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Second-generation (2G) Lactic Acid Production and New Developments – A Mini-review

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Lactic acid (LA) production is already a global reality. Its applications cover the most diverse industrial sectors and have rapidly consolidated in recent years. Currently, the most prominent use of LA is the production of polylactic acid to replace plastics from the petrochemical industry. A great part of this rapid change is due to the rising worldwide concerns about the excess of non-degradable plastics used daily and the accumulation of this material in nature. In this scenario, LA production becomes even more relevant when considering its production from renewable raw materials, especially second-generation (2G) substrates, such as lignocellulosic biomass. This reduces the human dependence on oil for both energy and fuel production, as well as for the production of plastics and other chemicals since LA is still one of the most relevant building block chemicals. Nowadays it is possible to produce LA from the most diverse 2G-substrates available around the world. Thus, LA production by fermentation of 2G-sugars can be associated with several existing biorefinery models, such as for biofuels and chemicals production. In this scenario, for example, it is possible to associate LA production with ethanol production in a biorefinery model, producing 1G-ethanol, 2G-LA, sugar for food, and electricity. This kind of approach may represent a break from current production model of energy and chemicals to a more sustainable and democratic scenario, including new players in the world market and reducing the dependence of other countries to supply oil and its derivates, especially when associated with new and powerful genetic engineering tools. Front this scenario, this review presents the state of the art of 2G-LA production.

1. Introduction

Lactic acid (LA) is classified as 2-hydroxy-propanoic acid ($C_3H_6O_3$) and is one of the most relevant carboxylic acids in the world. Several well-known industrial applications include their constant use in the food, pharmaceutical and cosmetics industries (Mazzoli et al., 2014). In addition, its use in the production of polylactic acid (PLA) with broad applications in the substitution of petroleum-derived polymers has sparked worldwide interest in this versatile chemical molecule. Its versatility is mainly due to its natural occurrence in the isomeric forms of L and D LA. Each of the isomers has different applications, being the L-isomer the most used by the food, cosmetic and pharmaceutical industries, due to its long-known compatibility with the human body. On the other hand, different mixing rates of the D and L isomers may confer interesting properties in the construction of LA derived polymers, altering their resistance, flexibility, crystallinity and degradation rate (Mazzoli et al., 2014). Thus, the PLA industry can build polymers that replace almost any known polymer derived from the petrochemical industry, besides producing biodegradable plastics for daily use.
Petrochemical LA production generates a racemic LA mixture, that, once polymerized will result in an amorphous PLA (Figure 1a), with a low real use for the industry. The ability to produce a high purity isomer has important ramifications in the chemistry and ultimate process/property relationships achievable in the

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polymers produced from LA. In fact, LA polymers with specific characteristics may be produced to medical applications using controlled amounts of L and D isomers. In this sense, efficient producers of LA microbial species have LA as a single fermentation product from hexoses and pentoses. The fermentation pathways of lactic acid bacteria (LAB) have high conversion rates, which means large amounts of sugar are fermented and not much sugar is converted for cell biomass production. It leads to high yields of LA and makes them industrially interesting (Sauer et al., 2017). A further interesting ability is that many LAB are able to utilize various hexoses and pentoses (Sauer et al., 2017), making them perfect to exploit lignocellulosic sugars to produce second-generation (2G) LA.

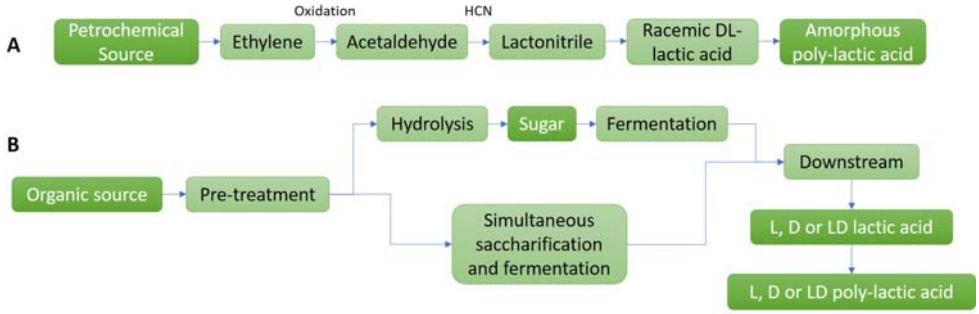

Figure 1: a) Lactic acid production route from a petrochemical source; and b) Lactic acid production route from an organic source.

Thus, considering different sugar release technologies already available, LAB have the potential to convert almost any organic source into isomeric pure LA (Figure 1b). LAB have high sugar uptake rates, which strongly contribute to high productivities and economically benefits the microbial production process of LA production. The high sugar uptake rates are comparable to other largely used microbial biotech microorganisms, such as *E. coli* or *S. cerevisiae*.

Considering the presented characteristics, the next steps of biotech development related to LAB goes toward the development of genetic toolboxes to make these microorganisms efficient cell factories, not only regarding LA production, but also other industrial molecules (Sauer et al., 2017). LAB are considered fastidious microorganisms, requiring organic sources of nitrogen and vitamins. In some cases, it can be considered a disadvantage for the use of LAB for chemical production. However, the use of 2G substrates has the potential to overcome those needs, since they can be complex organic material instead of pure processed sugars. In this sense, different types of biomass, such as energy crops, forestry residues, or by-products from agroindustry activity, featuring both the low purchase cost and circular economy, have already been tested as fermentative substrates for 2G-LA production. Taking these into account, the main achievements of the 2G-LA research are presented in this short review.

2. Fermentation feedstock for 2G-lactic acid production

Nowadays, LA applications are limited due to its high cost of production, mainly because of the cost of carbon source (glucose), showing the importance of exploring alternative cheaper carbon sources for LA production (Jiang et al., 2019). According to Guo et al. (2015), 2G-products are those produced from non-food materials, such as agricultural residues, wood, and energy crops typically high in lignocellulose, among others. Many studies propose 2G-LA production as a viable scenario, showing that besides the numerous obstacles to be overcome, this technology presents many advantages. Considering this definition of 2G-products, some recent studies of 2G-LA production are presented in Table 1.

Considering the data, it is clear that the viability of 2G-LA production broadly varies according to the combination of several factors, such as substrate, microbial strain, and operational conditions. Besides, it is also important to consider the stable availability of the substrates over the year, as well as its transportation, storage, and logistics, in order to make the process economically feasible and sustainable. Once considered these factors, an important advantage of using those substrates is its availability in several regions of the globe, which makes it possible to produce LA (and other bulk chemicals) in a great diversity of places around the world.

Finally, some of the main challenges in LA production using 2G-substrates can be solved by new genetic engineering tools in development for LAB, such as substrate recalcitrance, carbon catabolite repression, by-product formation, optical purity, LA and pH inhibition, sensibility to inhibitors released in the biomass pretreatment (Cubas-Cano et al., 2018; Upadhyaya et al., 2014).

Table 1: Second-generation substrates evaluated for lactic acid production.

2G Substrate	Strain	°C	Titer g/L	Productivity g/L/h	Yield g/g	Isomer	Reference
Bagasse sulfite pulp	*B. coagulans* CC-17	50	110.0	0.55	0.72	L	Zhou et al., 2016
Brewers' spent grains	*L. rhamnosus* ATCC 7469	37	48.0	0.96	0.87	L	Radosavljević et al., 2018
Coffee pulp	*B. coagulans*	52		4.02	0.78	L	Pleissner et al., 2016
Corn stover	*L. pentosus* FL0421	37	92.3	1.92	0.66		Hu et al., 2016
	B. coagulans NBRC 12714	50	92.0	13.8	0.91	L	Ma et al., 2016
Corncob residue	*B. coagulans* H-1	50	68.0		0.85	L	Jiang et al., 2019
	B. coagulans LA204	50	123.0	1.37	0.77		Zhang et al., 2016b
	B. coagulans IPE22	52	53.5	2.97	0.92	L	Wang et al., 2018
Dried distiller's grains	*L. coryniformis torquens* DSM 20004	37	38.1	0.80	0.35	D	Zaini et al., 2019
Food waste	*L. casei* Shirota	37	94.0	2.61	0.94		Kwan et al., 2016
	Streptococcus sp. A620	35	58.0	2.16	0.81	L	Pleissner et al., 2017
Jackfruit seed powder	*Streptococcus* sp. A620	37	109.0			L	Nair et al., 2016
Oil palm empty fruit bunch	*B. coagulans* JI12	50	120.0	4.30	0.49	L	Juturu and Wu, 2018
Orange peel	*L. delbrueckii delbrueckii* CECT 286	37		6.72	0.88	D	de la Torre et al., 2019
	L. casei 2246	37	209.6 g/kg		0.88		Ricci et al., 2019
Paper sludge	*L. rhamnosus* ATCC 7469	37	108.2		0.62		Marques et al., 2017
S. flavescens residues and food waste	*L. casei* CICC 6106	37	48.4	0.73	0.90		Zheng et al., 2017
Sugarcane bagasse	*L. plantarum* CCT 3751	37	34.5	0.58	0.34		Oliveira et al., 2018c
	B. coagulans DSM 14-300	52	56.0	1.70	0.87	L	Oliveira et al., 2019b
	B. coagulans DSM2314	50	91.7	0.92	0.94	L	van der Pol et al., 2016
	L. pentosus	37	72.7	1.01	0.61		Unrean 2018
Wheat straw	*B. coagulans* MA-13	55		1.11	1.23		Aulitto et al., 2019

3. Genetic engineering microorganisms for 2G-lactic acid production

Metabolic engineering of LAB presents a novel approach for re-routing metabolic reactions to produce desired compounds in higher amounts, such as LA, flavor compounds, sweeteners, exopolysaccharide, vitamins, among others (Sauer et al., 2017; Stefanovic et al., 2017). Interesting options for improving the phenotype and genotype of LAB are mutation, directed evolution, and genetic engineering (Cubas-Cano et al., 2018). The

rapid developments in genomics and its associated technologies have transformed the understanding of the diversity and functionality of LAB (McAuliffe, 2017). The interest in LAB genomes, considering them as important microbial cell factories started in the early ’90s (Stefanovic et al., 2017). However, their potential as microbial cell factories for the chemical industry is only emerging (Sauer et al., 2017). Besides of technology development, one of the reasons for this late development are concerns regarding the safety od genetically engineering microorganism for the environment and for the workers, as well as the acceptance of the general public to products from genetically engineered microorganisms.

Regarding 2G-LA production, genetic engineering has concentrated on improving the LA fermentation parameters, enhancing the acid tolerance of production organisms and their abilities to utilize a broad range of substrates, including fermentable 2G-sugars (Upadhyaya et al., 2014). Substrates may represent one of the major costs in the LA production chain (Upadhyaya et al., 2014), one of the reasons why genetic engineering is expected to enhance and be a tool enabling 2G-LA production both, from lignocellulosic biomass and biomass-derived waste streams. The efforts are currently focused on increasing microbial resistance toward inhibitory compounds derived from biomass pretreatment and avoid carbon catabolite repression (CCR) when using mixed sugars for fermentation (Upadhyaya et al., 2014), always associated with high titers and high isomeric purities. Front this scenario, Table 2 present some recent examples of LAB genetic modifications towards currently challenges in the LA production chain.

Table 2: Genetically engineering lactic acid bacteria for second-generation lactic acid production.

Challenge addressed	Approach	Outcome	Organism	Substrate	Reference
Direct conversion of xylan to LA	*xynR8* expression	Direct SSF xylan to produce LA in one step	*L. brevis*	Xylan	Hu et al., 2011
D-LA fermentation from a mixture of xylose and glucose	Introduction of *xylAB* operon into *ldhL1* gene-deficient	D-LA fermentation from mixed sugars without CCR	*L. plantarum*	Glucose Xylose Arabinose	Yoshida et al., 2011
L-LA fermentation from xylose	Disruption of *ptk* gene, introduction of *xylRAB* genes and insertion of *tkt* gene	L-LA production from xylose with a high optical purity	*L. lactis*	Xylose	Shinkawa et al., 2011
D-LA production from cellulosic feedstocks in SSF	Introduction of *xylAB* operon and *tkt* gene in a *ldhL1*-deficient	Increased D-LA production and productivity with high purity	*L. plantarum*	Hardwood pulp	Hama et al., 2015
High tolerance to inhibitors and L-LA optically pure production	Interruption of *ldhD* gene	Improved L-LA production from lignocellulosic biomass	*L. paracasei*	Non-detoxified wood and rice straw	Kuo et al., 2015
Improve L-LA production from crude glycerol	Disruption of *pflB* gene and expression of the *ldhL1LP* gene	High conversion of crude glycerol to L-LA	*E. faecalis*	Glycerol	Doi, 2015
D-LA production from renewable resources	xylose-assimilating genes cloned into an L-lactate-deficient strain	Increased D-LA production with high purity	*L. plantarum*	Corn stover	Zhang et al., 2016a
High titer L and D-LA production from corn stover feedstock	*ldh*/*ldhD* genes separately disrupted	High titer L and D-LA	*P. acidilactici*	Detoxified corn stover	Yi et al., 2016

CCR: carbon catabolite repression; SSF: simultaneous saccharification and fermentation

4. Conclusions

2nd generation lactic acid production still has challenges to overcome before becoming a world reality. However, the current scenario shows good perspectives of 2G-lactic acid production reach industrial-scale production, especially considering the biorefinery concept. The use of waste and/or lignocellulose material remaining from already consolidated industrial processes, especially in food and chemical production, opens the possibility of expanding sustainable and renewable processes to produce 2G-LA. With the possibility of

replacing petrochemical derivates and not competing with food industry, 2G-LA produced from already available material has not only an interesting economic appeal, but also a high social impact due to the growing consciences that it is important to reduce the world petrochemical dependence and change the current production model to a more sustainable one.

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