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Review

Lactic acid properties, applications and production: A review

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Lactic acid was discovered in 1780 by C.W. Scheele in sour milk, and in 1881 Fermi obtained lactic acid by fermentation, resulting in its industrial production. The yearly world lactic acid production is expected to reach 259,000 metric tons by the year 2012. The interest in lactic acid is related to many aspects, among which is its relatively high added-value. In addition, such a chemical is GRAS (Generally Recognized As Safe), being recognized as harmless by the United States Food and Drug Administration, has a market with great growth potential, can be alternatively produced by fermentation or chemical synthesis and can employ a large variety of different waste materials as substrates. Lactic acid has many applications. Its existence in the form of two stereoisomers does in fact make the application of one of them or of the racemic mixture of great concern in different fields. In particular, the food and pharmaceutical industries have a preference for the isomer L(+), the only one that can be metabolized by the human body; however, the chemical industry requires one of the pure isomers or a mixture of both, according to the application. This review describes biotechnological processes to obtain lactic acid from polymeric substrates such as starchy and lignocellulosic materials. Open challenges are related to the technological optimization of the fermentation process and product purification and recovery. In addition, the opportunities and difficulties associated with using raw materials for lactic acid production are discussed.

Introduction

Because of a number of different properties (Abdel-Rahman, Tashiro, & Sonomoto, 2011), lactic acid is an important industrial product that is used as a precursor of small (propylene glycol) or large (acrylic polymers) compounds (San-Martín, Pazos, & Coca, 1992). Their polymers are biodegradable, used as materials for packaging and labeling (San-Martín *et al.*, 1992), and biocompatible, being useful for the manufacture of prosthetic devices, sutures and internal drug dosing (Chahal, 2000, pp. 1–9). Among them, the polylactic acid (Boswell, 2001; Tsuji, Saeki, Tsukegi, Daimon, & Fujie, 2008) has several applications in the textile, medical and pharmaceutical industries (Singhvi, Joshi, Adsul, Varma, & Gokhale, 2010).

In the cosmetic industry, lactic acid is used in the manufacture of hygiene and esthetic products, owing to its moisturizing, antimicrobial and rejuvenating effects on the skin, as well as of oral hygiene products. Lactic acid derivatives such as lactate esters are widely used because of their hygroscopic and emulsifying properties (Gao, Ma, & Xu, 2011). In the pharmaceutical industry it is used as a supplement in the synthesis of dermatologic drugs and against osteoporosis (Bai, Zhao, Li, & Xu, 2004).

Approximately 70% of lactic acid produced is used in the food industry because of its role in the production of yogurt and cheese (Salminen, Ouwehand, Wright, & Daly, 1993). In the preparation of yogurts it is the main product of *Streptococcus thermophilus* and *Lactobacillus bulgaricus*

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co-fermentation. In the manufacture of cheese, the pH decrease consequent to lactic acid release triggers the aggregation of casein micelles. Sometimes, depending on the sensory characteristics desired in the final product, direct acidification with lactic acid is exploited to avoid the risk of proliferation of undesirable microorganisms. In the field of grain production, lactic acid forms spontaneously because of the presence of microorganisms that carry out the lactic acid fermentation of the raw material (for example, wet processing of corn), leads to changes in the aroma and taste preparations and causes a decrease in pH that prevents the growth of pathogenic bacteria (Lee & Lee, 1993).

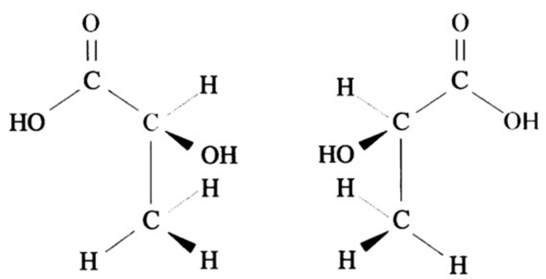
As far as the animal nutrition is concerned, controlled lactic fermentation increases the shelf life, palatability and nutritive value of silage. Ammonium lactate is an excellent non-protein nitrogen source, which is preferred in cattle to urea and ammonium citrate because it results in milk with higher nutritive value (Norton, Lacroix, & Vuillemard, 1994) and does not require any expensive purification.

Physico-chemical properties

Lactic acid (2-hydroxypropanoic acid) is an organic acid widely distributed in nature. It is the simplest 2-hydroxycarboxylic acid with a chiral carbon atom and exists in two enantiomeric forms (Fig. 1). The chemical behavior of lactic acid is determined by its physico-chemical properties, among which are a) acidic character in aqueous medium; b) bifunctional reactivity associated with the presence of a carboxyl and a hydroxyl group, which gives it great reaction versatility; and c) asymmetric optical activity of C2.

Production technologies and purification

The worldwide demand of lactic acid in 2007 was estimated to be 130,000–150,000 metric tons per year, with commercial prices of food-grade lactic acid ranging between 1.38 US$ kg^{-1} (50% of purity) and 1.54 US$ kg^{-1} (88% of purity) (John, Nampoothiri, & Pandey, 2007). According to forecasts, its production should increase significantly over the coming years mainly to provide the polylactic acid manufacturing sites, and is expected to reach 259,000 metric tons in 2012 (Mujtaba, Iqbal, Edreder, & Emtir, 2012). The Global Industry Analyst Inc. announced in January 2011 that the global market for lactic acid is forecast to reach approximately 329,000 metric tons by the year 2015.



Isomer L(+) Isomer D(-)

Fig. 1. Structure of D(−) and L(+) isomers of the lactic acid.

Commercial manufacturers

As regards the world production of lactic acid, several authors reported the most relevant commercial manufacturers (Datta & Henry, 2006; Datta, Tsai, Bonsignore, Moon, & Frank, 1995; John, Nampoothiri, *et al*., 2007). Currently, the major manufacturers of lactic acid include Archer Daniels Midland Company (USA), NatureWorks LLC (USA), Purac (The Netherlands), Galactic S.A. (Belgium) and several Chinese companies, among them are the CCA (Changzhou) Biochemical Co. Ltd., Henan Jindan Lactic Acid Co. Ltd., and Musashino Chemical Co. Ltd.

Chemical synthesis

For lactic acid chemical synthesis, acetaldehyde is let to react in liquid phase and under high pressure with hydrogen cyanide in the presence of a base to produce lactonitrile. After its recovery and purification by distillation, hydrochloric acid or sulfuric acid is added to hydrolyze lactonitrile to lactic acid, which is then esterified with methanol to produce methyl lactate, and this is recovered and purified by distillation. The purified methyl lactate is finally hydrolyzed in acidic aqueous solution to lactic acid and methanol, the latter being recycled in the same process (Dey & Pal, 2012; Narayanan, Roychoudhury, & Srivastava, 2004a). Other chemical routes for lactic acid synthesis include base-catalyzed degradation of sugars, oxidation of propylene glycol, carbon monoxide and water at high temperature and pressure, hydrolysis of chloropropionic acid, and nitric acid oxidation of propylene, among others (John, Sukumaran, Nampoothiri, & Pandey, 2007).

Fermentation

Lactic fermentation is relatively fast, has high yields and can lead, selectively, to one of the two stereoisomers of lactic acid or to their racemic mixture (Axelsson, 2004). After supplementation of nutrients, sugar solutions are inoculated with the selected microorganism, and the fermentation takes place. It is necessary to select the most favorable fermentation conditions, in terms of temperature, pH, aeration, agitation, and so on, which vary depending on the microorganism.

The search for low-cost raw materials to be used in the production of lactic acid by fermentation has been promoting the development of competitive processes. The materials most frequently used to this purpose can be classified into two groups, namely the monosaccharides and disaccharides and the polymeric substrates.

Monosaccharides and disaccharides

In theory, any carbohydrate source containing pentoses or hexoses could be used for the production of lactic acid. This category of carbon sources includes food industry byproducts such as molasses and whey. Molasses have high sucrose content and are cheap and plentiful (Kotzamanidis, Roukas, & Skaracis, 2002), while whey has high lactose content whose disposal constitutes a serious environmental challenge (Alvarez, Aguirre-Ezkauriatza, Ramírez-Medrano, & Rodríguez-Sánchez, 2010; Büyükkileci & Harsa, 2004). Another byproduct that was successfully used as substrate for lactic acid production is the date juice (Nancib *et al.*, 2001; Nancib, Nancib, & Boudrant, 2009).

Polymeric substrates

These substrates contain polysaccharides that, in most cases, cannot be directly assimilated by microorganisms, requiring an earlier stage of hydrolysis.

The so-called starchy materials contain starch, a biopolymer of glucose units linked *via* α(1−4) bonds forming chains of variable length, branched *via* α(1−6) bonds or not. Two different polysaccharide fractions are present in starch, namely the amylose that has a few branches and long linear chains and the amylopectin with opposite characteristics. Preparation of glucose solutions from starchy materials requires submitting the material to preliminary liquefaction by thermostable α-amylase and subsequent saccharification by α-amylase and amyloglucosidase, which prevents starch gelatinization (Massoud & El-razek, 2011; Palmarola-Adrados, Juhász, Galbe, & Zacchi, 2004). The resulting glucose solutions can be used directly as carbon source to produce lactic acid. These materials can also be fermented by some microorganisms directly without any preliminary hydrolysis stage because of their ability to release extracellular amylases.

On the other hand, lignocellulosic biomass represents the most abundant global source of biomass, and for this reason it has been largely utilized in many applications. It is mainly composed of cellulose, hemicellulose and lignin which form approximately 90% of the dry matter (Taherzadeh & Karimi, 2008). Lignocellulosic materials can be used to obtain sugar solutions that may be usefully exploited for the production of lactic acid through the following steps: a) pretreatment to break down the lignocellulosic structure, b) enzymatic hydrolysis to depolymerize lignocellulose to fermentative sugars, c) sugar fermentation to lactic acid by lactic acid bacteria and d) separation and purification of lactic acid (Abdel-Rahman *et al.*, 2011; Bustos, Moldes, Cruz, & Domínguez, 2005a; Chang, Lu, Yang, Zhao, & Zhang, 2010; Moldes, Alonso, & Parajó, 2001b; Parajó, Alonso, & Moldes, 1997; Yáñez, Alonso, & Parajó, 2004). In recent years, one of the most used processes to obtain lactic acid from lignocellulosic materials is the simultaneous saccharification and fermentation (Cui, Li, & Wan, 2011; Nakano, Ugwu, & Tokiwa, 2012; Ou, Ingram, & Shanmugam, 2011), which is able to prevent enzyme inhibition by the product (Romaní, Yáñez, Garrote, & Alonso, 2008).

Direct fermentation by fungi

Fungi and bacteria are the most widely employed microorganisms for lactic acid production. The main advantages of the use of fungi as fermenting agents are their ability to release extracellular amylases able to hydrolyze starchy materials, thus not requiring any prior stage of hydrolysis (Deng, Li, Xu, Gao, & Huang, 2012; Jin, Yin, Ma, & Zhao, 2005), and the easy separation of biomass because of mycelium formation. These fungi, which usually belong to the genus *Rhizopus* and produce especially the L(+) isomer (Wang, Sun, Wei, & Wang, 2005), have been employed with starches from corn (Bai *et al.*, 2004), rice (Fukushima, Sogo, Miura, & Kimura, 2004), potato, wheat and pineapple (Jin, Huang, & Lant, 2003; Jin *et al.*, 2005), and hydrolyzed corn cobs (Miura *et al.*, 2004), pine wood (Woiciechowski, Soccol, Ramos, & Pandey, 1999) and waste paper (Marques, Santos, Gírio, & Roseiro, 2008; Park, Anh, & Okuda, 2004).

Fermentation by bacteria

Lactic acid bacteria are named according to their ability to produce lactic acid as the major (and sometimes the sole) product of sugar fermentation. Many lactic acid bacteria also encode the enzymes required for aerobic respiration, but none synthesize heme (some lactic acid bacteria also lack menaquinones). Thus, the respiration chain is non-functional unless heme (and for some bacteria heme and menaquinones) are added to the culture medium (Pedersen, Gaudu, Lechardeur, Petit, & Gruss, 2012). Most lactic acid bacteria are catalase negative, immobile, do not form spores and have optimum growth temperature between 20 and 45 °C. In addition, they have high tolerance to acidic conditions (pH < 5), which confers them a competitive advantage over other bacteria. As shown in Table 1, the selection of a suitable microorganism enables one to ferment sugar solutions of different origin.

Lactic acid purification

Lactic acid purification is one of the most costly steps of the production process (Abdel-Rahman *et al.*, 2011; Tong *et al.*, 2004). Great attention should be paid to the addition of low-cost residues or other nutrients to the medium, because removal of impurities can significantly increase the costs of purification steps (Büyükkileci & Harsa, 2004). Methods to reduce impurities in the final product include extraction (Järvinen, Myllykoski, Keiski, & Sohlo, 2000), membrane separation (Persson, Jönsson, & Zacchi, 2001), ion exchange (Moldes, Alonso, & Parajó, 2001a), electrodialysis (Bailly, 2002) and distillation with chemical reaction (Choi & Hong, 1999; Edreder, Mujtaba, & Emtir, 2011).

According to Khunnonkwao, Boontawan, Haltrich, Maischberger, and Boontawan (2012), distillation is extremely difficult owing to the low volatility of lactic acid, and electrodialysis cannot separate charged components

Table 1. Microorganisms and raw materials used in the production of lactic acid.

Material	Microorganisms	Carbon source	References
Monosaccharides and disaccharides			
Molasses	*L. casei*	Saccharose	Hofvendahl and Hähn-Hägerdal, 2000; Kotzamanidis *et al.*, 2002
	L. lactis	Saccharose	Milcent and Carrere, 2001
Pineapples syrup	*L. lactis*	Saccharose	Ueno, Ozawa, Ishikawa, Nakanishi, & Kimura, 2003
Camel milk	*L. delbrueckii*	Lactose	Gassem & Abu-Tarboush, 2000
Cow milk	*L. delbrueckii*	Lactose	Gassem & Abu-Tarboush, 2000
Whey	*L. acidophilus*	Lactose	Gupta & Gandhi, 1995; Kumar, Jha, & Chauhan, 2001
	L. bulgaricus	Lactose	Chakraborty & Dutta, 1999
	L. delbrueckii	Lactose	Chakraborty & Dutta, 1999
	L. casei	Lactose	Göksungur, Gündüz, & Harsa, 2005
	L. helveticus	Lactose	Amrane, 2001, 2003, 2005; Fitzpatrick and O'Keeffe, 2001;
	Lactococcus lactis	Lactose	Roukas & Kotzekidou, 1996, 1998
	S. thermophilus	Lactose	Liu, Liu, Liao, Wen, & Chen, 2004
Date juice	*L. rhamnosus*	Saccharose	Nancib *et al.*, 2001, 2005
Starchy materials			
Corn	*L. amylophilus*	Starch	Vishnu, Seenayya, & Reddy, 2002
Potato	*L. amylophilus*	Starch	Vishnu *et al.*, 2002
	L. delbrueckii	Glucose[a]	Ray, Mukherjee, & Majumdar, 1991
Wheat (bran) (flour)	*L. amylophilus*	Starch	Naveena, Altaf, Bhadrayya, Madhavendra, & Reddy, 2005
	L. bulgaricus	Glucose[a]	Hofvendahl and Hahn-Hägerdal, 1997
	L. casei	Glucose[a]	Hofvendahl and Hahn-Hägerdal, 1997
	L. lactis	Glucose[a]	Hofvendahl and Hahn-Hägerdal, 1997
Rice	*L. delbrueckii*	Glucose[a]	Fukushima *et al.*, 2004
Barley	*L. casei*	Glucose[a]	Linko and Javanainen, 1996
Yucca	*L. lactis*	Glucose[a]	Sirisansaneeyakul *et al.*, 2000
	L. plantarum	Starch	Shamala & Sreekantiah, 1988
	L. delbrueckii	Glucose[a]	John, Nampoothiri, *et al.*, 2007; John, Sukumaran, *et al.*, 2007
	L. casei	Glucose[a]	John, Nampoothiri, *et al.*, 2007; John, Sukumaran, *et al.*, 2007
Tapioca	*L. plantarum*	Glucose[a]	Shamala & Sreekantiah, 1988
Lignocellulosic hydrolyzates			
Bamboo	*L. plantarum*	Glucose	Asada, Nakamura, & Kobayashi, 2005
Corrugated	*L. coryniformis*	Glucose	Yáñez, Alonso, & Parajó, 2005
Alfalfa fifer	*L. delbrueckii*	Glucose	Sreenath, Moldes, Koegel, & Straub, 2001a, 2001b
	L. pentoaceticus	Glucose	Sreenath *et al.*, 2001b
	L. plantarum	Glucose	Sreenath *et al.*, 2001a,b
	L. xylosus	Glucose	Sreenath *et al.*, 2001b
Soy fiber	*L. delbrueckii*	Glucose	Sreenath *et al.*, 2001a
	L. plantarum	Glucose	Sreenath *et al.*, 2001a
Wood of eucalyptus	*L. delbrueckii*	Glucose	Parajó, Alonso, & Santos, 1996
Grape marc	*L. pentosus*	Xylose	Portilla, Moldes, Torrado, & Domínguez, 2007
Wheat straw	*L. pentosus*	Xylose	Garde *et al.*, 2002
	L. brevis	Xylose	Garde *et al.*, 2002
Waste paper	*L. rhamnosus*	G/X/C[c]	Marques *et al.*, 2008
Pulp	*L. delbrueckii*	Glucose	Roberto *et al.*, 2007
Cellulosic residue	*L. casei*	Glucose	Thomas, 2000
RSU[b]	*L. pentosus*	X/G/A[c]	McCaskey, Zhou, Britt, & Strickland, 1994
	L. plantarum	X/G/A[c]	McCaskey *et al.*, 1994
		Glucose	Bustos *et al.*, 2005b
Corn cobs	*L. delbrium*	Glucose	Luo, Xia, Lin, & Cen, 1997

[a] Starch hydrolyzates.
[b] Municipal waste.
[c] X = xylose/G = glucose/A = arabinose/C = cellobiose; *L.* = *Lactobacillus*.

especially contaminating amino acids and organic acids. On the other hand, nanofiltration combined with bipolar electrodialysis in downstream purification can replace multiple purification steps with only two steps, while yielding a monomer grade lactic acid from a mixture of unconverted sugars and lactic acid (Sikder, Chakraborty, Pala, Drioli, & Bhattacharjee, 2012).

Chromatography has been developed for many years as a very useful tool for pharmaceutical industry, biotechnology as well as in the production of fine chemicals (Tong *et al.*, 2004); in particular, the ion exchange technique is widely used in bioseparations, and several different ion exchangers have been successfully employed in the past few years to recover lactic acid (Thang & Novalin, 2008).

Fundamentals of biochemistry and metabolism of lactic acid bacteria

The largest and most diverse genus of lactic acid bacteria is *Lactobacillus*, which includes species with very different biochemical and physiological properties along with special resistance against acidic environment. Because of their high growth rate and productivity, microorganisms belonging to this genus are used in important industrial productions (Kylä-Nikkilä, Hujanen, Leisola, & Palva, 2000) and make use of two main routes to ferment glucose (Gao *et al*., 2011; Mayo, Piekarczyk, Kowalczyk, Pablo, & Bardowski, 2010).

Lactic acid production from glucose and related fermentation pathways

Homolactic fermentation

This process takes place in two steps. In the former step, called glycolysis or Embden–Meyerhof–Parnas pathway, glucose is transformed into pyruvic acid, while in the latter this is reduced to lactic acid by the reducing power previously produced in the form of NADH. Thus, lactic acid is obtained from glucose as the sole product (Fig. 2) according to the overall equation:

$$\text{Glucose} \rightarrow 2\ \text{Lactic Acid} + 2\ \text{ATP} \quad (1)$$

Microorganisms that use only this route for the consumption of carbohydrates are called *Obligatory Homofermentative*, and these include, among others, *Lactobacillus acidophilus*, *Lactobacillus amylophilus*, *L. bulgaricus*, *Lactobacillus helveticus* and *L. salivarius* (Mayo *et al*., 2010; Nigatu, 2000; Sanders & Klaenhammer, 2001).

Homolactic fermentation should theoretically yield 2 mol of lactic acid per mole of consumed glucose with a theoretical yield of 1 g of product per g of substrate, but the experimental yields are usually lower (0.74–0.99 g g^{-1}) because a portion of the carbon source is used for biomass production (0.07–0.22 g g^{-1}) (Bruno-Bárcena, Ragout, Córdoba, & Siñeriz, 1999; Burgos-Rubio, Okos, & Wankat, 2000; Hofvendahl & Hahn-Hägerda, 1997; Srivastava, Roychoudhury, & Sahai, 1992). Under stress conditions such as carbon source limitation, presence of different carbon sources other than glucose, high pH or low temperature, some homofermentative microorganisms can produce formic acid by mixed acid fermentation (Hofvendahl & Hahn-Hägerda, 2000) by the action of pyruvate-formate lyase (Gao *et al*., 2011; Mayo *et al*., 2010).

Heterolactic fermentation

This process is characterized by the formation of co-products such as CO_2, ethanol and/or acetic acid in addition to lactic acid as the end product of fermentation (Fig. 3). The first step of glucose degradation, which is called pentose phosphate pathway, leads to glyceraldehyde 3-phosphate, acetyl-phosphate and CO_2. Glyceraldehyde 3-phosphate enters the glycolysis through which it is transformed into lactic acid, while acetyl-phosphate is converted into acetic acid and/or ethanol according to the overall equations:

$$\text{Glucose} \rightarrow \text{Lactic acid} + CO_2 + \text{Ethanol} + \text{ATP} \quad (2)$$

$$\text{Glucose} \rightarrow \text{Lactic acid} + CO_2 + \text{Acetic acid} + 2\ \text{ATP} + 2\ \text{NADH} \quad (3)$$

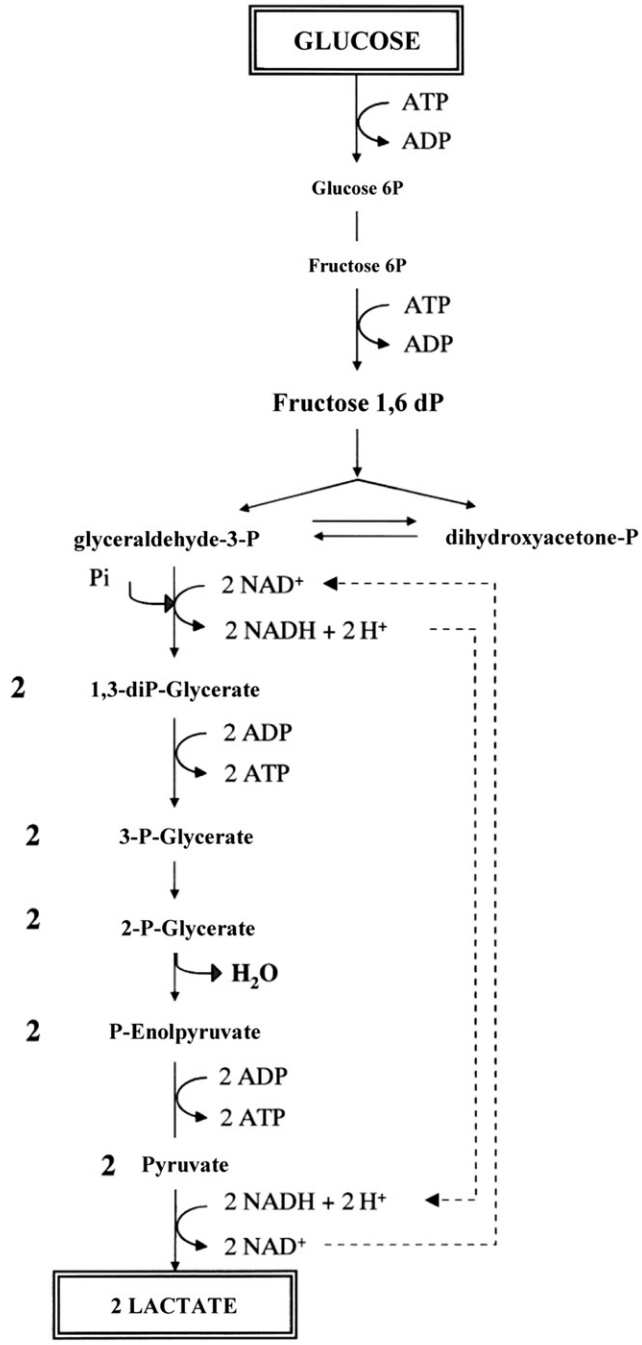


Fig. 2. Scheme of homofermentative pathway of glucose fermentation in lactic acid bacteria. Modified after Axelsson (2004) and Mayo *et al*. (2010).

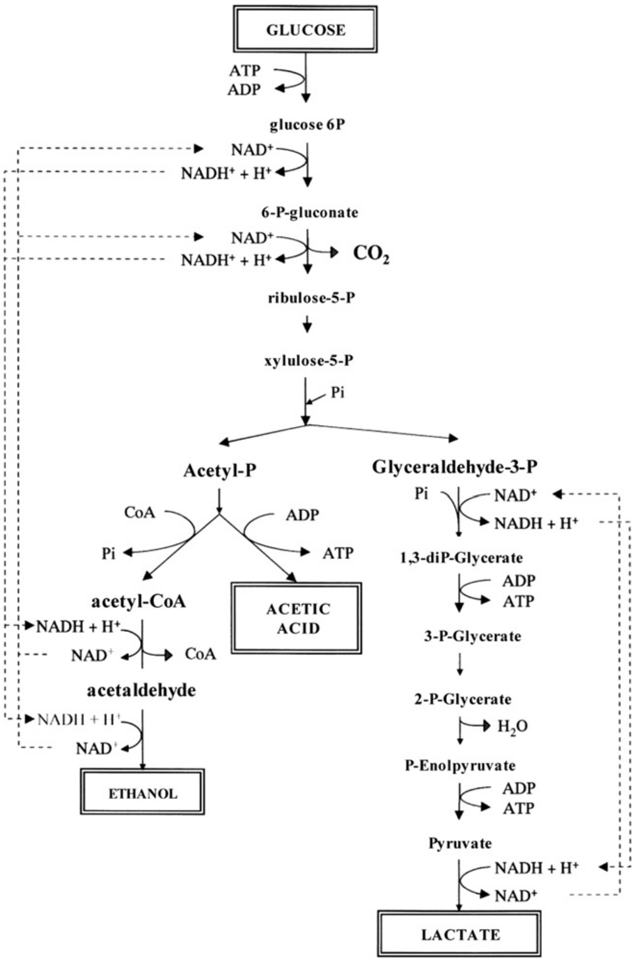


Fig. 3. Scheme of heterofermentative pathway of glucose fermentation in lactic acid bacteria. Modified after Axelsson (2004) and Mayo *et al.* (2010).

The relationship between the amounts of acetic acid and ethanol, which reduces the theoretical yield to 0.50 g g^{-1}, depends on the ability of the microorganism to reoxidize the NADH generated in the early stages of the process along with its energy requirements. Microorganisms that use only this metabolic pathway for the consumption of carbohydrates are called *Obligatory Heterofermentative*, among which are *Lactobacillus brevis*, *L. fermentum*, *L. parabuchneri* and *L. reuteri* (Mayo *et al.*, 2010; Nigatu, 2000; Sanders & Klaenhammer, 2001).

Lactic acid production from other carbon sources

In addition to glucose, there are other hexoses such as fructose, mannose or galactose, which can be consumed by lactic acid bacteria (Table 2). On the other hand, hexose-fermenting lactobacilli are unable to ferment pentoses. There are some species of this genus, classified as *Facultative Heterofermentative*, among which *L. alimentarius*, *Lactobacillus plantarum* (Gobbetti, Lavermicocca, Minervini, de Angelis, & Corsetti, 2000), *Lactobacillus casei*, *Lactobacillus rhamnosus* (Nigatu, 2000; Rivas, Torrado, Rivas, Moldes, & Domínguez, 2007; Romaní *et al.*, 2008), *Lactococcus lactis* (Ishizaki, Ueda, Tanaka, & Stanbury, 1992, 1993; Joshi, Singhvi, Khire, & Gokhale, 2010), *Lactobacillus pentosus* (Bustos *et al.*, 2005a; Moldes *et al.*, 2001a, 2001b) and *Lactobacillus xylosus* (Tyree, Clausen, & Gaddy, 1990), that perform both fermentations, consuming hexoses by the homolactic pathway and pentoses by the heterolactic one. The catabolism of pentoses requires additional conversion steps through which they are transformed into metabolic intermediates of the pentose phosphate pathway. By this way, as an instance, xylose is transformed into xylulose and then phosphorylated to xylulose 5-phosphate, arabinose into ribulose, and this in turn is phosphorylated to ribulose 5-phosphate (Gao *et al.*, 2011; Mayo *et al.*, 2010).

In recent years, the utilization of lignocellulosics as raw material for lactic acid production has required the development of methods for efficient utilization of xylose (Yoshida, Okano, Tanaka, Ogino, & Kondo, 2011). *L. xylosus* (Tyree *et al.*, 1990) and *L. rhamnosus* (Iyer, Thomas, & Lee, 2000) have been used in media containing a mixture of xylose and glucose and acidic hemicellulosic hydrolyzates of wood, respectively. *L. pentosus* allowed obtaining 33 g L^{-1} of lactic acid and 17 g L^{-1} of acetic acid from detoxified hemicellulosic liquor made from reeds (Perttunen, Myllykoski, & Keiski, 2002) and 44.8 g L^{-1} of lactic acid and 6.5 g L^{-1} of acetic acid from concentrated hemicellulosic hydrolyzates of trimming vine shoots (Bustos, Moldes, Cruz, & Domínguez, 2005b). In fermentations with *Bacillus coagulans* high levels of lactic acid were obtained from xylose and glucose (Ou *et al.*, 2011). Wang *et al.* (2009) reached 83 g L^{-1} of lactic acid from the co-fermentation of glucose and xylose by *Rhizopus oryzae* using low-energy ion beam irradiation. Mixed culture of lactic acid bacteria were also employed in the simultaneous fermentation of hexoses and pentoses, thereby allowing for efficient utilization of both cellulose- and hemicellulose-derived sugars (Cui *et al.*, 2011).

From the metabolic viewpoint, contrary to hexoses, the heterolactic fermentation of pentoses does not imply any excess of NADH; therefore, the only way to utilize acetyl-phosphate is its direct dephosphorylation to acetate with recovery of an additional mol of ATP:

$$\text{Pentose} \rightarrow \text{Lactic acid} + \text{Acetate} + 2\ \text{ATP} \tag{4}$$

Lactic acid bacteria can also metabolize disaccharides such as lactose, maltose and sucrose, which are cleaved by the action of endocellular hydrolases. Additionally, certain species such as *L. rhamnosus* are able to consume cellobiose (Marques *et al.*, 2008), a disaccharide made up of two glucose units linked through β(1–4) bonds, which has special importance in processes employing cellulose hydrolyzates.

Stereospecific lactic acid production

Lactic acid bacteria may selectively produce one specific stereoisomer of lactic acid (D or L) or a mixture of them in various proportions. Such an ability is determined by the presence of the enzyme lactate dehydrogenase, which possesses

Table 2. Microorganisms used in the production of lactic acid from synthetic media.[a]

Microorganism	Carbon source	References
L. amylophilus	Glucose	Mercier, Yerushalmi, Rouleau, & Dochain, 1992
	Starch	Vishnu *et al.*, 2002
L. bulgaricus	Fructose	Amoroso, Manca de Nadra, & Oliver, 1988
	Galactose	Burgos-Rubio *et al.*, 2000
	Glucose	Burgos-Rubio *et al.*, 2000; Chakraborty and Dutta, 1999
	Lactose	Burgos-Rubio *et al.*, 2000; Chakraborty and Dutta, 1999
L. casei	Glucose	Ha, Kim, Lee, Kim, & Kim, 2003; Kurbanoglu, 2004
	Lactose	Büyükkileci and Harsa, 2004; Göksungur *et al.*, 2005
L. coryniformis	Glucose	Yáñez *et al.*, 2005
	F/G/S	Zorba, Hancioglu, Genc, Karapinar, & Ova, 2003
L. delbrueckii	Glucose	Hofvendahl and Hähn-Hägerdal, 2000
	Fructose	Robison, 1988; Suskovic, Beluhan, Beluhan, & Kurtanjek, 1992
	Galactose	Kadam, Patil, Bastawde, Khire, & Gokhale, 2006
	Lactose	Hofvendahl and Hähn-Hägerdal, 2000; Welman & Maddox, 2003
	Maltose	Robison, 1988
	Saccharose	Kotzamanidis *et al.*, 2002; Srivastava *et al.*, 1992; Suskovic *et al.*, 1992; Vinderola, Costa, Regenhardt, & Reinheimer, 2002; Zlotkowska, 2000
L. helveticus	Lactose	Amrane, 2001, 2005
L. lactis	G/X/L	Bai *et al.*, 2003
	Saccharose	Milcent and Carrere, 2001; Ueno *et al.*, 2003
L. manihotivorans	Starch	Guyot, Calderon, & Morlon-Guyot, 2000
L. paracasei	Glucose	Xu *et al.*, 2006
L. pentosus	Glucose	Bustos, Moldes, Cruz, & Domínguez, 2004b
	Xylose	Portilla *et al.*, 2007
L. plantarum	Starch	Pintado, Guyot, & Raimbault, 1999; Shamala & Sreekantiah, 1988
L. rhamnosus	Gal/G/M/X	Iyer *et al.*, 2000; Romaní *et al.*, 2008
Lactococcus lactis	Glucose	Loubiere *et al.*, 1997; Sakai, 2004
	Xylose	Kanagachandran, Stanbury, Hall, & Ishizaki, 1997; Tanaka *et al.*, 2002
	Lactose	Hofvendahl and Hähn-Hägerdal, 2000
	Maltose	Sato, Tokuda, & Nakanishi, 2002
	Saccharose	Ueno *et al.*, 2003

[a]*L.* = *Lactobacillus*; G = glucose, X = xylose, L = lactose, Gal = galactose, M = mannose, F = fructose, S = saccharose.

stereospecific NAD^+-dependent activity (Hofvendahl & Hahn-Hägerda, 2000).

Among the bacteria that produce L(+) lactic acid are *L. amilophylus* (Yumoto & Ikeda, 1995), *L. brevis* and *L. buchneri* (Wu-Tai, Driehuis, & Van Wikselaar, 2003), *L. casei* (Büyükkileci & Harsa, 2004; Hujanen, Linko, Linko, & Leisola, 2001; John, Nampoothiri, *et al.*, 2007; Korbekandi, Abedi, Jalali, Fazeli, & Heidari, 2007), *Lactobacillus delbrueckii* (Hofvendahl & Hahn-Hägerda, 1997; John, Sukumaran, *et al.*, 2007; Thomas, 2000), *L. rhamnosus* (Lu, He, Shi, Lu, & Yu, 2010; Marques *et al.*, 2008; Narayanan, Roychoudhury, & Srivastava, 2004b), *L. lactis* (Bai *et al.*, 2003; Hofvendahl & Hahn-Hägerda, 1997) and *Streptococcus* sp. (Ishizaki & Ohta, 1989), whereas *Lactobacillus coryniformis* produces stereospecifically D(−)-lactic acid (Bustos, Alonso, & Vázquez, 2004; Yáñez, Moldes, Alonso, & Parajó, 2003), and *L. helveticus* (Kylä-Nikkilä *et al.*, 2000; Schepers, Thibault, & Lacroix, 2002), *L. plantarum* (Hofvendahl & Hahn-Hägerda, 2000; Yoshida *et al.*, 2011) and *L. pentosus* (Hammes & Vogel, 1995) mixtures of both isomers.

Factors affecting lactic fermentation by bacteria

Nutritional requirements of lactic acid bacteria

Several bottlenecks remain in lactic acid production processes, among which are meeting nutritional requirements of lactic acid bacteria, excess acidity, and substrate and product inhibition. To achieve good production, lactic acid bacteria need to be cultured under conditions that also ensure cell growth and viability, for which the necessary nutrients (carbon, nitrogen, minerals and vitamins) should be in directly available form (Roberto, Mussatto, Mancilha, & Fernandes, 2007).

Carbon can be present in the culture medium in the form of sugars, amino acids and organic acids that have high energy content (Cui *et al.*, 2011). Nitrogen, which is implied either in anabolic or catabolic processes, is available in the form of amino acids, peptides and inorganic compounds that can be added to the culture media as peptone, yeast extract, urea or ammonium sulfate (Nancib *et al.*, 2001). Mineral elements (Mg, Mn and Fe), which are provided in the medium in the form of salts ($MgSO_4$, $MnSO_4$ and $FeSO_4$) (Büyükkileci & Harsa, 2004; Fitzpatrick & O'Keeffe, 2001), and vitamins (mainly belonging to the B group) present in yeast extract are essential elements that act as cofactors in many enzymatic reactions.

Studies have been addressed to the optimization of nutrients (Fitzpatrick & O'Keeffe, 2001; Nancib *et al.*, 2001; Pauli & Fitzpatrick, 2002) as well as the utilization of corn steep liquor (Oh *et al.*, 2005; Wee, Yun, Lee, Zeng, & Ryu, 2005) and wastes from the winemaking process

(Bustos, Alonso, & Vázquez, 2004; Bustos, Moldes, Cruz, & Domínguez, 2004a, 2005a, 2005b) as cheap sources of nitrogen, nutrients and minerals.

The cost of nutrients is one of the main drawbacks for the competitive biotechnological production of lactic acid. In an economic study carried out to produce lactic acid by fermentative means, it was found that yeast extract supplementation represented 38% of medium cost (Tejayadi & Cheryan, 1995). Consequently, it is economically interesting to find low-cost media to replace the traditional nutrients employed in these processes (Salgado, Rodríguez, Cortés, & Domı́nguez, 2009).

Acidity

Since lactic acid bacteria grow preferentially at pH between 5 and 7, the medium acidification associated with lactic acid production inhibits fermentation (Nomura, Iwahara, & Hongo, 1987; Roberto *et al.*, 2007). To minimize this occurrence, the pH can be maintained around 6 by addition of calcium carbonate at the beginning of batch fermentations, so that lactic acid can be neutralized at the same time it is formed. Hetényi, Németh, and Sevella (2011) tested five different compounds to control pH, namely ammonium hydroxide, sodium hydroxide, dimethylamine, trimethylamine and calcium carbonate. Trimethylamine proved to be the best neutralizing agent, even though the use of ammonium hydroxide would also be advisable from the technological viewpoint. Peeva and Peev (1997) used a combined method for lactic acid production by *L. casei*, where, in line with fermentation, enzymatic urea hydrolysis released the ammonium hydroxide required to neutralize lactic acid.

The use of mutant strains able to grow under low pH may be an alternative strategy to overwhelm inhibition by the acidic product. Several authors reported that the increase in acid resistance of lactic acid bacteria may be due to the restoration of the optimum intracellular pH through arginine utilization by arginine deiminase and NH_3 production (Araque, Bordons, & Reguant, 2012; Bourdineaud, 2006; Sanders, Vemena, & Kok, 1999). In addition, the use of strains able to tolerate acidic conditions would help to reduce the addition of buffering agents like calcium carbonate, thereby reducing the cost and pollution problems and making the recovery of free lactic acid from the fermentation broth easier (John & Nampoothiri, 2008).

Substrate inhibition

Substrate inhibition seems to depend on both the microorganism and the carbon source. Whereas an increase in the initial glucose concentration was shown in fact to delay the growth of *L. delbrueckii* and *L. bulgaricus* reducing both the specific productivity (Gonçalves, Xavier, Almeida, & Carrondo, 1991) and product yield (Burgos-Rubio *et al.*, 2000), such an inhibition was not observed using *L. casei* on sucrose up to 100 g L^{-1} (Büyükkileci & Harsa, 2004), *L. brevis* and *L. pentosus* on xylose up to 20 g L^{-1} (Garde, Jonsson, Schmidt, & Ahring, 2002) and *L. helveticus* on lactose up to 110 g L^{-1} (Schepers *et al.*, 2002). However, xylose inhibition of *L. lactis* fermentation was an order of magnitude stronger than that exerted by glucose (Ishizaki *et al.*, 1992, 1993). To minimize this inhibition, substrate can be added to the fermentation medium according to the fed-batch process (Roukas & Kotzekidou, 1998), but low initial substrate concentrations are required to obtain high lactic acid concentration (210 g L^{-1}), yield (0.97 g g^{-1}) and productivity (2.2 g L h^{-1}) (Bai *et al.*, 2003).

Product inhibition

Lactic acid was shown to exert an inhibitory effect on cell growth, which is stronger than that on fermentation activity (Madzingaidzo, Danner, & Braun, 2002; Milcent & Carrere, 2001). Loubiere, Cocaign-Bousquet, Matos, Goma, and Lindley (1997) suggested that lactic acid inhibition on cell proliferation and metabolism is possibly due to the increase in medium osmotic pressure, and that also some fermentation byproducts such as formic acid, acetic acid or sodium formate may exert individual inhibitory effects (Lin, Du, Koutinas, Wang, & Webb, 2008; Loubiere *et al.*, 1997). For example, Loubiere *et al.* (1997) observed a decrease of 50% on the growth of *Lc. lactis* in the presence of 76 and 187 mmol L^{-1} of formic acid and acetic acid, respectively. The concentration of the undissociated form of lactic acid plays a role in the inhibition (Bajpai & Ianotti, 1988) more important than that of lactate (Monteagudo, Rodríguez, Rinco, & Fuertes, 1997). To mitigate the effect of inhibition, various strategies have been proposed, among which are the use of fermentation technologies able to remove the product from the medium at the same time it is released (Kaufman, Cooper, Budner, & Richardson, 1996; Moldes *et al.*, 2001a); the neutralization of lactic acid to give its dissociated form that has a less inhibitory effect (Madzingaidzo *et al.*, 2002; Milcent & Carrere, 2001); and the microorganism adaptation and/or the use of mixed cultures (Cui *et al.*, 2011; Robison, 1988; Tsai, Coleman, Moon, Schneider, & Millard, 1993).

Fermentation technologies

Lactic acid production from sugar solutions

Even though only one type of microorganism is usually employed in the production of lactic acid, mixed cultures of various lactobacilli (Cui *et al.*, 2011; John, Sukumaran, *et al.*, 2007; Tsai *et al.*, 1993) or lactobacilli and *Kluyveromyces marxianus* (Plessas *et al.*, 2008) were shown to ensure better results compared to pure cultures. Other authors have used mixed cultures of two microorganisms, one of them to carry out the fermentation and the other to carry out the hydrolysis of a polymeric substrate (Ge, Qian, & Zhang, 2009; Kurosawa, Ishikawa, & Tanaka, 1988; Romaní *et al.*, 2008).

Suspended-cell systems

Most of the published work on fermentative production of lactic acid by free cells was carried out operating in batch mode (Amrane, 2001; Büyükkileci & Harsa, 2004; Chen *et al*., 2012; Korbekandi *et al*., 2007), although there are examples of continuous (Dey & Pal, 2012; Lunelli *et al*., 2011; Nishiwaki & Dunn, 2005; Salgado, Rodríguez, Cortés, & Domínguez, 2012; Xu *et al*., 2006) and fed-batch (Bai *et al*., 2003; Ge *et al*., 2009; Zhang, Cong, & Shi, 2011) productions.

Ultrafiltration of effluents from continuous suspended-cell systems allows retaining and separating cells from the fermented medium and recirculating them to the bioreactor (Lu, Wei, & Yu, 2012; Richter & Nottelmann, 2004; Xu *et al*., 2006), ensuring higher cell concentrations and productivities (33–57 g L^{-1} h) than batch systems with comparable yields (Dey & Pal, 2012; Ishizaki & Vonktaveesuk, 1996; Kwon, Yoo, Lee, Chang, & Chang, 2001). Dey and Pal (2012) obtained efficient production of lactic acid from sugarcane juice in a novel two stage membrane-integrated fermenter.

Immobilized-cell systems

Immobilization of lactic acid bacteria is able to remarkably increase yields and productivities compared with suspended-cell systems, because it allows preventing the limits related to washout. Support materials are usually alginate gel (Cortón, Piuri, Battaglini, & Ruzal, 2000; Voo, Ravindra, Tey, & Chan, 2011), *k*-carrageenan (Norton *et al*., 1994) or agar (Zayed & Zahran, 1991). However, the entrapment within gel has some drawbacks such as the formation of pH gradients inside the particles, occlusions and preferential flow, loss of gel mechanical stability, reduction of cell activity along the time and occurrence of diffusion limitations (Elezi *et al*., 2003).

Owing to these drawbacks, more stable immobilization supports have been proposed; among them are ceramic and porous glass particles (Bruno-Bárcena *et al*., 1999) or gluten beads (Chronopoulos *et al*., 2002), which, however, are relatively expensive. In other works, it was proposed the immobilization of *L. brevis* on delignified lignocellulosic materials (Elezi *et al*., 2003), *L. plantarum* on polypropylene matrices treated with chitosan (Krishnan, Gowthaman, Misra, & Karanth, 2001) and *R. oryzae* on a fibrous matrix composed of stainless-steel mesh and cotton cloth (Chen *et al*., 2012), which ensured high yields and productivities.

Lactic acid production by simultaneous saccharification and fermentation of polysaccharides

The aim of the "simultaneous saccharification and fermentation" (SSF) process is the one-step production of lactic acid from a polysaccharide material, consisting in the preliminary enzymatic hydrolysis of substrate to monosaccharides (saccharification) and their subsequent fermentation to lactic acid. This process has been studied using either starchy (Ge *et al*., 2009; Linko & Javanainen, 1996) or lignocellulosic (Bustos *et al*., 2005a; John, Nampoothiri, *et al*., 2007; Marques *et al*., 2008; Moldes *et al*., 2001b; Romaní *et al*., 2008; Yáñez *et al*., 2003) waste materials.

There are some interesting advantages that make the SSF of great interest from an industrial point of view such as the cost reduction associated with the use of only one reactor for hydrolysis and fermentation (Bustos *et al*., 2004a; Lee, Koo, & Lin, 2004). From the technological point of view, since the limiting step of SSF is the biopolymer enzymatic hydrolysis, the microorganism consumes glucose at the same rate it is formed, which allows reducing the substrate inhibition and, consequently, the enzyme loading and the risk of external contamination.

Using *Eucalyptus globulus* wood as raw material and *L. delbrueckii* NRRL-B445 as a fermenting agent, Moldes *et al.* (2001b) obtained interestingly 108 g L^{-1} of lactic acid after 115 h of SSF, corresponding to a yield of 0.94 g g^{-1}, by intermittent addition of substrate (after 8–75 h), cellulases and nutrients (48 h) and simultaneous elimination of produced lactic acid by ion exchange. Even higher lactic acid concentration (162 g L^{-1}) and excellent productivity (1.4 g L^{-1} h^{-1}) were reported by Lee *et al.* (2004) for similar exploitation of paper industry wastes. Lactic acid was also produced by SSF of broken rice, reaching a volumetric productivity of 3.59 g L^{-1} h^{-1} (Nakano *et al*., 2012).

Conclusions

This review paper reports on the fermentative and biotechnology processes to produce lactic acid. Polymeric substrates cannot be directly assimilated by lactic acid bacteria; therefore, they require an earlier stage of hydrolysis prior to lactic acid fermentation. On the other hand, fungi as fermenting agents are able to release extracellular amylases and, consequently, to directly hydrolyze starchy materials, thus not requiring any prior stage of hydrolysis. In fact, the high cost of hydrolytic enzymes for the saccharification of hemicellulosic materials is a serious drawback lactic acid industry, but it is noteworthy that lignocellulosic biomass represents the most abundant global source of biomass, and for this reason it can be largely utilized to give bioproducts. Therefore, different technologies and microorganisms have to be developed with the aim to increase the fermentation yield and the volumetric productivity of lactic acid.

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