH instead of NADH as a cofactor for LDH and introduction of a lactic acid transporter. However, this attempt resulted in low *d*-lactic acid production of 1.31 g/L with a productivity of 221 mg/L per day.

The drawback to using genetically engineered strains for industrial purposes in the European Union is in the regulation of genetically modified food and feed. In general, the fermentation waste can be used to produce animal feed which can be sold as well as the product, but the sale of animal feed within the EU is strictly regulated if the fermentation waste contains genetically modified biomass (European Parliament and the Council 2003). For this reason, there would be additional costs for waste disposal which could make the production process economically inefficient.

Fermentation strategies to optimize *d*-lactic acid production

The fermentation strategy to achieve optimal fermentation conditions depends on the used microorganism and substrate. The following section discusses strategies suitable for homofermentative *d*-lactic acid producing bacteria including batch, fed batch, continuous methods, and immobilized cells.

Batch and fed-batch fermentation

Batch fermentation strategies are less susceptible to contaminations in comparison to fed batch fermentations and high lactic acid concentration with appropriate yield can be attained (Hofvendahl and Hahn-Hagerdal 2000; Sun et al. 2015; Xu et al. 2010). A drawback of this method is the occurring substrate and product inhibition so that batch experiments generally suffer from low productivities.

In order to increase the productivity and to decrease the fermentation times, fed batch strategies are more favorable in comparison to batch methods. Advantages of this method are that substrate concentrations are kept on a subcritical level which reduces inhibition effects and minimizes the *lag*-phase of microbial growth (Abdel-Rahman et al. 2011a). Consequently, the sugar consumption and the productivity of the biocatalyst can be increased. By applying a two-step fed batch strategy on the fermentation of *Sporolactobacillus laevolacticus* DSM442, Li et al. (2013) demonstrated that keeping the glucose concentration (60 g/L) on a subcritical level results in a high productivity of 4.13 g/(L h) with a final concentration of 144.4 g/L *d*-lactic acid after 35 h (Table 4).

Continuous fermentation and cell immobilization

Continuous techniques are useful to reduce process costs by delivering the needed nutrients for fermentation with a constant flow to keep them optimally concentrated. More

Table 3 Genetically modified organisms (GMOs) for the *d*-lactic acid production

Microorganism	Substrate	*d*-Lactic acid [g/L]	Yield [g/g]	Productivity [g/(L h)]	Purity [%]	Cultivation time [h]	Reference
Bacillus sp.N16–5 (*ΔldhΔepsD*-pDlac)	Glucose/ peanut meal	142.1	0.94	3.02[B]	99.85	90	(Assavasirijinda et al. 2016)
Bacillus coagulans QZ19 (*Δ ldh* and *ΔalsS*)	Glucose/ LB-Medium	99.8	0.96	1.39	UD	72	(Wang et al. 2011b)
Bacillus coagulans QZ19–2 (*Δ ldh* and *ΔalsS*)	Sorghum juice, corn steep liquor	124.4	0.93	–	>99	168	(Ou et al. 2016)
Corynebacterium glutamicum (ΔldhA/pCRB204)	Glucose/ mineral salt medium	120.0	0.87	4.00	99.9	30	(Okino et al. 2008)
Corynebacterium glutamicum LPglc267/pCRB2015	Glucose/ mineral salt medium	195.0	0.90	2.44	99.9	80	(Tsuge et al. 2015)
Escherichia coli HBUT-D (ΔpflB ΔfrdABCD ΔadhE Δpta ΔaldA ΔcscR)	Glucose/NBS-medium/yeast extract	127.0	0.93	6.35	99.5	20	(Liu et al. 2014)
Escherichia coli CICIM B0013–070B (ldhAp::kan-cI(ts)857-p(R)-p(L))	Glucose/mineral salt medium	122.8	0.84	4.32	–	28	(Zhou et al. 2012)
Escherichia coli BLac-2106	Crude glycerol/NBS medium	105.0	0.87	2.63	99.9	40	(Wang et al. 2015b)
Escherichia coli HBUT-D (*ΔfrdBC, Δadh, Δpta, ΔpflB, ΔcscR, ΔaldA*)	Sucrose	85.0	0.85	1.00	98.3	72–84	(Wang et al. 2012)
Escherichia coli JH15	Glucose/xylose	83.0	0.83	0.86	~100	96	(Lu et al. 2016)
Klebsiella oxytoca KMS002 (*ΔadhE*)	maltodextrin derived from cassava starch	33.6	0.92	0.35	99.5	96	(Sangproo et al. 2012)
Klebsiella pneumoniae (*ΔdhaT ΔyqhD* pBAD18-*ldhA*)	Glycerol/beef extract/peptone/yeast extract	142.1	0.82	2.96	~100	48	(Feng et al. 2014)
Lactobacillus plantarum NCIMB 8826 (*Δ ldhL1-::xylAB Δxpk1::tkt Δxpk2::xylAB*)	MRS medium/glucose/ xylose	141.8[a]	0.90/ 0.93	–	–	48	(Tsuge et al. 2014)
Lactobacillus plantarum NCIMB 8826 (*ΔldhL1::PxylAB-Δxpk1::tkt-Δxpk2::PxylAB)*	SSF/delignified hardwood pulp	102.3	0.88	2.29[b]	99.2	140	(Hama et al. 2015)
Lactobacillus plantarum NCIMB 8826 (*ΔldhL1*-pLEM-*xylAB*	Corn stover/ soybean meal extract	61.4	0.77	0.32	>99	192	(Zhang et al. 2016b)
Leuconostoc citreum 95 (pMBLT02)	LAB medium/ peptone, yeast extract/ glucose	61.0	0.48	–	>99.9	70	(Chae et al. 2013)
Pediococcus acidilactici ZP26 (*ldh* deficient strain)	Corn stover/ peptone, yeast extract	77.8	0.58	1.02	99.32	76	(Yi et al. 2016)
Saccharomyces cerevisiae OC 2 (pdc1::Ppdc1-D-LDH (*L. mesenteroides* d-LDH))	YPD medium/ peptone, yeast extract/ glucose	61.5	0.61	–	99.9	72	(Ishida et al. 2006)
Saccharomyces cerevisiae JHY5330 (d-ldh *dld1Δjen1Δadh1Δ gpd1Δgpd2Δpdc1Δ* (haploid))	YPD medium/ peptone, yeast extract/ glucose	112.0	0.80	2.20	–	51	(Baek et al. 2016)

UD undetectable, less than 0.5 mM

[a] Two-step *d*-lactic acid production involving cells cultured under growing conditions in MRS medium followed by their high-cell density cultivation in normal saline solution

[b] Maximum productivity

Table 4 Examples of different fermentation strategies and experimental setups for *d*-lactic acid production

Fermentation method	Neutralizing agent	*d*-Lactic acid [g/L]	Yield [g/g]	Productivity [g/(L h)]	Time [h]	Reference
Batch (300 mL Erlenmeyer flask, 100 mL working volume)	$CaCO_3$ at pH 5.5–6.0	72.0	0.90	-	24	(Wang et al. 2011a)
Fed batch (5 L reactor, 2 L working volume)	$CaCO_3$ at pH 5.5	144.4	0.96	4.13	35	(Li et al. 2013)
Fed batch (7.5 L FBB reactor, immobilized cells 1.5 L working volume)	NH_3H_2O at pH 6.5	218.8	-	1.65	132	(Zhao et al. 2014)
Continuous (2 L reactor, 1.5 L working volume)	5 M $Ca(OH)_2$ at pH 6.0	67.3	0.97	11.2	800	(Mimitsuka et al. 2012)
Continuous (1 L reactor, 400 mL working volume)	10 M NH_4OH at pH 6.0	-	1.00	18	35	(Tashiro et al. 2011)

importantly, this method is reported to gain significantly higher productivities compared to other fermentation strategies for *d*-lactic acid production (Table 4) (Mimitsuka et al. 2012; Tashiro et al. 2011). Critical factors using continuous methods are the efflux of non-utilized substrate, cell loss, and a decreased lactic acid concentration by an increasing dilution rate (Abdel-Rahman et al. 2013; Zhang et al. 2011).

A combination of continuous fermentation with cell recycling or cell immobilization is an efficient method to gain high cell densities and high productivities. By separating the product from the fermentation broth or diluting it with fresh medium, product inhibition effects can be avoided. Tashiro et al. (2011) applied a continuous, cell-retaining method using *L. delbrueckii* ssp. *lactis* QU 41 for fermentation. The MRS medium was supplemented with 20 g/L glucose and refreshed with dilution rates of 0.56 and 0.87 per hour, which resulted in a productivity of 18 g/(L h) with a low residual glucose concentration. Unfortunately, only a short fermentation time of 35 h was applied so that the durability of this continuous process was not proven (Tashiro et al. 2011). A second study concerning continuous fermentation by retaining cells is published by Mimitsuka et al. (2012) using *S. laevolacticus* JCM 2513. This study focused on the reduction of nutrients for the fermentation and the examination of the long-term stability of this process over 800 h. By using a membrane-integrated fermentation reactor and a reduced amount of yeast extract, an average productivity of 11.2 g/(L h) could be achieved.

Zhao et al. (2014) recently reported results applying fed batch fermentation using a multi-pulse feeding strategy (with hydrolyzed corn flour as substrate) in a fibrous bed reactor (FBB) in combination with immobilized cells. A final titer of 218.8 g/L *d*-lactic acid can be achieved within 132 h.

Fermentation of alternative substrates

Glucose is a widely used substrate in fermentation processes, but refined sugars are expensive and the raw material costs have a significant influence on the product price (Tejayadi and Cheryan 1995). For this reason, the utilization of alternative substrates is desired. Alternative substrates are polysaccharides, such as starch or cellulose, as well as agricultural raw materials and side products which contain a high amount of polysaccharides or monomeric sugars. Furthermore, the utilized substrate should not conflict with the food industry. Table 5 shows many attempts cited in literature to replace refined glucose by alternative substrates.

Due to the fact that the *d*-lactic acid-producing strains do not provide the enzymes to directly convert such alternative substrates, high molecular carbohydrates have to be disintegrated to fermentable monomer sugars either by enzymatic or chemical hydrolysis. Whereas chemical pretreatment/hydrolysis can exclusively be carried out prior to fermentation, the enzymatic digest can be carried out either prior to the fermentation or during fermentation. For this purpose, enzymes such as amylases, pullulanase, cellulase, and β-glucosidase can be used, depending on the substrate (Fukushima et al. 2004; Nakano et al. 2012; Nguyen et al. 2012; Singhvi et al. 2010).

A separate hydrolysis and fermentation (SHF) strategy is time consuming due to two step processing and the product formation, in particular intermediately formed cellobiose, leads to product inhibition of the enzymes (Lu et al. 2009; Singhvi et al. 2010). Consequently, higher amounts of enzyme are needed to achieve an appropriate yield of hydrolyzed sugar which makes this method more cost-intensive. Yanez et al. (2005) figured out that the efficiency of the enzymatic hydrolysis can be further increased when the substrate is pre-treated with NaOH, but another more established strategy is to avoid the product inhibition of enzymes in a simultaneous saccharification and fermentation (SSF). In this process, the fermentable sugars are gradually hydrolyzed to substrate level and simultaneously converted into lactic acid by the bacteria. Furthermore, by applying SSF, the bacteria benefit from an initial low substrate concentration which avoids substrate inhibition and the productivity can be enhanced. A disadvantage of this method is the fact that the optimal conditions of the enzymatic hydrolysis (pH value and temperature) can differ

Table 5 *d*-Lactic acid production from alternative substrates: (A) carbon sources, (B) nutrient sources, (C) carbon and nutrient sources

	Substrate, nutrient source	Microorganism	*d*-Lactic acid [g/L]	Yield [g/g]	Productivity [g/(L h)]	Purity [%]	Reference
A	Sweet potato[c]	*Lactobacillus coryniformis* ATCC 25600	186.4	0.85[d]	3.11	–	(Nguyen et al. 2013a)
	Rice saccharificate[a]	*Lactobacillus delbrueckii* LD 0028 (IFO3202)	62.6	0.73[b]	–	98.4	(Fukushima et al. 2004)
	Rice bran[c]	*Lactobacillus delbrueckii* IFO 3202	28.0	0.78[b]	0.78	95	(Tanaka et al. 2006)
	Sugarcane molasses	*Lactobacillus delbrueckii* JCM 1148	104.0	0.9[b]	1.48	97.2	(Calabia and Tokiwa 2007)
	Sugarcane juice	*Lactobacillus delbrueckii* JCM 1148	118.0	0.95[b]	1.66	98.3	(Calabia and Tokiwa 2007)
	Sugar beet juice	*Lactobacillus delbrueckii* JCM 1148	82.0	0.88[b]	1.16	97.6	(Calabia and Tokiwa 2007)
	Broken rice[c]	*Lactobacillus delbrueckii* JCM 1106	79.0	0.81[b]	3.59	96.1	(Nakano et al. 2012)
	Pulp hydrolyzate	*Lactobacillus delbrueckii* ATCC 9649	36.3	0.83[f]	1.01	99.8	(Zhang and Vadlani 2013)
	Filter paper[c]	*Lactobacillus coryniformis* subsp. *Torquens* ATCC 25600	24.0	0.89[d]	0.5	99.9	(Yanez et al. 2003)
	Waste cardboard[c,e]	*Lactobacillus coryniformis* subsp. *Torquens* ATCC 25600	23.4	0.51[b]	0.48	-	(Yanez et al. 2005)
	Hydrodictyon reticulatum[c]	*Lactobacillus coryniformis* subsp. *Torquens* ATCC 25600	36.6	0.46[d]	1.02	99.5	(Nguyen et al. 2012)
	α-Cellulose[c]	*Lactobacillus lactis* RM2–24	73.3	0.73[d]	1.52	-	(Singhvi et al. 2010)
	Corn flour[a]	*Sporolactobacillus inulinus* Y2–8	145.8	0.97	1.62	>99.0	(Zhao et al. 2014)
	Starch[c]	*Weissella* sp. S26 *Bacillus* sp. ADS3	23.6	–	–	99.5	(Li et al. 2016)
B	Mineral salts[e]	*Corynebacterium glutamicum* ΔldhA/ pCRB204	120.0	0.87[f]	4	99.9	(Okino et al. 2008)
	Peanut meal[e,c]	*Sporolactobacillus inulinus* CASD	207.0	0.93[f]	3.8	99.3	(Wang et al. 2011a)
	Cottonseed[e,c]	*Sporolactobacillus laevolacticus* DSM 442	144.4	0.96[f]	4.13	99.3	(Li et al. 2013)
C	Glycerol, mineral salt[e]	*Escherichia coli* CICIM B0013–070/ pTH-*ldhA*	103.1	0.78[d]	3.65	99.9	(Kangming 2012)
	Crude glycerol, mineral salt	*Escherichia coli* LA02Δ*dld*(pZSglpKglpD)	45.0	0.83	0.54	99.9	(Mazumdar et al. 2010)
	Unpolished rice[a], wheat bran	*Lactobacillus delbrueckii* HG 106	90.8	0.73[d]	1.5	97.5	(Lu et al. 2009)
	Sugarcane juice, yeast autolysate	*Leuconostoc mesenteroides* NRRL B512	60.2	0.51[b]	1.25	–	(Coelho et al. 2011)
	Palmyra palm jaggery, whey protein hydrolysate	*Sporolactobacillus inulinus* NBRC 13595	189.0	0.94	5.25	>98	(Reddy Tadi et al. 2015)
	Corncob residues, cottonseed meal[a,e]	*Sporolactobacillus inulinus* YBS1–5	107.2	0.85	1.19	99.2	(Bai et al. 2016)

[a] Separate hydrolysis and fermentation

[b] Yield refers to initial sugar amount

[c] Simultaneous saccharification and fermentation

[d] Yield refers to initial substrate amount

[e] Fed-batch process

[f] Yield refers to substrate consumption

from the optimal fermentation conditions, which lead to a lower efficiency (Hofvendahl and Hahn-Hagerdal 2000).

Table 5 highlights the most important *d*-lactic acid fermentations based on alternative carbon sources. These works show large differences in their final concentrations caused by the different bacterial strains, the utilized substrate and nutrient source, the initial sugar amounts, and the fermentation techniques.

Zhao et al. (2014) demonstrated that high *d*-lactic acid concentrations of 145.8 g/L in a batch fermentation with immobilized cells and 218 g/L in a fed-batch fermentation (Table 4) can be obtained by fermenting corn flour with *Sporolactobacillus inulinus* Y2–8. Nguyen et al. (2013a) conducted a batch SSF process with raw sweet potato as carbon source with *Lactobacillus coryniformis*. *L. coryniformis* produced homofermentatively a final titer of 186.4 g/L *d*-lactic acid, with a productivity of 3.11 g/(L h) and a yield of 0.85 (g/g). However, an increasing concentration of yeast extract and peptone led to an increased *d*-lactic acid production and yield through the SSF process. The supplementation with 7 g/L yeast extract and 3 g/L peptone showed the optimized values for the SSF process.

The *d*-lactic acid yields vary. Nguyen et al. (2012) reached a low yield of 0.46 g/g, while Calabia and Tokiwa (2007) reached a much higher yield of 0.95 g/g, but these results are only conditionally comparable due to their differing reference of initial sugar amount and the initial substrate amount, which differs in its sugar content. Concerning the productivities, Kangming (2012) and Nakano et al. (2012) achieved distinguished results with more than 3.5 g/(L h). The highest productivity of 5.25 g/(L h) and a final titer of 189 g/L *d*-lactic acid was attained by Reddy Tadi et al. (2015) in the batch fermentation of unrefined palmyra palm jaggery and whey protein hydrolyzate as nutrient source with *S. inulinus*.

Besides the carbon source, lactic acid bacteria grow in nutrient-rich media so that the addition of supplines is necessary. However, yeast extract is very expensive and Tejayadi and Cheryan (1995) estimated it to be 38 % of total production cost.

Yeast extract contains a lot of necessary nutrients, such as free amino acids and peptides, B vitamins, trace elements, and nucleotides which can also be supplied by protein-rich agricultural raw materials as alternative nutrient source. Fermentations using such alternative nutrient sources are shown in Table 5, sections B and C. In Table 5, section C, both the carbon and the nutrient sources are replaced. So far, the best result was achieved by Wang et al. (2011a) in an enzymatic hydrolysis and simultaneous fermentation (similar to the SSF), yielding in a high-end concentration of 207 g/L *d*-lactic acid with a productivity of 3.8 g/(L h). Li et al. (2013) carried out an analog experiment with *S. laevolacticus* and cottonseed as alternative nutrient source. Okino et al. (2008) used a metabolically engineered *C. glutamicum* strain, which was able to grow on mineral salt medium. Kangming (2012) achieved similar results with an *E. coli* strain.

In most cases, the use of yeast extract substitutes has a negative impact on the *d*-lactic acid production. The high content of B vitamins in yeast extracts is often named as a reason for this, but such assumptions are difficult to make because the nutritional requirements are specific for each strain (Curk et al. 1993; Nancib et al. 2005).

Product recovery and purification

The fermentative production of *d*-lactic acid requires efficient product purification methods. Depending on the purification method, the utilization of renewable raw materials can entail higher challenges than pure substrates.

Product recovery and purification are said to amount to up to 50 % of the production costs, and thus, they are crucial to the quality and the price of the product (Eyal and Bressler

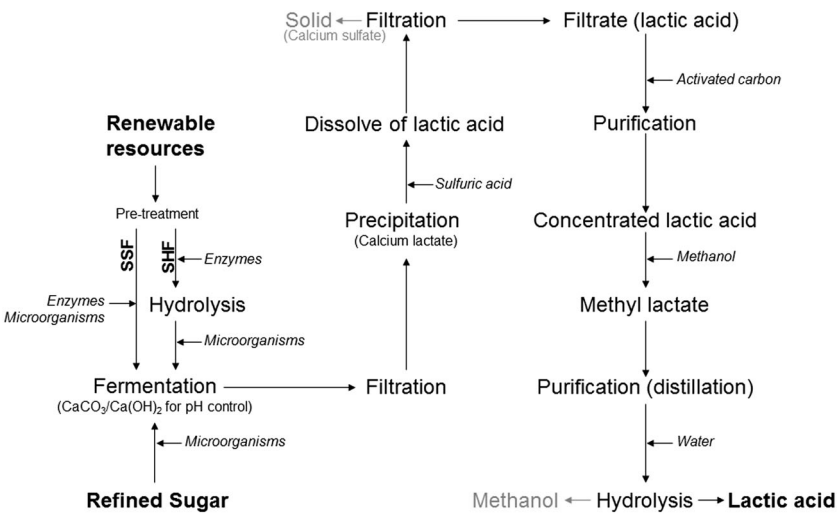

Fig. 3 Lactic acid fermentation, product recovery by precipitation of calcium lactate, and purification steps (*SSF* simultaneous saccharification and fermentation, *SHF* separate hydrolysis and fermentation)

Table 6 Purification techniques for lactic acid removal

Purification method		Advantages	Disadvantages	References
Precipitation	Precipitation and filtration of calcium lactate followed by several purification steps	• Industrially established	• Expensive • Large amounts of calcium sulfate accrue	(Wasewar 2005) (Groot et al. 2010)
Electro dialysis	Removal of sodium lactate ions through an ion exchange membrane, afterwards acidification	• In situ product removal	• Membrane fouling • High operating costs and equipment • Demineralization of the medium	(Heriban et al. 1993) (Habova et al. 2004) (Hongo et al. 1986) (Wasewar 2005)
Reactive extraction	Mostly use of organic solvents, containing phosphorus-bonded oxygen donors or high molecular mass aliphatic amines.	• Continuous product removal	• Selectivity and toxicity of several extractants can influence the cultivation	(Kertes and King 1986) (Huang et al. 2004)
Membrane extraction	Extraction through hollow fiber membranes	• No back-mixing and therefore no toxicity	• Membrane clogging can occur	(Huang et al. 2004) (Buzatu et al. 2012) (Iyer and Lee 1999)
Adsorption	Usually ion exchange resins consisting of tertiary amines, pyridines or quaternary ammonium ions	• Biocompatible	• Essential ions can be removed from the broth • Resin regeneration needs large amounts of chemicals (not always completely regenerable)	(Gao et al. 2010) (Keil et al. 1985) (Wasewar 2005) (Chen and Ju 2002)

1993). The purification processes for racemic or *l*-lactic acid has already been reviewed by Wasewar, López-Garzón and Straathof and do not differ from the purification of *d*-lactic acid (Lopez-Garzon and Straathof 2014; Wasewar 2005).

The method most commonly used in industrial processes is the precipitation of calcium lactate that can be induced by the application of calcium carbonate or calcium hydroxide for pH control during the fermentation. Calcium lactate is separated from the broth by filtration and dissolved again as lactic acid adding sulfuric acid, whereby calcium sulfate precipitates. After filtration of calcium sulfate, the filtrate is purified using activated carbon, separated, and concentrated. The obtained lactic acid is esterified with methanol, resulting in methyl lactate, which can be easily purified by distillation. Methyl lactate is finally hydrolyzed to lactic acid and methanol by the addition of water (Groot et al. 2010; Wasewar 2005). These reaction steps are shown in Fig. 3. Although large amounts of $CaSO_4$ are formed as by-products, this recovery method is still applied in industry.

Alternatively, in situ product removal methods can be applied. Table 6 shows a summary of the most important continuous purification techniques in comparison to the precipitation of lactic acid.

Further, but less common, work-up methods are the separation by supported liquid membranes, emulsion liquid membranes, aqueous two-phase systems, and reverse osmosis (Wasewar 2005).

Economic aspects The total polymer consumption of western Europe is about 50 million tonnes per year, and technically 85 % of the these polymers could be substituted by biobased plastics (Shen et al. 2009). According to the projections of the European Bioplastics Association, there is ongoing rapid market growth concerning bio-based plastics by increasing the global production capacity from 1.7 million tonnes in 2014 to approximately 7.85 million tonnes in 2019. An illustration of the material share (in %) of the bioplastic production of 2014 is given in Fig.4. PLA has one of the largest shares of

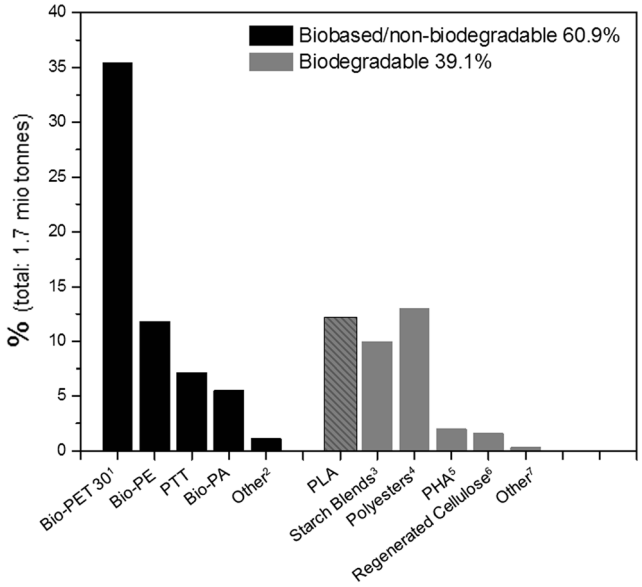

Fig. 4 Global production capacities of bioplastics 2014 (by material type) (European-Bioplastics 2015). *1* Biobased content amounts to 30 %, *2* contains durable starch blends, bio-polycarbonate, bio-thermoplastic elastomers, bio-polyurethane (except thermosets), *3* blend components incl. in main materials, *4* contains fossil-based polybutyrate adipate terephthalate, polybutylene succinate, polycaprolactone, *5* incl. newlight technologies (CO_2-based), *6* compostable hydrated cellulose foils, *7* biodegradable cellulose ester (*Bio-PET* bio-based polyethylene terephthalate, *Bio-PE* bio-based polyethylene, *PTT* polytrimethylene erephthalate, *Bio-PA* bio-based polyamide, *PLA* polylactic acid, *PHA* polyhydroxyalkanoates)

12.2 % of the total biopolymer production capacities after Bio-PET 30 (35.4 %) and bio-based polyethylene (Bio-PE 11.8 %). Moreover, the PLA market is still expected to grow fourfold between 2013 and 2020 due to its variety of applications. PLA has extensive applications as a biopolymer in the textile and automotive industries, but it can especially be used for daily use packing material (European Bioplastics, Institute for Bioplastics and Biocomposites, nova-Institute (2014), (Cellulac 2013; European-Bioplastics 2015). NatureWorks is the largest producer of bio-based lactides, with high-purity, polymer-grade lactide rich in meso-lactide (NatureWorks 2016). Today, the world's largest lactic acid company and first industrial producer of *d*-lactic acid is Corbion Purac. With the fermentative technology from Myriant, Corbion Purac has been producing *d*-lactic acid for bioplastic applications since 2008 (Myriant-Corporation 2011).

In May 2014, Corbion Purac started developing heat-resistant PLA in a partnership with FKuR Kunststoff GmbH (Corbion-Purac 2014). The Company Cellulac possesses the technology to produce commercial quantities of lactic acid, *l*(+) and *d*(−), and lactate esters from a range of agricultural residues and food by-products. Cellulac optimized the usage of lignocellulosic materials for lactic acid production (Cellulac 2016). An industrial level of continuous production of enantiomerically pure *d*-lactic acid, suitable for conversion to bioplastics, from deproteinized lactose whey was shown in 2014 (Cellulac 2014). Another leading supplier in lactic acid and *d*-lactic acid products is Galactic, which founded, together with Total Petrochemicals, the joint venture Futerro in 2007 to develop innovative technologies for PLA production. In 2010, they inaugurated a PLA pilot plant in Belgium which was also the first in Europe (Futerro 2010). Furthermore, Galactic supplies lactic acid products for food, feed, cosmetics, pharmaceutical products, and neuraceutical industry.

The selling price of lactic acid/PLA is extremely variable and depends on the degree of purity. For example, Cellulac sells lactic acid for bioplastic applications in a price range of US$1300–5000 per metric ton and the prices for PLA as substitute for petrochemical derived polymers range between US$2300 and 6000 per metric ton (Cellulac 2013).

Concluding remarks

d-Lactic acid plays an important role in the establishment of PLA as a substitute for our daily used petrochemical plastics. Even though, to date, there are only pilot scale industrial production processes, the market for *d*-lactic acid is estimated to grow significantly in the next years. The implementation of an industrial production is simplified because the production steps are similar to *l*-lactic acid production. However, the selection of highly productive *d*-lactic acid producing bacterial strains and the decrease of production cost by the fermentation of agricultural side products is still a focus for further research. However, some cost-associated difficulties have to be overcome to establish an economical process for the industrial production of *d*-lactic acid. The final cost of producing PLA depends on the efficiency of the initial fermentation process (Petersen et al. 1999). This includes the nutrients for the fermentation process, such as the carbon and nitrogen source, which are major cost factors and have to be substituted by inexpensive raw materials. Another high cost factor is the purification of lactic acid by precipitation with calcium carbonate ($CaCO_3$) or calcium hydroxide ($Ca(OH)_2$) as neutralizing agents. The generated calcium lactate requires several purification steps, large amount of sulfuric acid is needed, and subsequent gypsum is produced as by-product.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights and informed consent This article does not contain any studies with human participants or animals performed by any of the authors.

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