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Research review paper

Recent advances in lactic acid production by microbial fermentation processes

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ABSTRACT

Fermentative production of optically pure lactic acid has roused interest among researchers in recent years due to its high potential for applications in a wide range of fields. More specifically, the sharp increase in manufacturing of biodegradable polylactic acid (PLA) materials, green alternatives to petroleum-derived plastics, has significantly increased the global interest in lactic acid production. However, higher production costs have hindered the large-scale application of PLA because of the high price of lactic acid. Therefore, reduction of lactic acid production cost through utilization of inexpensive substrates and improvement of lactic acid production and productivity has become an important goal. Various methods have been employed for enhanced lactic acid production, including several bioprocess techniques facilitated by wild-type and/or engineered microbes. In this review, we will discuss lactic acid producers with relation to their fermentation characteristics and metabolism. Inexpensive fermentative substrates, such as dairy products, food and agro-industrial wastes, glycerol, and algal biomass alternatives to costly pure sugars and food crops are introduced. The operational modes and fermentation methods that have been recently reported to improve lactic acid production in terms of concentrations, yields, and productivities are summarized and compared. High cell density fermentation through immobilization and cell-recycling techniques are also addressed. Finally, advances in recovery processes and concluding remarks on the future outlook of lactic acid production are presented.

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1. Introduction

In recent years, concerns over the microbial production of commercially valuable products have been growing. This is mainly attributed to escalating global energy and environmental problems, which have stimulated researchers worldwide to develop methods for producing almost everything through green methods. Of these, lactic acid is a most important product that has attracted a great deal of attention due to its widespread applications, mainly in food, chemical, cosmetic, and pharmaceutical industries. Also, it has great potential for the production of biodegradable and biocompatible polylactic acid (PLA) polymers that drive the current market expansion for lactic acid. PLA products can be used in a wide variety of applications ranging from packaging to fibers and foams. In comparison with petrochemical plastics, PLA production is considered a relatively immature technology at the industrial scale. This is mainly attributed to the high production cost of lactic acid, which is the starting raw material for PLA. Lactic acid production can be achieved either by chemical synthesis routes or fermentative production routes (lactic acid fermentation). By the chemical synthesis route, a racemic mixture of DL-lactic acid is usually produced. On the other hand, fermentative production routes offer advantages of utilization of cheap renewable substrates, low production temperatures, low energy consumption, and production of optically pure D- or L-lactic acid when the appropriate microorganism is selected as the lactic acid producer. Presently, almost all lactic acid produced worldwide comes from the fermentative production route (Abdel-Rahman et al., 2011c).

The demand for lactic acid has been estimated to grow yearly at 5–8% (Yadav et al., 2011). The annual world market for lactic acid production was expected to reach 259,000 metric tons by the year 2012 (Martinez et al., 2013), and is forecasted to reach 367,300 metric tons by the year 2017. The major manufacturers of fermentative lactic acid production are NatureWorks LLC, which had been wholly owned by Cargill Incorporated (USA), Purac (The Netherlands), Galactic (Belgium), and several Chinese companies (John et al., 2007b). In late 2002, NatureWorks LLC started the world's first full-scale PLA plant in Blair, Nebraska, USA, capable of producing 140,000 metric tons per year. NatureWorks LLC entered into a joint venture between Cargill and Teijin Limited of Japan to become 50–50 partners in December 2007. This company has done extensive work on the development of lactic acid-based polymers, which are of two types — the polydilactide-based resins (NatureWorks PLA®), used for plastics or packaging, and the Ingeo™ polydilactide-based fibers that are used in specialty textiles and fibers. PLA resins have been approved for all food-type applications by the US Food and Drug Administration and European regulatory authorities. Presently, NatureWorks LLC is the leader in PLA technology, and has over 95% of the current PLA worldwide production capacity. Other manufacturers involved in PLA production such as Toyobo, Dai Nippon Printing Co., Ltd., Mitsui Chemicals, Inc., Shimadzu Corporation, NEC Corporation, Toyota Motor Corporation (Japan), Purac Biomaterials, Hycail (The Netherlands), Futerro and Galactic (Belgium), Cereplast Inc. (USA), FKuR Plastics Corporation, Biomer Technology Ltd, Stanelco RF Technologies, Uhde Inventa-Fischer (Germany), and Hisun Industries Co. Ltd and Snamprogetti (China) account for the remaining capacity (Jamshidian et al., 2010).

Although the demand for PLA is increasing, its current production capacity of only 450,000 metric tons per year is dwarfed by the 200 million metric tons per year of total plastics produced (Okano et al., 2010), which results from the high manufacturing cost of raw material, that is, lactic acid monomer as mentioned above. Furthermore, the primary costs associated with lactic acid production include the fermentative substrates of nutrients, expensive nitrogen sources and sugars required for the cell growth and the fermentation along with the downstream recovery and purification process. In addition, to produce high concentration of lactic acid, fermentation processes require the pH control in the range of ca. 5–7 using neutralizing agents during fermentation, which also increases the costs in terms of acidulation of the fermentation broth to regenerate free lactic acid followed by downstream steps. To meet recent applications of lactic acid for PLA and to be commercially viable, overall lactic acid production costs should be at or below $ 0.8 per kilogram of lactic acid, as the selling price of PLA must decrease by roughly half of its present price to compete with fossil-fuel-based plastics (Okano et al., 2010). To this end, a strain for the industrial lactic acid production should produce more than 100 g/L of lactic acid with a high yield at near maximal theoretical value, a high optical purity of lactic acid (>99%), and a high productivity in cheap media (Litchfield, 2009). In addition, the fermentation process improvements will lead to enhanced operating efficiency and yields of lactic acid production. Therefore, improvements and engineering of new effective fermentation processes are important to fit the worldwide requirements.

The efficiency of lactic acid fermentation processes mainly depends on the lactic acid producer, fermentation substrate, and operational modes. Lactic acid can be produced from renewable materials by various microbial species, including bacteria, fungi, yeast, microalgae, and cyanobacteria. Selection of the strain is of great importance, particularly in terms of high optical purity of lactic acid and high production capacity. A major concern in lactic acid fermentation is to reduce the cost of raw materials and improve the production efficacy. Pure sugars and food crops have been partially replaced by nonfood carbohydrates in the fermentation industry in recent years. The use of various low-cost

raw materials has been extensively investigated (Abdel-Rahman et al., 2011c; Budhavaram and Fan, 2009; Laopaiboon et al., 2010; Mazumdar et al., 2010; Talukder et al., 2012). Another method that reduces the cost of lactic acid production is to improve the production, productivity and yield of lactic acid fermentation. Although batch fermentation is the most widely used in lactic acid production, it suffers from low productivity due to long fermentation times and low cell concentrations. In addition, substrate and end product inhibition are also considered major bottlenecks of this fermentation manner. To overcome such problems, fed-batch fermentation, repeated fermentation, and continuous fermentation have been investigated. However, each of these methods has some limitations, and great efforts have been made to further develop these processes to achieve efficient lactic acid production. Fermentation methods using high cell densities (HCDs) via immobilization or cell recycling have been shown to achieve high lactic acid productivity. Also, advances in integrated-membrane fermentation reactor systems are a promising technology for future industrial lactic acid production.

This paper reviews the characteristics of lactic acid producers, their abilities to utilize different substrates, and the metabolic pathways involved in the production of lactic acid. Alternative substrates to pure sugars and food crops that have been recently used for lactic acid production are also pointed out. Recent advances in process engineering, methods for lactic acid production, the limitations of each method, and how to overcome these limitations are also discussed.

2. Microbial lactic acid producers

Lactic acid can be produced by several microorganisms classified into bacteria, fungi, yeast, cyanobacteria, and algae. Each biocatalyst has achieved one or more improvements over the others, such as a broader substrate range, improved yield and productivity, reduction of nutritional requirements, or improved optical purity of lactic acid. The use of mixed strains in fermentation may provide useful combinations of metabolic pathways for the utilization of complex materials and consequently enhance lactic acid production (Cui et al., 2011; Kleerebezem and van Loosdrecht, 2007; Nancib et al., 2009; Taniguchi et al., 2004). The genetic-engineering approaches have been exploited in a big way for the improvement of lactic acid yield and optical purity by various microbial producers. The reference by Okano et al. (2010) provides an extensive review of reports on the subject of genetically engineered-microorganisms for lactic acid production. In this section, the characteristics of lactic acid producers and their applicability for fermentation processes are discussed.

2.1. Bacteria

Lactic acid-producing bacteria include wild-type and engineered producers. These organisms can be divided into 4 main *producers*, namely, lactic acid bacteria (LAB), *Bacillus* strains, *Escherichia coli*, and *Corynebacterium glutamicum*. In general, bacterial lactic acid fermentation suffers from several limitations, including (i) production of both L- and D-lactic acid via L-lactate dehydrogenase (L-LDH) and D-lactate dehydrogenase (D-LDH), respectively; (ii) low yield due to byproduct formation; (iii) use of nutritionally rich medium; and (iv) high risk of bacteriophage infection that results in cell lysis and subsequent cessation of lactic acid production (Budhavaram and Fan, 2009; Litchfield, 2009; Singh et al., 2006). Various studies have investigated methods to overcome these problems in the field of metabolic engineering, i.e., (i) improvement of optical purity via the deletion of either D- or L-LDH genes (Kyla-Nikkila et al., 2000); (ii) increased lactic acid yields through reduction of byproduct levels by the deletion of genes encoding pyruvate formate lyase (formic acid production), alcohol dehydrogenase (ethanol production), and/or acetate kinase (acetic acid production) (Zhou et al., 2003b); (iii) development of bacterial strains, e.g., *E. coli*, producing lactic acid on chemically defined media (Zhou et al., 2003a); and (iv) strain improvements for blocking steps in phage life cycle (Allison and Klaenhammer, 1998; Forde and Fitzgerald, 1999). Usage of mixed strains and/or development of phage-resistant strains are sometimes necessary to prevent bacteriophage infection (Hassan and Frank, 2001).

2.1.1. Lactic acid bacteria (LAB)

LAB constitute a diverse group of Gram-positive microorganisms that exist within plants, meat, and dairy products and can produce lactic acid as an anaerobic product of glycolysis with high yield and high productivity. The optimal growth conditions vary depending on the producers, since these bacteria can grow in the pH range of 3.5–10.0 and temperature of 5–45 °C.

The major pathways for the metabolism of hexoses and pentoses by LAB are indicated in Fig. 1. LAB are grouped as either homofermentative or heterofermentative based on the fermentation end product as described in Table 1. Homofermentative LAB possess aldolase enzymes and produce lactic acid as the major end product. They are of interest for commercial scale lactic acid production. On the other hand, heterofermentative LAB produce byproducts besides lactic acid and, therefore, the maximal yield of lactic acid to glucose reaches only 0.5 g/g or 1.0 mol/mol (Abdel-Rahman et al., 2011c). Heterofermentative LAB use the alternate pentose monophosphate pathway, converting 6-carbon sugars (hexoses) to 5-carbon sugars (pentoses) and carbon dioxide catalyzed by several enzymes (Fig. 1). Then, the resulting pentose is cleaved to glyceraldehyde 3-phosphate and acetyl phosphate by phosphoketolase. Most heterofermentative LAB strains convert the pentose sugars to lactic acid and byproducts (e.g., acetic acid) through phosphoketolase pathways with a maximum lactic acid yield at 0.6 g lactic acid per gram of pentoses. Recently, *Enterococcus mundtii* QU 25 (Abdel-Rahman et al., 2011a) and engineered *Lactobacillus plantarum* (Okano et al., 2009a, 2009b) were reported to metabolize pentose to lactic acid homofermentatively.

Most LAB, including *Lactobacilli*, are considered to be safe for industrial lactic acid production because they have had a long history of industrial-scale production without adverse health effects on either consumers or production workers. Commercially important LAB strains, such as *Lactobacillus* strains, have been particularly useful due to their high acid tolerance and their ability to be engineered for selective production of D-or L-lactic acid (Benthin and Villadsen, 1995; Kyla-Nikkila et al., 2000; Lapierre et al., 1999). On the other hand, most LAB species require complex nutrients, including amino acids, peptides, nucleotides, and vitamins, for their growth because they lack many biosynthetic capabilities, which hampers the recovery of lactic acid and increases production costs (Hofvendahl and Hahn-Hägerdal, 2000; Lapierre et al., 1999; Litchfield, 2009; Reddy et al., 2008; Singh et al., 2006). In addition, the low fermentation temperature for lactic acid production required by most LAB strains not only increases contamination risks, but also hampers its use in the simultaneous saccharification and fermentation (SSF) of lignocellulosic biomass using hydrolytic enzymes at higher optimal temperatures for saccharification than that required for cell growth of LAB strains.

Alkaliphilic or thermotolerant LAB strains may be promising producers of lactic acid due to their tolerance to high pH temperature levels that would minimize contamination problems during processing (Calabia et al., 2011; Liu et al., 2010). Calabia et al. (2011) isolated an alkaliphilic *Halolactibacillus halophilus* from a marine environment that produced 65.8 g/L of L-lactic acid at pH 9.0. Although lactic acid production by LAB is very efficient, further improvements in the strain (especially, high acid tolerance) and the process can help to make it more cost-competitive with petroleum-based polymers for PLA production.

2.1.2. Bacillus strains

Lactic acid production has also been reported by some *Bacillus* species, including *Bacillus coagulans*, *Bacillus stearothermophilus*, *Bacillus*

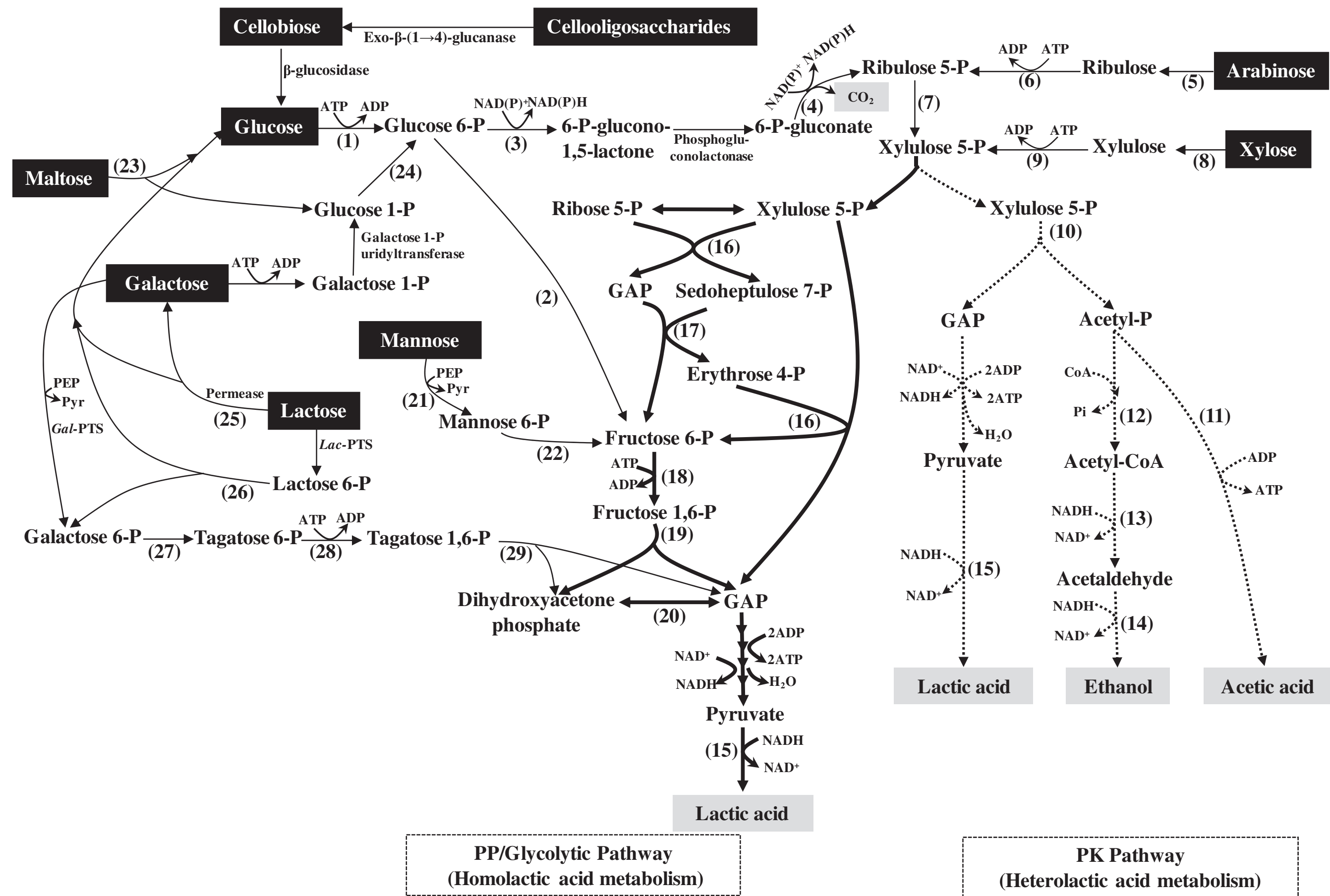

Fig. 1. Metabolic pathways for lactic acid production from various sugars by LAB. Enzymes: (1) hexokinase; (2) glucose 6-phosphate isomerase; (3) glucose 6-phosphate dehydrogenase; (4) 6-phosphogluconate dehydrogenase; (5) arabinose isomerase; (6) ribulokinase; (7) ribulose 5-phosphate 3-epimerase; (8) xylose isomerase; (9) xylulokinase; (10) phosphoketolase; (11) acetate kinase; (12) phosphotransacetylase; (13) aldehyde dehydrogenase; (14) alcohol dehydrogenase; (15) lactate dehydrogenase; (16) transketolase; (17) transaldolase; (18) 6-phosphofructokinase; (19) fructose bisphosphate aldolase; (20) triosephosphate isomerase; (21) mannose phosphotransferase system; (22) phosphomannose isomerase (23) maltose phosphorylase; (24) phosphoglucomutase ; (25) β-galactosidase; (26) phospho-β-galactosidase; (27) galactose 6-phosphate isomerase; (28) tagatose 6-phosphate kinase; and (29) tagatose 1,6-diphosphate aldolase. Solid lines indicate the homofermentative pathway. Thick-solid lines and dashed lines indicate PP/glycolytic pathway and PK pathway, respectively. Lac-PTS: phosphoenolpyruvate-lactose phosphotransferase system.

licheniformis, *Bacillus subtilis*, and *Bacillus* sp. In comparison to LAB, *Bacillus* spp. have several potential improvements to lactic acid production that may help for the reduction of costs in lactic acid fermentation as follows: (i) *Bacillus* ssp. can grow and produce lactic acid by using mineral salt medium with few nitrogen sources instead of expensive media (Q. Wang et al., 2011); (ii) alkaliphilic strains such as *Bacillus* sp. WL-S20, isolated by Meng et al. (2012), produced L-lactic acid at a concentration of 225 g/L and a yield of 0.993 g/g in fed-batch fermentation at pH 9.0, which would reduce a risk of the contamination during fermentation; and (iii) *Bacillus* ssp. can produce lactic acid in thermal fermentation (≥50 °C). These characteristics should give *Bacillus* spp. several advantages over other bacteria. First, costs associated with the coolant water after medium sterilization would decrease. In addition, use of *Bacillus* spp. would enable the SSF of lignocellulosic biomass with cellulase at an optimum temperature (Budhavaram and Fan, 2009; Maas et al., 2008a; Ou et al., 2011; Patel et al., 2006) and enable open fermentation using nonsterilized media at higher temperatures than 40 °C (Qin et al., 2009; Zhao et al., 2010b). Open fermentation has been reported using thermotolerant *Bacillus* strains, including *B. coagulans* (Ou et al., 2009, 2011; Patel et al., 2006; Rosenberg et al., 2005; Sakai and Ezaki, 2006), *B. licheniformis* (Wang et al., 2011b; Sakai and Yamanami, 2006), and *Bacillus* strains 36D1 and 2-6 (Patel et al.,

Table 1
Homoferementative and heterofermentative lactic acid bacteria.

Characterization	Homofermentative LAB	Heterofermentative LAB
Products	Lactic acid	Lactic acid, ethanol, diacetyl, formate, acetoin or acetic acid, and carbon dioxide
Metabolic pathways	Hexose:Embden–Meyerhof pathway Pentose:pentose phosphate pathway	Hexose: phosphogluconate and phosphoketolase pathway Pentose:phosphoketolase pathway
Theoretical yield of lactic acid to sugars	Hexose: 1.0 g/g (2.0 mol/mol) Pentose: 1.0 g/g (1.67 mol/mol)	Hexose: 0.5 g/g (1.0 mol/mol) Pentose: 0.6 g/g (1.0 mol/mol)
Genera	*Lactococcus*, *Streptococcus*, *Pediococcus*, *Enterococcus*, some *Lactobacillus*	*Leuconostoc*, *Oenococcus*, some *Lactobacillus* species
Availability for commercial lactic acid production	Available due to high selectivity	Not available due to high by-product formation

2005; Qin et al., 2009; Zhao et al., 2010b). Furthermore, *Bacillus* strains are able to grow and ferment the hexoses and pentoses in lignocellulosic biomass to lactic acid. *B. coagulans* 36D1 was reported to utilize pentose sugar via the pentose–phosphate pathway, which maximizes the yield of lactic acid up to 1.0 g/g-consumed sugar (Patel et al., 2006).

2.1.3. *E. coli*

Screening for superior lactic acid producers from natural sources is time consuming and laborious. Therefore, recent studies have applied engineering methods for achieving better fermentation efficiency by using *E. coli* strains because they can rapidly metabolize hexose and pentose sugars, have simple nutritional requirement, and are easy to be genetically manipulated. Wild-type *E. coli* generally produces a mixture of ethanol and several organic acids (lactic acid, acetic acid, succinic acid, and formic acid) to accommodate reducing equivalents generated during glycolysis (Clark, 1989; de Graef et al., 1999; Zhou et al., 2003a). To improve lactic acid production, *E. coli* strains have been engineered in the field of metabolic engineering (Chang et al., 1999; Kochhar et al., 1992; Taguchi and Ohta, 1991; Zhou et al., 2003a). Several studies reported the use of engineered *E. coli* strains for lactic acid production from glucose (Chang et al., 1999; Dien et al., 2001; Zhou et al., 2003a, b, 2005; Zhu et al., 2007), xylose (Dien et al., 2001), sucrose (Wang et al., 2012; Zhou et al., 2005), and glycerol (Mazumdar et al., 2010). However, the productivity (≤1.04 g/L/h), final concentration (≤62.5 g/L), and tolerance of lactic acid by engineered *E. coli* strains were much lower than that achieved with many LAB and *Bacillus* spp (Chang et al., 1999; Portnoy et al., 2008; Zhou et al., 2003a). Thus, the major problem to be addressed is to realize high efficient lactic acid production using inexpensive resources.

More recently, direct production of PLA and its copolymers from glucose by engineered *E. coli* through a 1-step fermentation process was reported by the expression of respective genes encoding propionate CoA-transferase and polyhydroxyalkanoate synthase for the efficient generation of lactyl-CoA and incorporation of lactyl-CoA into the polymer, respectively (Jung et al., 2010; Yang et al., 2010). However, it was necessary to use an inducer for the expression of the introduced genes and to feed succinic acid for proper cell growth. Jung and Lee (2011) reported further engineering *E. coli* JLXF5. In pH-stat fed-batch fermentation, PLA and a copolymer of poly(3-hydroxybutyrate-*co*-39.6 mol% lactate) having a molecular weight of 141,000 Da could be produced at 20 g/L polymer with a 43 wt.% content of dry cells from glucose in a chemically defined medium without adding the inducer and succinate.

2.1.4. *C. glutamicum*

C. glutamicum is a Gram-positive, fast-growing, aerobic, nonsporulating, nonmotile, saprophytic bacterium that has been reported to excrete several organic acids at small amounts under oxygen-limited conditions (Yukawa et al., 2007). Several engineered *C. glutamicum* strains have been reported to produce combined organic acids (lactic acid, succinic acid, and acetic acid) under oxygen deprivation from various sugars, such as L-arabinose and D-glucose (Kawaguchi et al., 2008); D-xylose and D-glucose (Kawaguchi et al., 2006); D-glucose, D-xylose, and D-cellobiose (Sasaki et al., 2008); and L-arabinose (Sasaki et al., 2009). By knockout of the L-LDH gene and heterologous expression of the D-LDH encoding gene from *Lactobacillus bulgaricus*, engineered *C. glutamicum* produced 17.9 g/L of D-lactic acid (optical purity >99.9%) after 16 h of fermentation, which was 32.3% higher than the lactic acid production of the parental strain (Jia et al., 2011). Use of *Corynebacteria* under oxygen-deprived conditions at an HCD is advantageous since energy is primarily channeled to lactic acid production and not cell growth (Inui et al., 2004). Okino et al. (2005) reported a direct correlation between cell concentration and acid production rates, even at elevated cell densities, and achieved L-lactic acid productivities of 42.9 g/L/h at a cell concentration of 60 g dry cells/L in mineral medium for more than 360 h. Similarly, using an HCD in mineral salt medium with glucose, up to 120 g/L D-lactic acid (optical purity ≥99.9%) was produced in fed-batch fermentation within 30 h by engineered *C. glutamicum ΔldhA*/pCRB204 with expression of D-LDH-encoding genes derived from *Lactobacillus delbrueckii* (Okino et al., 2008). Therefore, *C. glutamicum* is a suitable bacterium that can achieve high lactic acid production without the requirement for complex nutritional media. On the other hand, low lactic acid yield due to formation of acetic acid and succinic acid also needs to be addressed. Recently, Song et al. (2012) succeeded in developing an engineered *C. glutamicum* strain that can produce a lactate-based polymer, poly(LA-co-3HB), with high LA fractions (96.8 mol%), from glucose through successive enzymatic reactions. These include generation of D-lactyl-CoA by D-LDH and propionyl-CoA transferase, 3-hydroxybutyryl-CoA generation catalyzed by β-ketothiolase and NADPH-dependent acetoacetyl-CoA reductase, and copolymerization of D-lactyly-CoA and 3-hydroxybutyryl-CoA catalyzed by lactate polymerizing enzyme. The functional expression of these enzymes led to the production of poly(LA-co-3HB) with high LA fractions (96.8 mol%).

2.2. Fungi

Several species of the genus *Rhizopus*, especially *R. oryzae*, have become the focus of studies of the production of optically pure L-lactic acid (Bai et al., 2008; Taskin et al., 2012; Wu et al., 2011). *Rhizopus* strains have many advantages compared to lactic acid-producing bacteria, including their amylolytic characteristics that enable them to utilize various starchy biomasses without prior saccharification (Jin et al., 2003), low nutrient requirements (Bulut et al., 2004; Marták et al., 2003; Oda et al., 2003), low-cost downstream process due to their filamentous or pellet growth that makes its separation from fermentation broth easier than that in bacteria or yeast (Zhang et al., 2007), and fungal biomass as a valuable fermentation byproduct. The different morphological forms of fungal growth (extended filamentous form, mycelial mats, pellets, or clumps) have a significant effect on the rheology of the fermentation broth, the oxygen supply, and the level of lactic acid production. Fungal growth in small pellets is the preferable morphology for industrial fermentations because it enhances rheology and mass transfer in fermentation broth and can be utilized for long operations using repeated batch fermentation (Maneeboon et al., 2010). Several studies attempted to use immobilization techniques for L-lactic acid production with *R. oryzae* (Dong et al., 1996; Efremenko et al., 2006); however, this technique is time consuming due to the requirement for entrapment of fungal cells on matrixes and is limited in volume.

Lactic acid production by *Rhizopus* strains using different renewable resources, including molasses, raw starch materials, and lignocellulosic biomass, has been reported by many authors (Bai et al., 2008; Maas et al., 2006, 2008b; Miura et al., 2004; Park et al., 2004; Saito et al., 2012; Taherzadeh et al., 2003; Taskin et al., 2012; Thongchul et al., 2010). However, there are some limitations that should be controlled for optimal lactic acid production by *Rhizopus* strains, such as production of undesirable byproducts, particularly ethanol and fumaric acid (Litchfield, 2009; Magnuson and Lasure, 2004; Vink et al., 2010), requirements of aeration for more than the oxygen transfer rate of 0.3 g O_2/L/h (T. Liu et al., 2006; Y. Liu et al., 2006), and the filamentous nature of the *Rhizopus* strains that create potential issues in mass transfer, bulk mixing, and lactic acid recovery (Bai et al., 2003a).

2.3. Yeasts

One major economic hurdle for commercial lactic acid production is the costly recovery procedure required to separate and purify the product from the fermentation broth. Yeasts have received much attention recently as lactic acid producers because they can grow in mineral media that can facilitate further recovery of lactic acid (Dequin and Barre, 1994). In addition, yeasts can tolerate pH values as low as 1.5, which strongly enables the establishment of non-

neutralizing fermentation. Moreover, this low pH eliminates the regeneration of precipitated lactate (calcium lactate), which would lead to decreases in the cost of neutralizing agents (i.e., calcium carbonate) (Praphailong and Fleet, 1997). Although most wild-type yeasts naturally produce little lactic acid as a major fermentation product, much effort has been made to develop engineered yeasts for lactic acid production. It is possible to obtain lactic acid production at high yields by partial or full replacement of ethanol production with deletion of pyruvate decarboxylase and/or pyruvate dehydrogenase activities (Bianchi et al., 2001).

Different yeast genera have been engineered to produce lactic acid, including *Saccharomyces* (Ishida et al., 2005; Saitoh et al., 2005; Tokuhiro et al., 2009; Valli et al., 2006), *Zygosacchromyces* (Branduardi et al., 2006), *Candida* (Osawa et al., 2009), *Pichia* (Ilmen et al., 2007), and *Kluyveromyces* (Bianchi et al., 2001). Recent advances in yeast engineering have focused on the use of a variety of sugars other than glucose and xylose. Tokuhiro et al. (2008) engineered a *Saccharomyces cerevisiae* strain that expresses the β-glucosidase gene derived from *Aspergillus aculeatus* in order to allow the yeast to utilize cellobiose as a substrate. The resulting engineered strain successfully produced approximately 80 g/L lactic acid from approximately 100 g/L cellobiose, with a yield of 0.70 g/g and a maximum production rate of 2.8 g/L/h. Further studies on lactic acid production from oligosaccharides and polysaccharides via integration of respective genes into the genome of yeast strains are required.

2.4. Microalgae and cyanobacteria

With the discovery of global warming, there is growing interest in processes that couple CO_2 capture to valuable chemical synthesis through the use of photosynthetic microorganisms. Photosynthetic microorganisms (i.e., algae and cyanobacteria) offer an alternative lactic acid production approach and would allow carbohydrate feedstock costs to be eliminated. Some microalgae have the ability to convert the starch they accumulated under light and aerobic conditions into organic matter, such as lactic acid, ethanol, acetic acid, and formic acid under dark and anaerobic conditions (Hirayama and Ueda, 2004; Oost et al., 1989). A few papers have reported the levels of lactic acid production by microalgal species, including *Scenedesmus obliquus* strain D3 (Hirt et al., 1971) and *Nannochlorum* sp. 26A4 (Hirayama and Ueda, 2004). Hirayama and Ueda (2004) reported 26 g/L D-lactic acid production with an optical purity of 99.8% by *Nannochlorum* sp. 26A4 from their starch (40% content per dry weight) at yield of 70% under dark and anaerobic conditions.

Cyanobacteria possess several advantages, including their photosynthetic capabilities, simple input requirements (namely, sunlight, CO_2, and water with few required mineral nutrients), their capacity for genetic engineering, and carbon-neutral applications that could be leveraged to address global climate change concerns (Ducat et al., 2011). Niederholtmeyer et al. (2010) engineered *Synechococcus elongatus* PCC7942 via expression of genes encoding invertase, glucose- and fructose-facilitated diffusion transporter, L-LDH derived from *E. coli*, and lactate transporter, and the resulting strain produced lactic acid in the extracellular broth at 600 μM. Angermayr et al. (2012) introduced an L-LDH gene derived from *B. subtilis* into the genome of *Synechocystis* sp. PCC6803 and reported the production of 3.2 mM lactic acid by the engineered strain after 2 weeks.

3. Alternative fermentation substrates for lactic acid production

Raw material cost is one of the major factors in the economic production of lactic acid. Pure sugars or edible crops have been a traditional substrate for lactic acid production that is advantageous in obtaining a pure lactic acid product and lowering costs of pretreatment and recovery. Since substrate cost cannot be reduced by process scale-up, extensive studies are currently underway to search for novel substrates for lactic acid production. Various materials have been considered as attractive alternative substrates and renewable resources, including byproducts of agricultural industries, food industries, and natural unutilized biomasses such as starchy biomass, lignocellulosic biomass, whey, yogurt, glycerol, and algal biomass.

3.1. Starchy materials, lignocellulosic biomass, agro-industrial and food wastes

Recently, lactic acid has been produced from a variety of carbohydrates, including starchy and lignocellulosic biomasses, depending on the substrate availability in the producing country (Litchfield, 2009; Vink et al., 2007). The pretreatment and saccharification of raw materials by physicochemical and enzymatic treatment are one of the bottleneck processes for cost-effective lactic acid production (Abdel-Rahman et al., 2011c). Direct fermentation of starchy biomass has been demonstrated to produce lactic acid; however, further development is still necessary before these processes are commercially feasible. The reference by Reddy et al. (2008) provides an extensive review of reports on the subject of using starchy biomass as a substrate for lactic acid production.

Lignocellulosic biomass is another abundant carbohydrate source that has recently drawn a lot of interest for lactic acid production. The use of this type of biomass would help to overcome many environmental problems and must not cause food problems; however, it is more difficult to ferment lignocellulosic biomass than starchy biomass to lactic acid. This is because lignocelluloic biomass contains cellulose as the main component. Cellulose is a persistent polymer, and its degradation requires physicochemical pretreatments and multi-enzymatic reactions (Okano et al., 2010). For example, corn stover or cobs, sugarcane bagasse, and wood processing waste are alternative substrates used for lactic acid production after pretreatment and chemical or enzymatic hydrolysis (Cui et al., 2011; L. Wang et al., 2010; Laopaiboon et al., 2010). Lactic acid production from different substrates using several fermentation modes are described in Table 2. We have recently reviewed the composition and the utilization of lignocellulosic biomass for lactic acid production and pointed out the challenges that must be overcome for their effective utilization (Abdel-Rahman et al., 2011c). Different organic wastes that used as substrate for lactic acid production are also summarized in Table 2.

3.2. Dairy products

Dairy industries all over the world generate ample amounts of whey from milk processing for various manufactured products. Whey is a byproduct in wastewater discharged through the cheese production process, and its disposal is currently a major pollution problem for the dairy industry. Whey is a potent and suitable raw material for lactic acid production because it consists of lactose, protein, fats, water-soluble vitamins, mineral salts, and other essential nutrients for microbial growth (Panesar et al., 2007). Nevertheless, LAB require supplementation with sources of amino acids and vitamins to the medium because they do not have sufficient proteolytic enzyme activities to utilize milk proteins in whey (Miller et al., 2011). In addition, deproteinized whey containing mainly lactose has been extensively studied for lactic acid production (Büyükkileci and Harsa, 2004; Kim et al., 2006; Li et al., 2007; Schepers et al., 2002, 2006).

Theoretically, 4 mol of lactic acid should be produced from 1 mol of lactose through a homofermentative pathway after the cleavage of lactose to 1 mol of glucose and 1 mol of galactose (Fig. 1). As shown in Table 3, different strains have been used for the production of lactic acid from whey, including *Lactobacillus helveticus*, *Lb. plantarum*, *Lb. delbrueckii* subsp. *bulgaricus*, *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactoccocus lactis*, and *Kluyveromyces marxianus*. Lactic acid production from the whey in conventional batch fermentation exhibited a long lag period, which required greater fermentor capacity and increased operational costs (Zayed and

Table 2
Lignocellulosic, agro-industrial and food waste materials used for the production of lactic acid.

Fermentation substrate	Strain	Fermentation mode	Lactic acid			Reference
			C (g/L)	*Y* (g/g)	*P* (g/L/h)	
Alfalfa fibers	*Lb. delbreuckii*	Batch (SSF)	35.4	0.35	0.75	Sreenath et al. (2001)
Alfalfa fibers	*Lb. plantarum*	Batch (SSF)	46.4	0.46	0.64	Sreenath et al. (2001)
Apple pomace	*Lb. rhamnosus* ATCC 9595 (CECT288)	Batch (SHF)	32.5	0.88	5.41	Gullon et al. (2008)
Banana wastes	*Lb. casei*	Batch	–	0.10	0.13	Chan-Blanco et al. (2003)
Cassava bagasse	*Lb. delbrueckii* NCIM 2025	Batch SSF	81.9	0.94	1.36	John et al. (2006)
Cellulose	*B. coagulans* 36D1	SSF-fed-batch	80.0	0.80	0.30	Ou et al. (2011)
Cellulosic biosludge	*Lb. rhamnosus* CECT-288	SSF-fed-batch	42.0	0.38	0.87	Romani et al. (2008)
Date juice	*Lb. casei* subsp. *rhamnosus* NRRL-B445 and *Lc. lactis* subsp. *lactis* ATCC19435	Batch	60.3	–	3.20	Nancib et al. (2009)
Defatted rice bran	*Lb. delbrueckii* subsp. *delbrueckii* IFO 3202	Batch (SSF)	28.0	0.28	0.78	Tanaka et al. (2006)
Food wastes	*Lb. manihotivorans* LMG18011	Batch (SSF)	48.7	0.1	0.76	Ohkouchi and Inoue (2006)
Kitchen refuse	*B. licheniformis* TY7	Batch	40.0	–	2.50	Sakai and Yamanami (2006)
Kitchen wastes	Lactic acid bacteria and *Clostridium* sp.	Batch	64.0	0.62	–	Zhang et al (2008a)
Mango peel	Indigenous microorganisms	Batch	17.4	–	–	Jawad et al. (2013)
Mussel processing wastes	*Lb. plantarum* A6	Batch	8.4	0.98	–	Pintado et al. (1999)
Paper sludge	*B. coagulans* strains 36D1	Repeated batch (SSF)	92.0	0.77[a]	0.96	Budhavaram and Fan (2009)
Paper sludge	*B. coagulans strains* P4–102B	Repeated batch (SSF)	91.7	0.78[a]	0.82	Budhavaram and Fan (2009)
Paper sludge	*Lb. rhamnosus* ATCC 7469	Batch (SSF)	73.0	0.97	2.90	Marques et al. (2008)
Ram horn hydrolysate	*Lb. casei* ATCC 10863	Batch	44.0	0.44	1.22	Kurbanoglu and Kurbanoglu (2003)
Sugar cane baggage	*Lc. lactis* IO-1	Batch	10.9	0.36	0.17	Laopaiboon et al. (2010)
Vine-trimming wastes	*Lb. pentosus* ATCC 8041	Batch	21.8	0.77	0.84	Bustos et al. (2004)
Waste cardboard	*Lb. coryniformis* ssp. *torquens* ATCC 25600	Batch (SSF)	23.4	0.51[b]	0.49	Yanez et al. (2005)
Waste sugarcane bagasse	*Lb. delbrueckii* mutant Uc-3	Batch (SSF)	67.0	0.83	0.93	Adsul et al. (2007)
Wastewater sludge	*Lb. paracasei* strain LA1	Batch (SSF)	23.4	0.72[b]	0.23	Nakasaki and Adachi (2003)
Wheat straw	*Lb. brevis* CHCC 2097 and *Lb. pentosus* CHCC 2355	Batch	7.1	0.95	–	Garde et al. (2002)

C, concentration; *Y*, yield; *P*, productivity; *B.*, *Bacillus*; *Lb.*, *Lactobacillus*; *Lc.*, *Lactococcus*.
[a] Based on consumed glucose and xylose.
[b] g/g-potential glucose in the substrate.

Winter, 1995). In addition, the produced lactic acid has an inhibitory effect in whey fermentation that can be alleviated to a certain extent by conducting fermentation in a continuous dialysis process in a hollow fiber fermentor (VickRoy et al., 1983a) or in an electrodialysis system with a monopolar or dipolar membrane (Bazinet, 2004; Hongo et al., 1986). Continuous fermentation of whey has resulted in high productivity and does not require high-volume fermentors (Aeschlimann and von Stockar, 1991; Boyaval et al., 1987; Roy et al., 1987).

The market for yogurt has also grown rapidly over the past few years. Consequently, rejects of damaged or expired yogurt create a huge amount of waste products. Yogurt is usually sweetened with additional sugars, such as sucrose and glucose, which would result in higher lactic acid production than cheese whey containing fewer sugars. *Lb. casei* ATCC 393 achieved a bioconversion of total sugars of around 44% to 25.9 g/L of lactic acid at a yield of 0.9 g/g and productivity of 0.76 g/L/h in a pH-controlled batch fermentation process using yogurt whey (Alonso et al., 2010); however, mixed sugar utilization of lactose, glucose, and sucrose is a major problem that has to be addressed for effective utilization of yogurt whey.

3.3. Glycerol

The biodiesel industry is one of the most important technological biomass-based platforms because it has been considered as an environmentally friendly fuel. Its production reached more than 11.1 million tons in 2008 with an annual growing production rate of close to 8%–10% (Posada et al., 2012a). Different kinds of edible and inedible vegetable oils and algae oils have been widely used for biodiesel production worldwide. Consequently, overproduction of raw glycerol as a byproduct is a continuous challenge, leading to byproduct wastes obtained at a weight ratio of 1:10 (glycerol: biodiesel) (Posada et al., 2012b). Therefore, effective glycerol utilization as a cheap raw material would solve both economic and environmental drawbacks. Several microorganisms were reported to convert glycerol to lactic acid, including *Klebsiella*, *Clostridium*,

Table 3
Lactic acid production from cheese whey in different fermentation modes by different producers.

Strain	Fermentation mode	Lactic acid			Reference
		C (g/L)	*Y* (g/g)	*P* (g/L/h)	
K. marxianus	Batch	8.8	0.24	4.3[a]	Plessas et al. (2008)
Lb. helveticus	Batch	10.1	0.23	5.1[a]	
Lb. bulgaricus	Batch	9.6	0.30	4.8[a]	
Lb. helveticus & *K. marxianus* (mixed culture)	Batch	15.5	0.45	10.0[a]	
Lb. bulgaricus& *K. marxianus* (mixed culture)	Batch	16.2	0.41	10.5[a]	
Lb. helveticus & *Lb. bulgaricus* (mixed culture)	Batch	14.6	0.35	9.4[a]	
Lb. helveticus & *Lb. bulgaricus* & *K. marxianus* (mixed culture)	Batch	19.8	0.47	12.8[a]	
Lb. casei NRRL B-441	Batch	96.0	0.93	2.2	Büyükkileci and Harsa (2004)
Lb. casei SU No. 22 and *Lb. lactis* WS 1042 (mixed culture)	Batch	22.5	0.48	0.93	Roukas and Kotzekidou (1998)
	Fed-batch	46.0	0.77	1.91	
Lb. bulgaricus ATCC 8001, PTCC 1332	Batch	24.6	0.81	–	Fakhravar et al. (2012)
Lb. helveticus R211	Continuous	38.0	–	19–22	Schepers et al. (2006)

C, concentration; *Y*, yield; *P*, productivity; *Lb.*, *Lactobacillus*; *K.*, *Kluyveromyces*.
[a] g/L/day.

and *Lactobacillus* (Biebl, 2001; Cheng et al., 2006; El-Ziney et al., 1998). Kishimoto (2008) developed a method for producing lactic acid from glycerol using *Achromobacter denitrificans* NBRC 12669. However, only 3.9 g/L lactic acid was produced from 9.4 g/L consumed glycerol. A common characteristic of glycerol metabolism by wild type *E. coli* under either anaerobic or microaerobic conditions is the heterofermentation behavior with the production of ethanol as the primary product and the negligible amount of lactic acid production (Dharmadi et al., 2006; Durnin et al., 2009; Gonzalez et al., 2008; Murarka et al., 2008). Hong et al. (2009) isolated *E. coli* AC-521, which produced 56.8 g/L and 85.8 g/L lactic acid with few byproducts in batch and fed-batch fermentations, respectively (Table 4). Recently, lactic acid production from glycerol using engineered *E. coli* has been investigated as shown in Table 4. Mazumdar et al. (2010) engineered a homofermentative route for D-lactate production by overexpressing pathways involved in the conversion of glycerol to D-lactic acid and by disrupting the pathways leading to the synthesis of competing by-products. Using that engineered strain, 32 g/L of D-lactic acid was produced from 40 g/L glycerol in batch fermentation with a minimal medium (Table 4). Based on the aforementioned study, process design, simulation, and assessment of optically pure D-lactic acid production from raw glycerol using engineered *E. coli* strains were reported by Posada et al. (2012a, 2012b). Higher concentrations of D-lactic acid up to 111.5 g/L (Mazumdar et al. (2010); Tian et al., 2012) or L-lactic acid up to 50 g/L (Mazumdar et al., 2013) were achieved in fed-batch fermentation (Table 4).

3.4. Microalgae

Microalgae have been recently utilized as the substrates for fermentative lactic acid production. In comparison to lignocellulosic biomass, microalgae do not contain lignin which simplifies its conversion into fermentable sugars (Nguyen et al., 2012a,b). In addition, it can grow almost anywhere and has an extremely short harvesting cycle of approximately 1–10 days (Schenk et al., 2008). The green microalga *Hydrodictyon reticulum* contains 47.5% reducing sugars, including 35% glucose, and has been used as a substrate for the production of L-lactic acid by *Lactobacillus paracasei* LA104 or D-lactic acid by *Lactobacillus coryniformis* spp. *torquenes* [Table 4] (Nguyen et al., 2012 a,b). Through SSF with cellulase, cellobiase, and amylase, *H. reticulum* achieved an L-lactic acid concentration of 37.1 g/L at a yield of 0.46 g/g algae and a productivity of 1.03 g/L/h [Table 4] (Nguyen et al., 2012a). In addition, Talukder et al. (2012) reported the extraction of lipids from the microalgae *Nannochloropsis salina* and used a lipid-free microalgae hydrolysate (containing glucose and xylose) as a substrate for fermentative lactic acid production by *Lactobacillus pentosus* with a lactic acid yield of 0.93 g/g and a productivity of 0.45 g/L/h (Table 4). Further studies, especially those associated with the pretreatment of microalgae, are required in order to achieve effective lactic acid fermentation from such a highly abundant biomass.

4. Advances in fermentation processes for enhanced lactic acid production

Selection of fermentation processes may vary with respect to the type and nature of substrate, microbial growth, and viscosity of fermentation broth. In the present section, fermentation processes and their developments for enhanced fermentative lactic acid production are described. This includes batch, fed-batch, repeated, and continuous fermentations. The advantages and disadvantages of these fermentation modes are described in Table 5.

4.1. Batch fermentation

Batch fermentation is the most simple and commonly used fermentation process, where all carbon substrates and other components are not added during fermentation, except for neutralizing agents for pH control. This closed system has advantages in reducing the risk of contamination and obtaining high lactic acid concentrations in comparison to other fermentation methods (Hofvendahl and Hahn-Hägerdal, 2000). On the other hand, batch fermentation suffers from low cell concentrations due to limited levels of nutrients and low productivity mainly because of either substrate and/or product inhibition. Kinetic studies on lactic acid production showed that the final lactic acid concentration increases with an increase in the initial glucose concentration as high as 200 g/L (Goncalves et al., 1991; Kadam et al., 2006; Yun et al., 2003). As shown in Table 6, Moon et al. (2012) reported the highest lactic acid concentration in batch fermentation by *Lb. paracasei* subsp. *paracasei* CB2121 — up to 192 g/L of lactic acid from 200 g/L glucose.

4.1.1. Fermentation methods

Different fermentation methods were applied in a batch fermentation mode, including SSF, separate hydrolysis and fermentation (SHF), use of mixed culture or open fermentation to improve lactic acid production from different substrates as shown in Table 6. The SSF method offers various advantages over SHF, such as the use of a single-reaction

Table 4
Lactic acid production from glycerol and microalgae.

Fermentation substrate	Strain	Fermentation mode	Lactic acid				Reference
			C (g/L)	*Y* (g/g or mol/mol)	*P* (g/L/h)	Isomer and optical purity (%)	
Glycerol	*Achromobacter denitrificans* NBRC 12669	Batch	3.9	0.41[a]	–	D-(≥99.9)	Kishimoto (2008)
	E. coli AC-521	Batch	56.8	0.88[b]	0.94	ND	Hong et al. (2009)
		Fed-batch	85.8	0.90[b]	0.97	ND	
	E. coli K12 strain	Batch	32.0	0.85[a]	0.44	D-(≥99.9)	Mazumdar et al. (2010)
	MG1655-LA02Δ*dld* (engineered)	Fed-batch	45.0	0.83[a]	0.54		
	E. coli strain CICIM B0013-070 (pUC-*ldh*A) (engineered)	Fed-batch	111.5	0.78[a]	2.80	D-(≥99.9)	Tian et al. (2012)
	E. coli (engineered)	Fed-batch	50.0	0.90[a]	0.60	L-(≥99.9)	Mazumdar et al. (2013)
Microalgae							
Hydrodictyon reticulum	*Lb. paracasei* LA104	Batch (SSF)	37.1	0.46[a]	1.03	L-(95.7–98.0)	Nguyen et al. (2012a)
	Lb. coryniformis sub. *torquens* ATCC 25600	Batch (SSF)	36.6	0.46[a]	1.02	D-(95.8–99.6)	Nguyen et al. (2012b)
Nannochloropsis salina	*Lb. pentosus* ATCC-8041	Batch (SSF)	23.0	0.93[a]	0.45	ND	Talukder et al. (2012)

C, concentration; *Y*, yield; *P*, productivity; *E.*, *Escherichia*; *Lb.*, *Lactobacillus*, ND, not determined.
[a] g/g.
[b] mol/mol.

vessel, rapid processing time, less enzyme loading, reduced end-product inhibition of hydrolysis, and increased productivity (Abdel-Rahman et al., 2011c). In SSF from broken rice by *Lb. delbrueckii* strain JCM1106, starch was gradually hydrolyzed to glucose and then converted to lactic acid while avoiding glucose repression (Nakano et al., 2012). Marques et al. (2008) reported a higher lactic acid yield of 0.97 g/g using SSF than that obtained using SHF (0.81 g/g) from recycled paper sludge with *Lactobacillus rhamnosus* ATCC7469. Moreover, the fermentation step of SHF is preceded by a prolonged period of separate enzymatic hydrolysis that decreases the real productivity.

Improvement of batch fermentation was also reported with a mixed culture. Cui et al. (2011) used mixed strains of *Lb. rhamnosus* and *Lactobacillus brevis* for the consumption of both cellulose- and hemicellulose-derived sugars from corn stover. During SSF using an NaOH-treated corn stover by mixed fermentation, an improved lactic acid yield of 0.70 g/g was obtained, which was approximately 18.6% and 29.6% higher than that obtained from single strains of *Lb. rhamnosus* and *Lb. brevis*, respectively [Table 6] (Cui et al., 2011). Similarly, 81 g/L of lactic acid was produced from cassava bagasse via the SSF method by mixed fermentation of *Lb. casei* and *Lb. delbrueckii* (John et al., 2006). Nancib et al. (2009) reported a higher lactic acid concentration of 60.3 g/L with the mixed strains of *Lb. casei* subsp. *rhamnosus* NRRL-B445 and *Lc. lactis* subsp. *lactis* ATCC 19435 as compared to those obtained by the single strains alone (53 and 46 g/L, respectively).

As shown in most studies stated in Tables 2–4 and 6, various strains of lactic acid producers are applied in fermentation using sterile media with lignocellulosic or waste materials. However, it is economically unfavorable to use autoclaving for sterilization of indigenous microorganisms and to inoculate other pure lactic acid-producing strains since it is difficult to metabolize the complex carbohydrate compositions by single strain (Sakai et al., 2004b). Therefore, nonsterile (open) fermentation has received more attention for lactic acid production not only for utilizing complex carbohydrate materials but also for its additional advantages in avoiding the Maillard reaction and formation of furfural compounds during sterilization, lowering energy consumption and equipment requirement, simplifying the fermentation process, and saving labor (Zhang et al., 2008a; Sakai et al., 2004a,b, 2006). Several studies have focused on enhancement of lactic acid optical purity in open fermentation by complex natural microbial composition (Ennahar et al., 2003; Payot et al., 1999; Sakai et al., 2004b). Variations in conditions and methods of feeding substrate in open fermentation have been shown to affect the microbial community structure and consequently the optical purity of lactic acid (Ennahar et al., 2003; Payot et al., 1999). Controlling pH in the fermentation broth has been reported to suppress the growth of indigenous bacteria for open D-lactic acid fermentation from rice bran powder. With the pH maintained at 5.0, *Lb. delbrueckii* IFO 3202 produced 28 g/L D-lactic acid from 100 g/L rice bran at a yield of 0.78 g/g and optical purity of 95% (Tanaka et al., 2006). Zhang et al., (2008a) reported that the optical purity of lactic acid was much higher at uncontrolled pH (82%), acidic pH (5.0, 80%), or alkaline pH (8.0, 72%) than that at neutral pH (6.0, 30% and 7.0, 20%) using kitchen wastes in open fermentation. Moreover, increasing the fermentation temperature from 35 °C to 45 °C at pH 7.0 enhanced the optical purity from 20% to 66%. Some researchers suggested that an unsterile feedstock should be used to assure economic viability. Such new fermentation methods can add significant value to the economy of batch fermentation for lactic acid production.

4.1.2. Factors affecting batch fermentation efficiency

Several factors were reported to improve lactic acid production efficacy including nitrogen sources, pH and neutralizing agents and aeration (Table 6). These factors are briefly discussed as follows.

Many studies on lactic acid production have reported that the addition of several nutrients in media and supplementation of nitrogen sources leads to higher production of lactic acid. In addition, selecting a suitable low-cost nutrient for the medium has usually been considered a major aspect for improvement and development of lactic acid production (Tinoi et al., 2005). Food wastes with whey are utilized not only as carbon sources for lactic acid production but also organic nitrogen sources (Panesar et al., 2007; Yao et al., 2010). Rivas et al. (2004) achieved a high lactic acid productivity of 2.38 g/L/h from glucose by *Lb. rhamnosus* using the biomass of *Debaryomyces hansenii* derived from xylitol production and corn steep liquor as the nitrogen sources. Substitution of corn steep liquor for yeast extract achieved an L-lactic acid concentration, yield, and productivity of 115.1 g/L, 0.96 g/g, and 4.58 g/L/h, respectively, in batch fermentation by *Lb. rhamnosus* CGMCC 1466 (Yu et al., 2008). Liu et al. (2010) reported that malt sprout and corn steep liquor have a more significant effects on L-lactic acid production by *Lb. plantarum* As.1.3, in which a higher yield of 0.98 g/g and a higher maximum productivity of 13.0 g/L/h were obtained than those obtained with MRS medium (0.87 g/g and 10.0 g/L/h, respectively). Furthermore, chicken feather hydrolysate exhibited a higher lactic acid production (38.5 g/L) and yield (7.7 g/g nitrogen source) than yeast extract (33.2 g/L and 6.6 g/g nitrogen source, respectively) and ammonium sulfate (28.5 g/L and 5.8 g/g nitrogen source, respectively) from molasses by *R. oryzae* TS-61 (Taskin et al., 2012).

Increased undissociated lactic acid in accordance with decreasing pH due to lactic acid production is considered to inhibit the fermentation of several lactic acid producers. Therefore, trapping the undissociated lactic acid during fermentation as lactate salt by the addition of neutralizing agents, such as sodium hydroxide, potassium hydroxide, calcium hydroxide, calcium carbonate, or ammonium solution, would partially overcome such inhibition and improve fermentation efficacy as shown in Table 6 (Abdel-Rahman et al., 2011a,b; Adsul et al., 2007; Qin et al., 2010; Tashiro et al., 2011). *B. subtilis* CH1 alsS produced 106 g/L of L-lactic acid from glucose with a productivity of 0.54 g/L/h at a pH of 7.0 controlled by potassium hydroxide (Romero-Garcia et al., 2009). At a pH of 6.5 controlled by the addition of sodium hydroxide, *Lb. paracasei* subsp. *paracasei* CHB2121 efficiently produced high

Table 5
Advantages and disadvantages of fermentation processes.

Fermentation mode	Advantages	Disadvantages
Batch fermentation	- Simple operation - High product concentration - Reduced risk of contamination	- Low productivity - Substrate and/or end product inhibition
Fed-batch fermentation	- Overcome substrate inhibition problem - High product concentration	- End product inhibition - Difficult to conduct optimal design
Repeated fermentation	- Time-saving processes - Labor-saving - Omission of seed preparation time - High growth rates - Short main culture	- Requirement of special devices (e.g., hollow fiber-module) or special connection lines used for cell concentration
Continuous fermentation	- High productivity - Control growth rates - Less frequency shut down process	- Incomplete utilization of the carbon source

Table 6
Lactic acid production in batch fermentation with different methods.

Fermentation substrate	Strain	Lactic acid				Fermentation method	Reference
		C (g/L)	*Y* (g/g)	*P* (g/L/h)	Isomer and optical purity (%)		
Broken rice	*Lb. delbrueckii*	79.0	0.81[a]	3.58	D (96.1)	●SSF with glucoamylase ●Performed in 5-l fermenter with 2.5-l basal medium at 40 °C, 150 rpm, pH controlled at 6.0 with $Ca(OH)_2$	Nakano et al. (2012)
Corn starch	*Lb. plantarum* NCIMB 8826 (engineered)	73.2	0.85	3.86[b]	D (99.6)	●Performed in a 2–l bioreactor with a 700-mL working volume, at 37 °C, 100 rpm, pH controlled at 5.5 by NH_3 solution	Okano et al. (2009c)
Corn stover	*Lb. rhamnosus* and *Lb. brevis* (mixed culture)	21.0	0.70	0.58	ND	●SSF with cellulases ●Performed in 250 mL-flasks containing 100 mL-media at 37 °C, shaking at 100 rpm, initial pH 5 with $CaCO_3$	Cui et al. (2011)
Glucose	*Lb. paracasei* subsp. *paracasei* CHB2121	192	0.96	3.99	L (96.6)	●Performed in a 2.5-l jar fermentor with a working volume of 1.5-l at 38 °C and 200 rpm, pH controlled at 6.5 by addition of NaOH	Moon et al. (2012)
Glucose	*Bacillus* sp. Na-2	106	0.94	3.53	L (99.5)	●Two stage aeration method ●Open fermentation ●Performed in a 5-l bioreactor containing 4-l unsterilized fermentation medium at 50 °C, pH controlled at 6.0 by NaOH	Qin et al. (2010)
Glucose	*Rhizopus oryzae* GY18	115	0.81	1.6	L (98.5)	●Performed in 500 mL-flask at 35 °C and $CaCO_3$ as a neutralizing agent	Guo et al. (2010)
Jerusalem artichoke tuber extract	*Lb. paracasei* KCTC13169	92.5	0.98	1.2	L (93.2)	●Performed in 5-l jar fermentor containing 2-l medium at 37 °C, at 150 rpm, pH controlled at 6.0 with NaOH.	Choi et al. (2012)
Liquid distillery stillage	*Lb. rhamnosus* ATCC 7469	18.6	0.73	–	L (ND)	●No supplementation with nitrogen or mineral salts ●Performed in 500 mL-flasks with 200 mL of liquid stillage under anaerobic conditions in a gas pack system for 72 h at 41 °C, shaking (90 rpm), $CaCO_3$ (1%) as a neutralizing agent.	Djukić-Vuković et al. (2012)
Sucrose	*H. halophilus* JCM 21694	65.8	0.83	1.1	L (98.8)	●Performed in a 5-l jar fermentor with 2.5-l fermentation medium at 30 °C, 250 rpm, pH-controlled at 9.0 by NaOH.	Calabia et al. (2011)
Sucrose	*Escherichia coli* (engineered)	85.0	0.85	1.0	D (98.3)	●Performed in 15-l fermentor with 10-l medium at 37 °C, 200 rpm, and pH 7.0 controlled by of a 3.5 M $Ca(OH)_2$ slurry	Wang et al. (2012)
Sucrose	*Rhizopus oryzae* GY18	80.1	0.89	1.67	L (98.5)	●Performed in a 500 mL-flask at 35 °C and $CaCO_3$ as a neutralizing agent	Guo et al. (2010)
Xylose	*Rhizopus oryzae* GY18	68.5	0.85	0.57	L (98.5)	●Performed in 500 mL-flask at 35 °C and $CaCO_3$ as a neutralizing agent	Guo et al. (2010)
Xylose	*Candida utilis* (engineered)	93.9	0.91	2.18	L (99.9)	●Performed in100 mL-spherical flat-bottom flasks containing 30 mL of medium at 35 °C, 100 rpm, and initial pH 6.8. Calcium carbonate was used as a neutralizing agent.	Tamakawa et al. (2012)
Xylose	*Rhizopus oryzae* NBRC 5378	14.4	–	0.56	L (ND)	●Performed in 1-l fermentor vessel with 600 mL-medium at 30 °C, 300 rpm, pH controlled at 3.5 by calcium hydroxide slurry. ●Aeration started at 1 vvm of air with changing agitation to 750 rpm 12 h after inoculation.	Saito et al. (2012)
White rice bran hydrolysate	*Lb. Rhamnosus* LA-04-1	82.0	0.81	3.73	L (ND)	●SHF with amylase and glucoamylase ●Performed in a 5-l jar fermentor with 2-l working volume at 42 °C, the rotation speed was 2.5 Hz, pH controlled at 6.25 by $Ca(OH)_2$ solution.	Li et al. (2012)

C, concentration; *Y*, yield; *P*, productivity; *H.*, *Halolactibacillus*; *Lb.*, *Lactobacillus*; SHF, separate hydrolysis and fermentation; SSF, simultaneous saccharification and fermentation; ND, not determined.
[a] Based on starch content of rice.
[b] Maximum lactic acid productivity.

concentrations of L-lactic acid at 192 g/L with a productivity of 3.99 g/L/h, yield of 0.96 g/g, and optical purity of 96.6% from 200 g/L glucose [Table 6] (Moon et al., 2012). Moreover, some studies reported that neutralizing agents could enhance lactic acid yield and productivity in batch fermentation (Karp et al., 2011; Nakano et al., 2012; Qin et al., 2010; Tashiro et al., 2011). We obtained higher D-lactic acid productivity of 1.67 g/L/h using NH_4OH than 1.3 g/L/h using NaOH (1.3 g/L/h) by *Lb. delbrueckii* subsp. *lactis* QU 41 (Tashiro et al., 2011). Nakano et al. (2012) reported that divalent cation (Ca^{2+}) is better than monovalent cation (Na^+ and NH^{3+}) as a neutralizing agent for lactic acid production in SSF by *Lb. delbruecki* JCM1106 from broken rice (Table 6).

Aeration exerts a remarkable effect on lactic acid production by some strains, including *Bacillus* and *E. coli* (Qin et al., 2010; Zhu et al., 2007). Without aeration, lactic acid production by *Bacillus* sp. is limited due to its low biomass, while too much aeration results in the formation of wasteful byproducts (Qin et al., 2010). To enhance fermentation efficacy in batch fermentation, a 2-stage aeration control method was employed by a few researchers (Chang et al., 1999; Qin et al., 2010; Zhu et al., 2007). In this method, aeration and agitation were controlled during the cell growth stage at the beginning of fermentation to increase biomass, and the aeration was then ceased. By applying such a method, Qin et al. (2010) improved lactic acid yield and significantly reduced byproduct formation using *Bacillus* sp. Na-2 (Table 6).

4.2. Fed-batch fermentation

Concentrations of substrate higher than the critical level cause substrate inhibition on strains, such as cell lysis and long lag phase, which would result in decreases in the fermentation rate and sugar utilization (Ding and Tan, 2006). To reduce substrate inhibition, fed-batch fermentation is thought to be a better fermentation system to maintain the substrate concentration at a low level by feeding nutrients to the fermentation broth, compared to batch and continuous fermentation (Abdel-Rahman et al., 2011c). In fed-batch fermentation, the substrate is fed continuously or sequentially to the fermentor without the removal of fermentation broth (Ding and Tan, 2006). It is especially advantageous when high substrate concentrations affect cell growth and productivity (Lee et al., 1999; Roukas and Kotzekidou, 1998). However, it still does not address severe product inhibition resulting from accumulating high lactic acid product (Table 5). To maximize the product concentration in fed-batch fermentation, several factors should be taken into consideration, including times and terms of feeding the substrate, the substrate concentration to be maintained in the fermentation broth, and how to feed the substrate (the feeding methods). It is rather difficult to perform trial and error tests with so many "open-ended" variables that may play key roles in the overall performance of the fed-batch fermentation. Several innovative fed-batch fermentation methods have been developed for lactic production (Table 7).

Common feeding methods include intermittent, constant, and exponential feeding as shown in Table 7. Pulse-feeding methods are easy to apply without much labor achieving high lactic acid production (L. Wang et al., 2011; Meng et al., 2012; Okino et al., 2008; Y. Liu et al., 2006). Ding and Tan (2006) employed several fed-batch feeding methods for L-lactic acid by *Lb. casei* LA-04-1 as summarized and compared in Table 7. By exponential feeding of glucose solution (850 g/L) and yeast extract (1%), a high L-lactic acid concentration of 180 g/L with a productivity of 2.14 g/L/h was obtained; these values were 56.5% and 59.7% higher, respectively, than those achieved by batch fermentation. Up to 210 g/L of lactic acid at a yield of 0.97 g/g and a productivity of 2.2 g/L/h was obtained by continuous feeding of glucose (Bai et al., 2003b). pH-controlled fed-batch fermentation by *Lb. lactis* BME5-18 M was developed by several authors (Bai et al., 2004; Zhang et al., 2010), maintaining the glucose concentration of the fermentation broth at a specific value (Table 7). Maas et al. (2008a) reported a novel process in which the alkaline substrate of lime-treated wheat straw was automatically fed into the fermentation broth not only as a carbon source but also to adjust the pH (Table 7). The performance of fed-batch fermentation by control the residual glucose concentration at constant was more effective at maintaining microbial activity (Li et al., 2010). Li et al. (2010) designed a high-performance glucose controller integrated with the fermentor, and achieved 170 g/L of L-lactic acid production by glucose feedback-controlled fed-batch fermentation with *Lb. rhamnosus* LA-04-1. This result was superior to that obtained either by pulse feeding or by feeding with a constant rate.

Equipment and labor could be reduced by using SSF-fed-batch fermentation in a single reactor. Romani et al. (2008) achieved production of 37.8 g lactic acid/100 g biosludge at a productivity of 0.87 g/L/h from cellulosic biosludge by *Lb. rhamnosus* CECT-288 using cellulase and β-glucosidase in SSF-fed-batch fermentation. Wang et al. (2011a) reported highly efficient D-lactic acid production from peanut meal hydrolysate and glucose in SSF-fed-batch fermentation, which resulted in 207 g/L and 226 g/L D-lactic acid by single pulse and multi-pulse feeding methods, respectively (Table 7). Similarly, Ou et al. (2011) have reported production of 80 g/L lactic acid from cellulose by *B. coagulans* 36D1 using multi-pulse feeding of cellulose in SSF-fed-batch fermentation. SSF-fed-batch fermentation using mixed strains of *Aspergillus niger* SL-09 and *Lactobacillus* sp. G-02 as the producers of hydrolytic enzymes (inulinase and invertase) and lactic acid, respectively, produced 120.5 g/L L-lactic acid from Jerusalem artichoke tubers with the L-lactic acid yield of 0.945 g/g-total sugars for 36 h of cultivation (Ge et al., 2009).

Although fed-batch process is an industrially preferred fermentation as it allows higher lactic acid concentration–up to 226 g/L as reported by Wang et al. (2011a), the productivity is relatively low ($\leq$4.7 g/L/h; Ge et al., 2010) [Table 7]. Methods that increase the lactic acid concentration along with productivity are required.

4.3. Repeated fermentation

Repeated fermentation with batch or fed-batch fermentation involves repeated cycles by inoculating a part or all of the cells from a previous run into the next run (Zhao et al., 2010a). Different methods applied for cell recycling by bacteria (centrifugation, use of hollow fiber module, or use part of the culture) and fungi (filtration or mycelial pellet precipitation) in repeated fermentation process are summarized in Table 8. In comparison with normal batch or fed-batch fermentation (Table 5), repeated fermentation has several advantages, including increase the yield, saving time and labor processes required for cleaning and sterilizing the fermentor, omission of seed preparation time, high cell concentration and high lactic acid productivity, and short fermentation time due to the high initial inoculation volume (Naritomi et al., 2002). A comparison of lactic acid fermentation results obtained from batch and fed-batch or repeated batch fermentations by some studies is summarized in Table 9.

It should be again emphasized that minimizing the fermentation time that would increase the productivity is of pivotal importance for lactic acid production by a microbial fermentation process. Zhao et al. (2010b) reported a maximum L-lactic acid production of 107 g/L with an optical purity of 99.8% using a thermophilic *Bacillus* sp. strain 2-6 in open (nonsterilized) repeated batch fermentation (Table 8). Kim et al. (2006) reported an improvement in lactic acid productivity (6.34 g/L/h) in repeated batch fermentation from cheese whey by *Lactobacillus* sp. RKY2, which was 6.2 times higher than that obtained from batch fermentation. Similarly, Wee et al. (2006) reported an enhanced lactic acid productivity of 4.0 g/L/h from wood hydrolysate and corn steep liquor in the repeated batch fermentation of *Enteroccocus faecalis* RKY1, which was 2.7-fold higher than that obtained from traditional batch fermentation. We have recently obtained the highest lactic acid productivity at 12.3 g/L/h in open repeated fermentation by *E. mundtii* QU 25 that was 5.5-fold higher than obtained by batch fermentation [Table 9] (Abdel-Rahman et al., 2013). Repeated fed-batch fermentation has also been reported using *Lb. casei* subsp. *rhamnosus* (ATCC 11443),

Table 7
Different methods used for lactic acid production in fed-batch fermentation process.

Feeding method	Fermentation substrate	Strain	Lactic acid				Fermentation method	Reference
			C (g/L)	Y (g/g)	P (g/L/h)	Isomer and optical purity (%)		
Continuous feeding	Glucose	*Lb. lactis* BME5-18M	210 161	0.97	2.2 2.02	L-(ND)	● Performed in 5-l fermentor at 37 °C, pH controlled at 6.2 by 50% (w/w) $CaCO_3$ slurry ●pH-controlled feeding with continuous feeding of glucose ●pH controlled at 7.0 by 5 M NH_4OH	Bai et al. (2003b) Bai et al. (2004)
Constant feed rate	Glucose	*Lb. casei* LA-04-1	135	0.88	1.61	L-(ND)	●Performed in a 5-l jar fermenter with an initial broth volume of 2.2 l at 42 °C ●pH controlled at 6.25 by 25% (w/w) NH_4OH	Ding and Tan (2006)
Constant residual substrate concentration			153	0.93	1.82			
Exponential feeding			158[a] 180[b]	0.91 0.90	1.88 2.14		●The nutrient feeding rate is determined by a specific equation, which is derived from a mass balance with the assumption of a constant cell yield on substrate and constant maintenance coefficient throughout the fermentation.	
pH feedback-controlled substrate feeding	Glucose	*Lb. lactis-11* *Lb. rhamnosus* LA-04-1	96.3 170	0.99 –	1.9 2.6	L-(ND) L-(ND)	●Performed in 5-l fermentor at 42 °C, pH controlled at 6.0 by 6 M NH_4OH/glucose solution ●Feeding by 770 g/L glucose using glucose controller ●Performed in 5-l fermentor at 42 °C, pH controlled at 6.25 by 33% (w/w) calcium hydroxide solution or ammonia	Zhang et al. (2010) Li et al. (2010)
	Lime-treated wheat straw	*B. coagulans* DSM 2314	40.0	0.43	–	L-(97.2)	●SSF-fed-batch with cellulose, cellobiase and xylanase ●Performed in 20-l fermentor at 50 °C and pH 6.0 ●Neutralization of acid by fed-batch addition of alkaline substrate	Maas et al. (2008a)
Pulse feeding	Glucose	*Lb. casei* LA-04-1 *Rhizopus oryzae* NRRL 395	130 92.0	0.89 0.60	1.55 0.7	L-(ND) L-(ND)	●Multi-pulse feeding ●Multi-pulse feeding ● Performed in7-l fermentor at 27 °C, pH controlled at 7.0 by 20% $Ca(OH)_2$	Ding and Tan (2006) Liu et al. (2006b)
		Corynebacterium glutamicum	120	0.87	4.0	D-(99.9)	●Multi-pulse feeding ●Performed in 100-mL bottles under oxygen deprivation conditions at 45 °C, pH-controlled at 7.0 by ammonia	Okino et al. (2008)
	Jerusalem artichoke tubers	*Aspergillus niger* SL-09 and *Lactobacillus* sp. G-02 (mixed culture)	121	0.95	3.3	L-(95)	●Multi-pulse feeding ●SSF fed-batch with inulinase and invertase produced by *A. niger* ●Multi-pulse feeding ●Performed in 7-l fermentor containing 4-l medium at 30 °C, aeration rate was 4.5 l/min, and the agitation speed was controlled at 140 rpm, initial pH was 7 (2% $CaCO_3$).	Ge et al. (2009)
		Lactobacillus sp. G-02	142	0.94	4.7	L-(95)	●Multi-pulse ●SSF-fed-batch with inulinase ●Performed in 7-l fermentor containing 4-l of a medium with enzyme and sodium citrate 10 g/L, at 30 °C, initial pH of 6.5, 5% $CaCO_3$	Ge et al. (2010)
	Peanut meal and glucose	*Sporolactobacillus* sp. strain CASD	207	0.93	3.8	D-(99.3)	●Pulse fed method ●Performed in 30-l bioreactor containing 24-l working volume at 42 °C, pH is self regulated at 5.0–6.0 with $CaCO_3$ inside the fermentor	Wang et al. (2011a)
			226	0.84	4.4		●Multi-pulse fed method	
		Bacillus sp. WL-S20	225	0.99	1.04	L-(100)	●Multi-pulse feeding ●Performed in a 1.5-l bioreactor with a working volume of 700 mL at 45 °C, 200 rpm, pH-controlled at 9.0 by NaOH.	Meng et al. (2012)
			180	0.98	1.61		●Pulse feeding	

C, concentration; *Y*, yield; *P*, productivity; *Lb.*, *Lactobacillus*; B., Bacillus.
[a] Feeding glucose solution (850 g/L).
[b] Feeding glucose solution (850 g/L) and yeast extract (1%).

Table 8
Different methods used for lactic acid production in repeated batch fermentation processes by bacteria and fungi.

Cell recycle methods	Strain	Fermentation substrate	Lactic acid				Fermentation method	Reference
			C (g/L)	*Y* (g/g)	*P* (g/L/h)	Isomer and optical purity (%)		
For bacteria								
1. Centrifugation	*Bacillus* sp. 2-6	Glucose	107	0.95	2.9	L-(ND)	●Open fermentation ●Performed in 5-l fermentor with a working volume of 3-l at 50 °C, at 200 rpm, pH controlled at 6.5 by NaOH ●At the end of each batch, the broth was centrifuged and all recycled cells were used as the seed for the next batch.	Zhao et al. (2010b)
	E. faecium No. 78	Liquefied sago starch	36.3	0.57	1.96	L-(ND)	●Performed in 3-l fermentor with a working volume of 3-l at 30 °C, at 200 rpm, pH controlled at 6.5 by 10 M NaOH ●At the end of each batch, the cells were harvested by centrifugation and used as the seed for the next batch.	Nolasco-Hipolito et al. (2012)
2. Hollow-fiber filtration module	*E. faecalis* RKY1	Glucose	92–94	–	6.03–6.2	L-(ND)	●Performed in 2.5-L jar fermentor containing 1 L of medium at 38 °C, 200 rpm, pH 7.0 controlled by 10 N NaOH ●Cell recycled was obtained using a hollow-fiber filtration module.	Oh et al. (2003)
	E. faecalis RKY1	Wood hydrolyzate	48.0	0.92	4.0	L-(ND)	●Performed in 2.5-L jar fermentor containing 1-L of medium at 38 °C, 200 rpm, pH 7.0 controlled by 10 N NaOH ●Cell recycle was obtained using a hollow-fiber filtration module.	Wee et al. (2006)
3. Using part of the culture	*Sporolactobacillus* sp. strain CASD	Glucose	82.8[a]	0.94[a]	1.72[a]	D-(98.9)	●Performed in one reactor system in 500 mL-flasks with 200 mL working volume, at 42 °C, 50 rpm, pH is self regulated by $CaCO_3$ at 5.6–5.8	Zhao et al. (2010a)
			87.3[a]	0.93[a]	1.81[a]		●Performed in two reactor system at same conditions as above	
For fungi								
1. Filtration	*R. oryzae* ATCC 9363	Glucose	113	0.90	4.3	L-(ND)	●Performed in 5 L stirred tank bioreactor containing 3 L medium at 35 °C, agitation rate 300 rpm, aeration rate 2 vvm, and pH controlled at 6.0 using 40% (w/w) $CaCO_3$ slurry ●The broth was filtered out using a glass tube and cells used for next runs.	Yu et al. (2007)
2. Mycelial pellet precipitation	*R. oryzae* NRRL 395	Corn starch	91.0[b]	0.76[b]	2.02[b]	L-(ND)	●Performed in 3 L stirred tank bioreactor containing 2 L medium at 35 °C, agitation rate 300 rpm, aeration rate 0.5 vvm, and pH controlled at 6.0 using 30% (w/w) $CaCO_3$ ●After batch culture and stopping aeration, mycelia pellets were precipitated and used for next run	Yin et al. (1998)

C, concentration; *Y*, yield; *P*, productivity; *E.*, *Enterococcus*; *R.*, Rhizopus.
[a] Data of the 2nd batch.
[b] Data of the first 6 batches.

Table 9
Comparison of lactic acid fermentation results obtained from batch and fed-batch or repeated batch fermentations in several studies.

Fermentation mode	Fermentation Substrate	Strain	Lactic acid			Ferm. time (h)	Performance and efficiency	Reference
			C (g/L)	*Y* (g/g)	*P* (g/L/h)			
Batch Fed-batch Batch Fed-batch	Glucose Xylose	*B. coagulans* strain 36D1	103.6 182.3 102.3 163.0	0.93 0.92 0.86 0.87	0.71 0.84 0.71 0.75	144 216 144 216	►Significant increase in lactic acid concentration ►Enhanced lactate productivity	Ou et al. (2011)
Batch Fed-batch	Glucose	*B. subtilis* MUR1 (mutant)	143.2 183.2	0.9 0.99	2.75 3.52	52 52	►Compared with batch, fed-batch showed 41.1% improvement in cell dry weight, 41.1% improvement in productivity and a 2.5-fold increase in the maximum productivity of lactic acid.	Gao et al. (2012)
Batch Fed-batch	Starch	*Lb. amylophilus* BCRC 14055	21.62 43.7	0.98 0.69	0.31[a] 0.75[a]	– –	►The productivity in the fed-batch with was 2.42-times higher than productivity obtained in the batch. ►Increase in cumulative lactic acid	Yen and Kang (2010)
Open batch Open fed-batch	Glucose	*Bacillus* sp. Na-2	118 182	0.97 0.96	4.37 2.88	27 60	►Using pulse feeding method, lactic acid concentrations significantly improved in open fermentation at 55 °C.	Qin et al. (2009)
Batch Repeated batch	Cheese whey	*Lactobacillus* sp. RKY2	94.06 95.11	0.98 0.99	1.06 6.34	92 15	 ►Improved productivity by 6.2 times	Kim et al. (2006)
Batch Repeated batch	Glucose	*Rhizopus oryzae*	103.7 81–95[b]	– –	2.16 3.4–3.85[b]	– –	 ►Increased productivity by repeated fermentation	Wu et al. (2011)
Open batch Open repeated batch	Glucose	*E. mundtii* QU 25	79.4 84.1	0.84 0.83	2.21 12.3	36 6	►By applying open repeated batch, a significant increase of productivity — up to 5.5-fold compared to open batch was achieved.	Abdel-Rahman et al. (2013)

C, concentration; *Y*, yield; *P*, productivity; *Lb.*, *Lactobacillus*; *B.*, *Bacillus*; *E.*, *Enterococcus*.
[a] Maximum lactic acid productivity.
[b] Data of the 1 cycles next to first batch.

Table 10
Advantages and disadvantages of high cell density culture using various techniques.
Source, Chang et al. (1994).

Technique	Advantages	Disadvantages
Cell immobilization	-Protection of cells from shear or environment -No washout at any dilution rate -High packed cell densities -Improves recombinant DNA-stability	-Poor oxygen and nutrient transfer -Instability of immobilized cell matrix -Scale-up difficulties -Limitation in the shape of support matrix -Low effectiveness factor
Cell recycle by settling/flocculation	-Simplicity of devices -Easy scale-up -Low energy requirement	-Limited to flocculent strains -Low cell density -Dilution rate limited by settling velocity
Cell recycle by centrifugation	-Applicable to industrial substrates containing many particles -Suitable for large scale operations	-Difficulties in maintaining sterile conditions -Expensive and complicated process
Cell recycle by external membrane	-High membrane surface area/culture working volume · (s/v) ratio -Ease of replacing the membrane module during the operation -High biomass density	-Recirculation needs extra pumps -Difficulty of sterilization -Decrease in flux due to fouling -Shear damage to cells -Inhomogeneity in reactor
Cell recycle by internal membrane	-Simple operation -No need for fluid circulation -Homogeneity in reactor (pH, DO, cell mass) -High biomass density	-Decrease in flux due to fouling -Limitation in s/v ratio -Inflexibility

which achieved lactic acid production of up to 146 g/L from glucose (Velázquez et al., 2001). Multiple-stage repeated fermentation was reported to improve productivity in repeated fermentations by avoiding the inhibitory effects of high product concentrations on lactic acid producing strains (Ito et al., 1991; Shimizu, 1996; Zhao et al., 2010a). Two-stage repeated batch fermentation exhibited a higher performance for D-lactic acid production than the 1-reactor system (Table 8) by *Sporolactobacillus* sp. CASD by increasing the cell concentration at an early stage of fermentation (Zhao et al., 2010a).

Repeated fermentation for L-lactic acid production using lactic acid-producing *R. oryzae* has been also reported (Bai et al., 2003a; Du et al., 1998; Jiang et al., 2008; Liu et al., 2008; Yin et al., 1998; Yu et al., 2007). Yin et al. (1998) used small mycelia pellets of *R. oryzae* NRRL395 for 9 cycles over 14 days and achieved lactic acid productivity up to 2.02 g/L/h from corn starch in an air-lift bioreactor, which was 1.9-fold higher than that obtained from batch fermentation. Du et al. (1998) used 2 different physical forms (filamentous and pellet) to produce L-lactic acid by *R. oryzae* ATCC 52311 in repeated batch fermentation, and the productivities reached up to 5.06 and 4.39 g/L/h, respectively. Bai et al. (2003a) achieved lactic acid productivity up to 3.51 g/L/h in repeated batch fermentation using *R. oryzae* R1021 from glucose. Yu et al. (2007) reported on repeated batch fermentation for 6 cycles using the floc-form of *R. oryzae* with a maximum lactic acid productivity and yield of 4.03 g/L/h and 0.90 g/g, respectively. Liu et al. (2008) developed a process for coproduction of lactic acid and chitin using pelletized *R. oryzae* NRRL 395 with a lactic acid concentration and productivity of 66 g/L and 2.4 g/L/h, respectively. Recently, Wu et al. (2011) performed repeated batch fermentation using *R. oryzae* AS 3.819 pellets for L-lactic acid production for 25 cycles in a 7-l magnetically stirred fermentor. During this fermentation process, lactic acid concentration and productivity were 103.7 g/L and 2.16 g/L/h for the first cycle, respectively; however, in the next 19 repeated cycles, the final lactic acid production reached 81–95 g/L, and the productivity reached 3.40–3.85 g/L/h (Table 9). Further studies on fungal growth characteristics and metabolic processes during repeated fermentation are still required; specifically concerning morphology of fungal strain that influences the rate of microorganism growth and product formation (Wu et al., 2011).

4.4. Conventional continuous fermentation

Production of lactic acid is strictly associated with cell growth, which allows the cells to obtain the necessary energy for growth from lactic acid producing pathways. Continuous lactic acid fermentation is attractive in terms of avoiding the end-product inhibition that occurs in batch/fed-batch fermentation by diluting the product in the fermentation broth with fresh medium (Table 5) (Amrane and Prigent, 1996; Wee and Ryu, 2009). Chemostat fermentation is a typical continuous fermentation system in which feeding of fresh medium to the fermentor and withdrawing fermentation broth are performed at the same rate to provide constant control of the concentration of a component in the fermentation broth. In chemostat fermentation, the concentrations of cells, products, and substrates in the fermentation broth can be stably maintained at constant levels during certain periods. The specific growth rate can be adjusted by the dilution rate because the specific growth rate would equal the dilution rate under steady state conditions in chemostat fermentation (Bustos et al., 2007). Therefore, the dilution rate is an important parameter that allows productivity to be maximized and should be further investigated. In addition, continuous fermentation is shut down with less frequency than batch fermentation (where the reactor must be emptied, cleaned, sterilized, and refilled), and there is less decrease in productivity during lag phases (Gassem et al., 1997; Ohara et al., 1992). However, the efflux of unutilized carbon sources and cells from the fermentor and the decrease in lactic acid concentration with an increase in the dilution rate are problematic points during lactic acid production with continuous fermentation (Zhang et al., 2011). These problems can be solved by using HCD fermentations, as described in Section 5.

In conventional continuous fermentation without HCD, we have reported an improved lactic acid productivity of 1.56 g/L/h from sago starch with the amylolytic LAB strain *Enteroccocus faecium* No. 78 (Shibata et al., 2007) and of 4.53 g/L/h from cassava starch by *Lb. plantarum* SW14 (Bomrungnok et al., 2012). Bustos et al. (2007) reported a lactic acid productivity of 3.1 g/L/h from trimming vine shoots hydrolysate at a dilution rate of 0.2 h^{-1} by *Lb. pentosus* CECT-4023 T. We have recently reported D-lactic acid productivities of 2.07–3.55 g/L/h in conventional continuous culture, which was higher than that obtained in the batch culture (1.67 g/L/h) from glucose by *Lb. delbrueckii* subsp. *lactis* QU 41 (Tashiro et al., 2011).

5. Improved lactic acid fermentation with high cell density

HCD is widely used for several fermentative production processes; however, it has not been clearly defined. Approximately 10-fold higher cell concentrations than those generally used for batch fermentation would be considered as HCDs (Chang et al., 2011). Fermentative production systems using HCD are desirable for cost-effective large-scale production, mainly because of their high productivities and lack of

Table 11
Performance of free/immobilized cells with fermentation modes for improved lactic acid production.

Fermentation mode	Cell immobilization technique	Strain	Fermentation substrate	Lactic acid production			Fermentation method	Performance and efficiency	Reference
				C (g/L)	*Y* (g/g)	*P* (g/L/h)			
Fed-batch with free cells	–	*Lb. lactis*-11	Glucose	98.6	0.98	2.0	●pH feedback feeding method	►Product inhibition occur	Zhang et al. (2011)
Fed-batch with free and immobilized cells	Attachment (adsorption)			115	0.94	2.25	●Performed in a packed bed-stirred fermentor (PBSF) system filled with ceramic beads using a pH feedback feeding method.	►Final lactic acid concentration and productivity in the PBSF system increased by 16.6 and 12.5%, respectively. ►Glucose was completely utilized. ►Immobilized cells were more tolerant to product inhibition.	
Repeated-fed-batch with free and immobilized cells	Attachment (adsorption)			117[a]	0.94	2.34	●As above with repeated cycles	►The inoculation preparation and lag phase of each batch were eliminated.	
Batch with free cells	–	*Lb. rhamnosus* ATCC 7469	Liquid distillery stillage	34.7	0.81	0.66		►Low lactic acid productivity	Djukić-Vuković et al. (2013)
Repeated batch with immobilized cells	Attachment (adsorption)			42.2[a]	0.99	1.22	●Cells were immobilized onto zeolite, a microporous aluminosilicate mineral.	►Immobilization allowed simple cell separation from the fermentation media and reuse in repeated batch. ►Almost double productivity was obtained.	
Batch with free cells	–	*Lc. lactis* ATCC19435	Jerusalem artichoke hydrolysate	92.5	0.68	0.5			Shi et al. (2012)
Batch with immobilized cells	Attachment (adsorption)			121	0.92	1.0	●Cells were immobilized in fibrous bed bioreactors.	►Compare with free cell, significant increase in lactate concentration, yield and productivity	
Fed-batch with free cells	–			103	–	0.86			
Fed-batch with immobilized cells	Attachment (adsorption)			142	–	1.5	●Cells were immobilized in fibrous bed bioreactors.	►Compare with free cell, significant increase in lactate concentration and productivity	
Repeated batch with immobilized cells	Attachment (adsorption)			–	0.84–1.01	0.71–2.85	●Cells were immobilized in fibrous bed bioreactors.	►Long-term operation with high fermentation efficiency	
Batch with immobilized cells	Containment (microencapsulation)	*Lc. lactis* IO-1	Glucose	29.8	0.98	2.16	●Cells were immobilized in a packed-bed reactor.	►High lactic acid concentration with low productivity	Sirisansaneeyakul et al. (2007)
Repeated batch with immobilized cells	Containment (microencapsulation)			23.0–27.6	0.66–0.92	2.16–2.47		►Feasibility of using immobilized cells for multiple fermentation cycles (3 cycles)	
Continuous process with immobilized cells (0.5 h^{-1})	Containment (microencapsulation)			8.9	0.89	4.46		►High lactic acid productivity but low glucose utilization	
Batch with immobilized cells	Entrapment	*Rhizopus oryzae* NBRC 5384	Glucose	145	0.95	1.42	●*R. oryzae* cells were immobilized in situ within sponge-like cubic particles made of polyurethane foam.	►Significant increase in lactic acid production	Yamane and Tanaka (2013)
Fed-batch with immobilized cells	Entrapment			231	0.93	1.83			

C, concentration; *Y*, yield; *P*, productivity; *Lb.*, *Lactobacillus*; *Lc.*, *lactococcus*.
[a] Data of the 3rd run.

contamination problems (John and Nampoothiri, 2011). In addition, fermentors with HCD can be more compact in size and allow stable long-term fermentation; however, these systems are difficult to design and operate (Ozturk, 1994).

Several methods are used to achieve HCD, including fed-batch fermentation, cell immobilization, and cell recycling. John and Nampoothiri (2011) reported a novel method for achieving HCD in *Lactobacilli* by coculturing *Lb. paracasei* subsp. *paracasei* with the fast-growing *Lb. delbrueckii* subsp. *delbrueckii* and then embedding the coculture on to polyurethane foam cubes as a biofilm. Among these methods, fed-batch fermentation is the most commonly used in commercial practice; however, cell immobilization and cell recycling methods are more suitable for continuous fermentation and permit operation at higher dilution rates than conventional continuous fermentation (Chang et al., 1994). Various supports and immobilization techniques have been proposed and tested for application in lactic acid production, as described in next section. Cell retention can be achieved by sedimentation, centrifugation, or collection via membranes. The membrane cell recycling technique is the most widely used as it allows complete recycling of cells (Chang et al., 1994). Table 10 shows the advantages and disadvantages of cell recycling methods. In this section, we will focus on cell immobilization and membrane-based cell recycling techniques for lactic acid production with HCD.

5.1. Cell immobilization

From an industrial standpoint, cell immobilization methods have become one of the most useful methods for increasing cell concentrations in fermentors, which should result in higher lactic acid productivity. In addition, cell immobilization improves cell and operational stability, reduces the need for nitrogen sources, enables re-utilization operations, reduces downstream processing by coupling fermentation and separation processes, and reduces risk of contamination because of a high concentration of used cells (Gao et al., 2004; Øyaas et al., 1996; Panesar et al., 2007; Tong et al., 2004). Furthermore, continuous fermentation can be operated at high dilution rates without cell washout using immobilized cells. However, mass-transfer limitations are considered to be a significant drawback for fermentation with immobilized cells Kosseva et al. (2009). Table 11 shows the performance of free/immobilized cells and operational processes in lactic acid fermentation. As shown in Table 11, fermentation with immobilized cells resulted in enhanced lactic acid production with higher productivities than those obtained using free cells.

In general, there are 4 categories of immobilization techniques (Fig. 2, Table 11), namely, attachment (adsorption), entrapment, containment, and self-aggregation (Kourkoutas et al., 2004; Pilkington et al., 1998). Adsorption (or attachment) on solid carrier surfaces is the most common because it is simple to carry out and has little influence on the conformation of the cells that are held to the surface of the carriers by physical (van der Waals forces) or electrostatic forces or by covalent binding between the cell membrane and the carrier (Goncalves et al., 1992). However, the relative weakness of the adsorptive binding forces is the major limitation of this technique. The forces of covalent binding using aggressive chemicals are stronger than physical forces; however, aggressive chemicals are harmful to the cells and are not preferred for cell immobilization (Panesar et al., 2007). A variety of support materials have been investigated for adsorption, including activated carbon Andrews and Fonta (1989), aluminum beads (Tango and Ghaly, 2002), glass and ceramics (Guoqiang et al., 1992; Zhang et al., 2011), wood chips (Krischke et al., 1991), plastic composite supports (Velázquez et al., 2001), porous bricks and cotton fibers (Goncalves et al., 1992; Tay and Yang, 2002), and foam (Dong et al., 1996). Loofa sponges (*Lufa cylindrica*) have been proposed to be the most promising matrix for an alternative carrier because it is renewable and biodegradable, easy to use, less expensive, and available naturally in abundance (Ganguly et al., 2007; Ogbonna et al., 1994, 1996; Roble et al., 2003; Slokoska and Angelova, 1998).

Entrapment techniques are also popular for the immobilization of cells because of the simplicity of using spherical particles containing cells, which can be obtained by dripping a polymer-cell suspension into a solution containing precipitate-forming counter ions or through thermal polymerization. Materials commonly used for entrapment are polysaccharide gels, like calcium alginate, agar, agarose, kappa-carrageenan, chitosan, and polygalacturonic, or other polymeric matrixes, like gelatin, collagen, and polyvinyl alcohol (Elezi et al., 2003; Lee et al., 2003; Park and Chang, 2000). Entrapment using calcium alginate gel beads has been used extensively for lactic acid production by immobilized cells (Champagne et al., 1992; Hamamci and Ryu, 1994; Hang et al., 1989; Wang et al., 1995; Xuemei et al., 1999). Slow leakage of cells during continuous long-term operation can also occur, which would comprise immobilized and free cells in the fermentor. To avoid this problem, double-layer beads have been developed (Tanaka et al., 1989), and further improvements can be made by using suitable cross-linking procedures. In addition, the insufficient oxygen supply due to the diffusional resistance of the gel matrixes may decrease fermentation efficiency, particularly aerobic fermentation (Sun et al., 1998). Moreover, preparation of large amounts of gel beads for industrial production may be uneconomical and cumbersome (Ogbonna et al., 1989).

Mechanical containments behind a barrier can be attained by use of microporous membrane filters, entrapment of cells in a microcapsule, or cell immobilization onto an interaction surface of 2 immiscible liquids (Chang et al., 2011). Mechanical containment is advantageous when cell-free products and minimum transfer of compounds are required (Park and Chang, 2000). However, mass transfer limitations and possible membrane biofouling caused by cell growth are the main disadvantages of this technique (Kourkoutas et al., 2004).

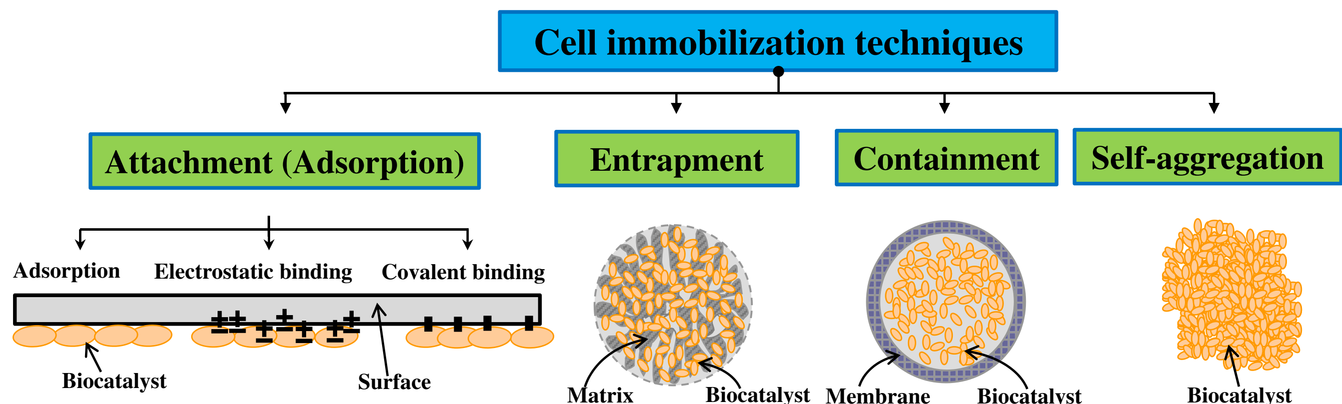

Fig. 2. Categories of immobilization techniques (attachment, entrapment, containment and self-aggregation).

Some microbial cells can aggregate to form larger units that adhere in clumps and sediment rapidly (Jin and Speers, 1998). Aggregation can be considered a natural immobilization technique that is mainly observed in molds and fungi. Artificial aggregating agents or cross-linkers can be used to enhance aggregation of cells that cannot aggregate naturally (Kourkoutas et al., 2004).

Fungal cell immobilization has been used to control fungal morphology and has been shown to achieve high lactic acid productivity by HCD (Ganguly et al., 2007; Zhang et al., 2007). Immobilized *Rhizopus* cells have been applied in many bioreactors used in submerged filamentous fungal fermentations, including air-lift bioreactors, drum contactors, reciprocating jet bioreactors, tower fermentors, and hollow fiber bioreactors (Lin et al., 1998; Park et al., 1998; Sun et al., 1998, 1999; Tamada et al., 1992; Tay and Yang, 2002; Y. Liu et al., 2006). However, in most immobilization studies, lactic acid yields were only 0.65–0.78 g/g, with lactic acid concentrations of 40–73 g/L (Dong et al., 1996; Hamamci and Ryu, 1994; Hang et al., 1989; Lin et al., 1998; Tamada et al., 1992; Xuemei et al., 1999). Although there are reports where lactic acid yields reached more than 85% (Efremenko et al., 2006; Kosakai et al., 1997; Tay and Yang, 2002), the complex operational processes of fungal immobilization, attrition of support, and possibility of bioreactor damage at high agitation speed limit their use (Chotisubha-anandha et al., 2011).

Generally, lactic acid production by cell immobilization has been reported in conventional batch fermentation (Chotisubha-anandha et al., 2011; John and Nampoothiri, 2011; Rangaswamy and Ramakrishna, 2008; Rosenberg et al., 2005; Sirisansaneeyakul et al., 2007; Yamane and Tanaka, 2013), fed-batch fermentation (Yamane and Tanaka, 2013), SSF-fed-batch fermentation (Shen and Xia, 2006), repeated fermentation (Ganguly et al., 2007; Rosenberg et al., 2005; Velázquez et al., 2001; Yen and Lee, 2010; Z. Wang et al., 2010; Zhang et al., 2011), and continuous fermentation (John et al., 2007a; Rangaswamy and Ramakrishna, 2008; Sirisansaneeyakul et al., 2007; Tango and Ghaly, 2002) using different bioreactors, such as packed-bed reactors, continuous stirred-tank reactors, fibrous-bed reactors, and fluidized-bed reactors. These findings are described in detail below.

5.1.1. Packed-bed reactors (PBRs)

A PBR is a simple operational system with high mass-transfer rates in which the microorganism can be packed into a column in the form of spheres, chips, disks, sheets, beads, or pellets. This system is especially appropriate to strains that do not require oxygen for lactic acid production (Sirisansaneeyakul et al., 2007). However, the periodic fluctuation in the viable cell population due to nutrient depletion along the reactor length is one of the limitations of this system (Kosseva et al., 2009). Although operation of the fermentor coupled with a packed bed in continuous fermentation has the potential to achieve simultaneous product removal and high productivities, low sugar utilization or high residual sugar concentrations are the main disadvantages of this system. In addition, large pH gradients are generated, and therefore, a large fraction of the immobilized cells do not experience optimal pH for lactic acid production (Senthuran et al., 1999).

PBRs with immobilized cells have been reported for lactic acid production in batch fermentation, repeated batch fermentation (Senthuran et al., 1997, 1999; Sirisansaneeyakul et al., 2007), and continuous fermentation (Roukas and Kotzekidou, 1996; Roy et al., 1987; Sirisansaneeyakul et al., 2007; Tango and Ghaly, 2002). Tango and Ghaly (2002) achieved a high lactic acid concentration of 75.6 g/L with a yield of 0.96 g/g and a productivity of 3.90 g/L/h from whey using *Lb. helveticus* cells immobilized on alumina beads in PBR after a hydraulic retention time of 18 h. A PBR using encapsulated *Lc. lactis* IO-1 in a membrane capsule and entrapment in a gel matrix achieved an even higher lactic acid productivity of 4.5 g/L/h in continuous fermentation at a dilution rate of 0.5 h^{-1}, compared to 2.16 g/L/h in batch fermentation and 2.16–2.47 g/L/h in repeated batch fermentation from glucose (Table 11) (Sirisansaneeyakul et al., 2007).

5.1.2. Continuous flow stirred tank reactors (CSTR)

CSTRs have been widely used in commercial fermentation processes due to its industrial capacity and reliability. In an ideal CSTR, the fermentation broth in the bioreactor is perfectly mixed. CSTR for lactic acid production by immobilized cells has been reported with co-immobilized *Lb. casei* SU No. 22 and *Lb. lactis* WS 1042 cells entrapped in Ca-alignate with a lactic acid productivity of 0.72–0.86 g/L/h in repeated fermentation (Roukas and Kotzekidou, 1991) and immobilized *Lb. casei* subsp. *casei* (DSM 20244) cells onto porous sintered glass beads with a lactic acid productivity of 5.5 g/L/h at a dilution rate of 0.22 h^{-1} (Krischke et al., 1991). A maximum lactic acid productivity of 28.5 g/L/h at a dilution rate of 1.21 h^{-1} was obtained in continuous fermentation from whey permeate by immobilized *Lb. helveticus* L89 cells entrapped in *k*-carrageenan-locust bean gum gel beads in CSTR (Norton et al., 1994). Immobilization of filamentous fungi in a CSTR is often limited by insufficient mixing and low mass transfer due to formation of mycelial clumps that cause operational problems and high shear rates and have relatively high power requirements (Chotisubha-anandha et al., 2011; Z.Y. Zhang et al., 2008).

The use of CSTR allows efficient control of pH, but often leads to attrition of the support. On the other hand, large pH gradients are generated in PBR that do not match the optimal pH for a large fraction of the immobilized cells (Senthuran et al., 1999). Therefore, a dual reactor system by connecting CSTR and PBR using immobilized cells has been also reported (Rangaswamy and Ramakrishna, 2008; Sirisansaneeyakul et al., 2007; Zhang et al., 2011). With this system, a significant enhancement of lactic acid productivities, yields, and final concentrations has been achieved by avoiding attrition of the support by efficiently controlling the pH. Rangaswamy and Ramakrishna (2008) operated a dual reactor in continuous fermentation for more than 1000 h and achieved constant lactic acid productivity of 5 g/L/h from sucrose by immobilized *Lb. delbrueckii* NCIM 2365 cells on polyurethane foams in comparison to productivities of 2.0–2.5 g/L/h in batch fermentation and 0.65 g/L/h in continuous fermentation using free cell systems (Rangaswamy and Ramakrishna, 2008). Similarly, Zhang et al. (2011) operated this dual system with immobilized *Lb. lactis* 11 cells on ceramic beads and enhanced lactic acid concentrations by 16.6% and productivities by 12.5% compared to those obtained from free cell systems in continuous fermentation (Table 11).

5.1.3. Fibrous-bed reactor

Fibrous-bed bioreactors have been reported for lactic acid production by cell immobilization in fibrous matrices, e.g., cotton cloths, packed in fermentor vessels (Shi et al., 2012; Silva and Yang, 1995). Fibrous-bed reactors have been greatly improved in terms of packing designs to allow for more uniform structures and to minimize diffusion limitations, greatly improving fermentation efficiency (Vijayakumar et al., 2008). Silva and Yang (1995) investigated the kinetics and long-term stability of fibrous-bed bioreactors for continuous lactic acid production from unsupplemented acid whey containing 3.7% (w/v) lactose and 0.8% (w/v) lactic acid using immobilized *Lb. helveticus* ATCC 15009 cells. Depending on the dilution rate and lactic acid concentration, productivities ranging from 2.6 to 7 g/L/h were achieved, which were10 times higher than those in batch fermentation with free cells. Shi et al. (2012) reported a high L-lactic acid production of 142 g/L from Jerusalem artichoke hydrolysate by immobilized *Lc. lactis* ATCC19435 in a fibrous-bed bioreactor with fed-batch fermentation; this value was 27.92% higher than that in fed-batch fermentation using free cells (103 g/L) as shown in Table 11. They also achieved high L-lactic acid yields ranging from 0.84 to 1.01 g/g and productivities ranging from 0.71 to 2.85 g/L/h with long-term persistence (approximately 780 h) by repeated fermentation with a fibrous-bed reactor [Table 11] (Shi et al., 2012). The fibrous-bed reactor was also reported as an effective system for lactic acid fermentation by *Rhizopus* sp., which allowed operational problems common to conventional fungal fermentation processes to be avoided. Tay and Yang (2002) used a rotating fibrous-bed bioreactor to produce

Table 12
Lactic acid production with high density culture using membrane cell recycling.

Fermentation mode, membrane cell recycling method	Strain	Substrate	Lactic acid production			Dilution rate (h^{-1})	Time of operation (h)	Reference
			C (g/L)	*Y* (g/g)	*P* (g/L/h)			
Continuous, cell recycle via ceramic microfiltration membranes	*Lc. lactis* sub sp. *cremoris* IF0 3427	Molasses	40.0	–	10.6	0.26	240	Ohashi et al. (1999)
Continuous, cell recycle via flat sheet	*Lb. delbrueckii*	Glucose	35.0	0.96	76.0	2.2	54	Vick-Roy et al. (1983b)
Continuous, cell recycle via polymeric hollow fiber module	*E. faecium* No. 78	Sago starch	11.7	0.76	3.04	0.26	–	Shibata et al. (2007)
	Lactobacillus sp. RKY2	Wood hydrolysate	42.0	0.95	6.7	0.16	–	Wee and Ryu (2009)
	Lb. bulgaricus	Sweet whey permeate	117	0.99	84.0	0.72	8	Mehaia and Cheryan (1987)
	Lb. bulgaricus	Cheese whey permeate	89.0	0.89	22.5	0.25	130	Tejayadi and Cheryan (1995)
	Lb. delbrueckii	Glucose	40.0	0.76	12.0	0.3	220	Major and Bull (1989)
	Lb. delbrueckii subsp. *lactis* QU 41	Glucose	20.7	1.03	18.0	0.87	14	Tashiro et al. (2011)
	Lb. plantarum SW14	Cassava starch	20.0	–	8.0	0.40	–	Bomrungnok et al. (2012)
Continuous, cell recycle via a hydrophilic polyvinylidene fluoride microfiltration module	*Lb. paracasei*	Glucose	91.0	0.85	31.5	0.3	156	Xu et al. (2006)
Continuous, cell recycle via ultrafiltration flat sheet	*Lb. delbrueckii* NRRL-B445	Glucose	57.0	0.98	160	2.80	14	Ohleyer et al. (1985)
Continuous, cell recycle via ultrafiltration tubular mineral membranes	*Lb. helveticus*	Sweet whey permeate	25.0	0.81	22.0	0.88	140	Boyaval et al. (1987)
Continuous, cell recycling by ultrafiltration tubular ceramic membrane	*Lb. rhamnosus* NRRL B445	Glucose	88.0	0.74	35.2	0.40	90	Xavier et al. (1995)
Continuous, via internal (submerged) polymeric hollow fiber membrane	*Lc. lactis* ssp. *cremoris* ASCC930119	Whey	60.0	–	9.7[a]	–	30	Ramchandran et al. (2012)
Repeated batch, cell recycle via ceramic microfiltration membranes	*Lb. rhamnosus* HG09F5-27	Glucose	157	0.98	8.77	–	–	Lu et al. (2012)

C, concentration; *Y*, yield; *P*, productivity; *Lb.*, *Lactobacillus*; *Lc.*, *lactococcus*, *E.*, *Enterococcus*.
[a] Maximum productivity.

L-lactic acid by *R. oryzae* NRRL 395 and obtained a lactic acid production of 126 g/L with a yield of 0.89 g/g and a productivity of 2.5 g/L/h from glucose in fed-batch fermentation. Similarly, a lactic acid production of 127 g/L with a yield of 0.90 g/g and a productivity of 1.65 g/L/h was obtained from cornstarch in fed-batch fermentation (Tay and Yang, 2002). Thongchul and Yang (2006) developed thin mycelial layers to increase oxygen transfer for the improvement of lactic acid production. Chotisubha-anandha et al. (2011) revealed that mass transport was the rate-limiting factor in a static fibrous-bed reactor using *R. oryzae*. Immobilized *R. oryzae* NRRL 395 on a cotton matrix in a fibrous-bed reactor achieved a maximum lactic acid concentration of 37.8 g/L from 70 g/L glucose with a yield of 0.62 g/g and a productivity of 2.09 g/L/h (Chotisubha-anandha et al., 2011).

5.1.4. Fluidized-bed reactors (FBRs)

FBRs are widely employed with cell immobilization systems. In these reactors, fluidization is achieved by the combined upward and downward movements of particles; therefore, FBRs provide a degree of mixing that is between the 2 extremes of the PBR and the CSTR. In addition, higher mass transfer and heat transfer rates are expected than those in PBRs. The application of FBRs for lactic acid production has rarely been studied due to their difficulty in scale-up, short-term operation and the requirement for regeneration of a biocatalyst (Davison and Scott, 1992; Kaufman et al., 1995; Krischke et al., 1991; Lin et al., 2007; Patel et al., 2008). Krischke et al. (1991) reported higher lactic acid productivities of 10 g/L/h at a dilution rate of 0.4 h^{-1} and of 13.5 g/L/h at a dilution rate 1.0 h^{-1} from whey permeate by *Lb. casei* subsp. *casei* DSM 20244 (immobilized by adsorption on sintered glass beads) in FBR than those achieved in CSTR (5.5 g/L/h at a dilution rate of 0.22 h^{-1}). Two solid particles (the immobilized biocatalyst and the adsorbent particle) were used to form the biparticle fluidized-bed bioreactor that enhanced lactic acid production. Davison and Scott (1992) achieved enhanced lactic acid production in biparticle FBR with gel beads of *Lb. delbreuckii* ATCC 9649 cells entrapped in *k*-carrageenan and activated carbon as an adsorbent (absorb lactic acid) for simultaneous production and recovery of lactic acid in batch fermentation. Similarly, Davison and Thompson (1992) immobilized *Lb. delbreuckii* in alginate beads and fluidized the beads by upward-flowing liquid media in a tubular reactor. After that, the adsorbent, polyvinyl pyridine resin Reillex 425 was added to the top of the reactor, fell through the biocatalyst bed, and was found to adsorb lactic acid, moderate broth pH, and increase lactic acid production nearly 4-fold over a control FBR without the addition of resin. Kaufman et al. (1995) used biparticle FBR with immobilized *Lb. delbreuckii* NRRL B445 cells in gelatin beads and for in situ removal of the inhibitory products and achieved a 12-fold increase in productivity (4.7 g/L/h) using absorbent addition (IRA-35 resin), compared to that achieved without absorbent addition (Kaufman et al., 1995). Lin et al. (2007) proposed an extractive fermentation process as a recovery method for L-lactic production with immobilized *R. oryzae* NRRL 395 by using trialkyl phosphine oxide as an extractant in 3-phase FBRs. By this method, product inhibition was alleviated and a high L-lactic acid productivity of 11 g/L/h was achieved. Patel et al. (2008) constructed a dual-particle liquid–solid circulating fluidized bed (DP-LSCFB) bioreactor for the simultaneous production and recovery of lactic acid using immobilized *Lb. bulgaricus* ATCC 11842 and ion-exchange resins with a production of 240 g lactic acid.

5.2. Membrane cell recycling

Membrane cell recycling systems are another method for achieving HCD (Table 10), where ultrafiltration membrane, microfiltration, or cross-flow membrane in a semi-closed loop is used for separating the permeate from the cells and recycling the cells back to the bioreactor. This system has advantages of achieving broth homogeneity, complete cell recycling, and in situ production and separation of the fermentation product. It can also enhance not only the conversion rate of the substrate in the medium but also the lactic acid productivity due to the much higher cell concentration achieved compared with conventional fermentation processes without HCD. Table 12 summarizes several studies used membrane cell recycling systems coupled with different fermentation modes. With this method, continuous fermentation can be operated at a higher dilution rate — up to 2.8 h^{-1} without cell washout achieving high lactic acid productivity up to 160 g/L/h [Table 12] (Ohleyer et al., 1985).

Polymeric membranes used in those fermentation methods suffer from intolerance to high temperatures required for sterilization, fouling problems, and the requirement for cleaning procedures that weaken the membrane, leading to increased replacement costs. These problems hindered its mass application in industry (Giorno et al., 2002; Wee and Ryu, 2009). To overcome fouling problems, membrane cell recycling bioreactors have been designed in different ways. Modifying the mechanical design of the bioreactor also achieved potential improvements in performance. Xu et al. (2006) employed an electromagnetic flow meter and a pneumatic diaphragm pump to a membrane cell recycling bioreactor to alleviate membrane fouling. They achieved continuous lactic acid fermentation with a productivity of 31.5 g/L/h and a long operational stability of 155.5 h, compared to those achieved using a peristaltic pump or diaphragm pump without an electromagnetic flow meter (56 and 85 h, respectively). Moreover, this system could repeat periodically with intermittent online cleaning and sterilization of the membrane filtration system. Ramchandran et al. (2012) applied a media-backwash method using fresh medium as a backwash medium to maintain the performance of the submerged hollow fiber membrane module. This process resulted in improved yield and a more than 2-fold increase in lactic acid production.

Ceramic membranes have proven to offer advantages of high thermal stability, easier cleaning, high resistance to acid and alkaline conditions, and high mechanical and abrasive resistance compared with polymeric membranes. As shown in Table 12, the operational stability using ceramic membrane is higher than polymeric membranes — up to 240 h in continuous couture (Ohashi et al., 1999). Jung and Lovitt (2010) used an external ceramic microfiltration membrane and achieved improvements in cell concentrations (~14-fold) with 10–33 times higher biomass production rates than those in the CSTR by using 4 industrially important LAB (*Lactobacillus buchneri*, *Lb. brevis*, *Oenococcus oeni*, and *Bifidobacterium longum*). Recently, Lu et al. (2012) reported enhanced pilot-scale (3000-L fermentor) production of L-lactic acid at 157.2 g/L with a productivity of 8.77 g/L/h using an external ceramic microfiltration membrane (Table 12).

Although increased lactic acid productivities were obtained with continuous fermentation by HCD with cell recycling, the lactic acid concentration was relatively low (less than 60 g/L in most studies) compared to those achieved during other fermentation processes (up to 231 g/L in fed-batch fermentation by Yamane and Tanaka, 2013, Table 11), which would greatly increase the energy cost for water removal in the downstream process (Kwon et al., 2001). With an increase in annual lactic acid production capacity, this bioprocess may be primarily influenced by production capacity and product concentrations and to a lesser extent by productivity (Timmer and Kromkamp, 1994). Kulozik et al. (1992) investigated the performance of a 7-stage cascade reactor with membrane cell recycling, which resulted in a lactic acid concentration of 72 g/L at a productivity of 28 g/L/h. Kwon et al. (2001) produced 92 g/L of D-lactic acid with a productivity of 57 g/L/h in a 2-stage bioreactor with membrane cell recycling by *Lb. rhamosus* ATCC 10863. A progress in multi-stage HCD continuous systems should be addressed and realized for lactic acid production that would be produced in a titer equivalent to the fed-batch, but with much higher productivity than the fed-batch.

6. Advances in lactic acid recovery processes

One of the major considerations in the commercial production of lactic acid is purifying the recovered product to meet quality standards requirements for specific applications. Conventional fermentation process produces lactate salt, as a result of pH neutralization, that must be precipitated and reacidified by a mineral acid such as sulfuric acid. These steps are considered as major economic hurdles for lactic acid production because it consumes expensive chemical that accounts for 50% of the production cost and that generates gypsum waste materials (Chaudhuri and Pyle, 1992; Eyal and Bressler, 1993). Several recovery techniques have been reported on the separation of lactic acid produced in the fermentation broth without precipitation such as diffusion dialysis (Narebskam and Staniszewski, 1997), solvent extraction (Hano et al., 1993), direct distillation (Cockrem and Johnson, 1993), liquid surfactant membrane extraction (Sirman et al., 1991), adsorption (Kaufman et al., 1994), chromatographic methods (Hauer and Marr, 1994), ultrafiltration (Hauer and Marr, 1994), reverse osmosis (Hauer and Marr, 1994; Timmer et al., 1994), drying (Hauer and Marr, 1994), conventional electrodialysis (Boyaval et al., 1987; Heriban et al., 1993; Hongo et al., 1986; Kim and Moon, 2001; Thang et al., 2005) and bipolar membrane electrodialysis (Bailly, 2002). Among those, the electrodialysis technique has been found to be potentially effective in the recovery of lactic acid from fermentation broth due to its rapid treatment, effective removal of non-ionic molecules, concentration of lactic acid, and environmentally sustainable process (Boniardi et al., 1997). Additionally, in-situ recovery technique has the potential to not only recover lactic acid but also relieve product inhibition. Conventional electrodialysis generally uses ion-exchange membranes under the influence of direct current for separating and concentrating ions in solution. In-situ conventional electrodialysis with the cathode located in the compartment of the fermentor has been shown to damage the bacterial cells by direct contact with the electrodes. To prevent the cells from contacting with the electrodes, an ultrafiltration step has been introduced before the electrodialysis process (Nomura et al., 1991). Furthermore, pH control is an important factor that should limit the technical and commercial viability in electrodialysis processes (Hongo et al., 1986; Vonktaveesuk et al., 1994). In order to maintain a pH at the suitable value, an additional pH control system with the addition of alkaline solution was incorporated into the electrodialysis process (Vonktaveesuk et al., 1994). Several recent studies have also applied electrodialysis to recover lactic acid from fermentation broth (Gao et al., 2005; Hábová et al., 2004; Wee et al., 2005; Yi et al., 2008).

To date, various attempts have been made to develop the technology of electrodialysis by using bipolar membrane. Bipolar membrane electrodialysis is equipped with the integration of conventional electrodialysis and water splitting within the bipolar membrane (Franken, 2000; Timbuntam et al., 2008). This process is advantageous in the capability of separation, purification and concentration of salts, and in the conversion of these salts into acid and base without generating waste effluents containing high concentrations of salts. In addition, the generated base can be recycled for the neutralization of the fermentation process (Franken, 2000). Li et al. (2004) developed a bioreactor with bipolar membrane electrodialysis for both lactic acid removal and pH control in lactic acid fermentation by *Lb. rhamnosus* NCIMB 6375, which increased the lactic acid yield to 0.61 g/g glucose, compared to that achieved without electrodialysis (0.46 g/g glucose). Min-tian et al. (2005) achieved production of 2637 g lactic acid from 4000 g glucose at a productivity of 8.18 g/L/h and a yield of 0.69 g/g in continuous fermentation integrated with bipolar membrane electrodialysis using *Lb. rhamnosus* IFO 3863. However, there is still a compatibility issue between electrodialysis and fermentation process that should be carefully arranged to achieve a synchronous operation of the fermentation and electrodialysis process.

7. Concluding remarks

In this review, the latest results and ideas relating to the key aspects of lactic acid production research were summarized and compared. Microbial lactic acid producers and fermentative substrates, including pure and edible sugars and their alternatives (i.e., lignocellulosic and starchy biomasses, dairy byproducts, agro-industrial and food wastes, glycerol and algal biomass), which have dual advantages in both overcoming current environmental problems and lowering lactic acid production costs were described. In addition, various fermentation processes and methods that enhance lactic acid concentrations, yields, and productivities were pointed out. New developments in lactic acid fermentation techniques that alleviate difficulties associated with production were also discussed; however, certain issues like end-product inhibition still have to be addressed.

End-product inhibition is still the major problem associated with efficient lactic acid fermentation, even with HCD. Controlling the pH during fermentation only partly mitigates this inhibition (Savoie et al., 2007). Removing lactic acid during fermentation has resulted in a 50-fold enhancement in cell concentrations with dialysis membranes; however, this process requires relatively large membrane areas, which must be accommodated outside of the fermentation vessel (Osborne et al., 1975). Although electrodialysis is a simple method that can remove acids selectively during fermentation, it has several limitations, including decreases in both volumetric and specific lactic acid productivity (Vaida et al., 1991). Some of these challenges have been addressed by the reverse electro-enhanced dialysis process, which has been shown to achieve higher lactic acid productivity and cell biomass as well as manage fouling by periodic charge reversal (Prado-Rubio et al., 2011; Rype et al., 2009). Further developments in such methods are required to ensure effective bioprocesses for better lactic acid fermentation characteristics, including greater purities, yields, and concentrations, in addition to their eco-friendly production resulting from the direct production of lactic acid instead of the lactate salts common to conventional processes.

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