Chapter

Bioconversion of Lactose from Cheese Whey to Organic Acids

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Abstract

Organic acids constitute a group of organic compounds that find multiple applications in the food, cosmetic, pharmaceutical, and chemical industries. For this reason, the market for these products is continuously growing. Traditionally, most organic acids have been produced by chemical synthesis from oil derivatives. However, the irreversible depletion of oil has led us to pay attention to other primary sources as possible raw materials to produce organic acids. The microbial production of organic acids from lactose could be a valid, economical, and sustainable alternative to guarantee the sustained demand for organic acids. Considering that lactose is a by-product of the dairy industry, this review describes different procedures to obtain organic acids from lactose by using microbial bioprocesses.

Keywords: lactose, cheese whey, organic acids, acetic acid, lactic acid, citric acid, L-ascorbic acid, succinic acid, propionic acid, butyric acid, hyaluronic acid

1. Introduction

Organic acids (OAs) are compounds with relatively weak acidity properties [1, 2]. Carboxylic acids with one or more carboxyl groups ($-COOH$) are the most common OAs, following the sulfonic acids ($-SO_2OH$). Under certain circumstances, alcohol (with a group $-OH$) can also act as acid. Other groups, like thiol ($-SH$), enol, and phenol, also can confer acidity character to solutions, but all of them are very weakly acidic. Nowadays, many industrially produced organic acids (OAs) are synthesized from nonrenewable sources like petroleum oil [3]. Still, as can be expected, these sources could be depleted shortly, and it would lead to finding new renewable sources to produce OAs [4, 5].

Among others, a promising raw material is agro-industrial wastes (AIWs) [6, 7]. By its nature, AIWs could classify as complex organic compounds, which include mono- and polysaccharides, fats, and proteins. These raw materials are biotransforming by microbes in nature, so it is also able to metabolize AIWs into several OAs. Some of AIWs are by their constitution liquids like cheese whey (CW), molasses; but others are solids like bagasse, and citrus, potato, and banana peels. For liquid AIWs, the submerged fermentation (SmF), anaerobic or aerobic, is a suitable alternative [8–10], while solids could use the solid-state fermentation (SSF)

[8, 11–13]. Some revisions regarding the microbial production of OAs have been published [3, 14–16]. Also, some authors focused their attention on the use of AIWs in SSF to produce OAs [11–13, 17–19].

Volatile fatty acids (VFAs) are the smallest and simplest organic acids [20]. VFAs can be classified as short-chain fatty acids (SCFA, C_2-C_6 carboxylic acids), medium-chain fatty acids (MCFAs, C_7-C_{12}), long-chain fatty acids (LCFA, C_{13}-C_{21}), and very-long-chain fatty acids (C_{22} and higher) [21, 22]. SCFAs and MSFAs are commonly involved in the anabolic process and in the energy metabolism of mammalian cells. SCFAs are produced by colonic bacteria and are metabolized by the liver and enterocytes, whereas MCFAs are gotten from triglycerides that are found, for example, in milk or dairy products [23, 24]. OAs have been used since time immemorial by humankind in the seasoning of foods and sauces, such as vinegar, and more recently has been widely used as food additives, preservatives, descaling and cleaning agents [3, 25, 26]. They can also be used as precursors of other more complex organic compounds of broad utility in fine and pharmaceutical chemistry [27, 28].

OAs have certain relevant usefulness characteristics like its preservative, buffering and chelating capacity, in addition to its traditional use as an acidulant in food formulations, and most of them are GRAS classified [9, 28]. Among others, the foremost OAs are citric, acetic, lactic, tartaric, malic, gluconic, ascorbic, propionic, acrylic, and hyaluronic acids [28]. Nowadays, citric acid is the most widely produced OA in the world [29, 30].

The preferred carbon source to achieve their biosynthesis is glucose. Other sugars like fructose, galactose, maltose, and cellobiose can be metabolized for many bacteria and yeast. While cellulose, lignin, and more complex polysaccharides could be adequately transformed by using fungi [31], in this review, however, are mainly discussed the different reports showing that lactose also can be used to produce organic carboxylic acids with different uses.

2. The cheese whey and lactose

Lactose ($C_{12}H_{22}O_{11}$, MW 342.297 g mol^{-1}, IUPAC name: β-D-galactopyranosyl-(1 → 4)-D-glucose) is a disaccharide present naturally in milk and dairy products [32]. Today lactose is produced mainly as sweet whey from cheese-making industry as a by-product [33]. Lactose contents in whole milk are 4.9% for cows, and 4.8% for sheep and goats [34]. Water (94% wt.), lactose (4.5% wt.), protein (0.6% wt.), mineral salts (0.35% wt.), ash (0.5% wt.), and some traces of fat (500 ppm) and lactic acid (500 ppm) are the main components in sweet whey [35].

There are numerous technologies for the processing of the whey generated from the production of the various types of cheese [36–39]. Almost all start with pasteurization of cheese whey (CW) to decrease the microbial bioburden and to reduce the degradation of lactose and whey proteins. Subsequently, solid–liquid separation stages are usually used to remove the casein micro-lumps and the fat that may still contain the CW, using clarifying and disk centrifuges, for this purpose [40].

The defatted and pasteurized CW can then be subjected to microfiltration to retain the bacteria debris, before proceeding to the separation of the proteins, lactose, and mineral salts [41]. Membrane filtration has been used to isolate the whey proteins, mineral salts, and water present in CW [38, 42–44]. In this sense, ultrafiltration membranes can be suitable to isolate whey proteins, while nano-filters can separate the remaining lactose and mineral salts. Finally, the separated products are usually concentrated using evaporators, and dried, using technologies such as spray drying (SD) [45–48].

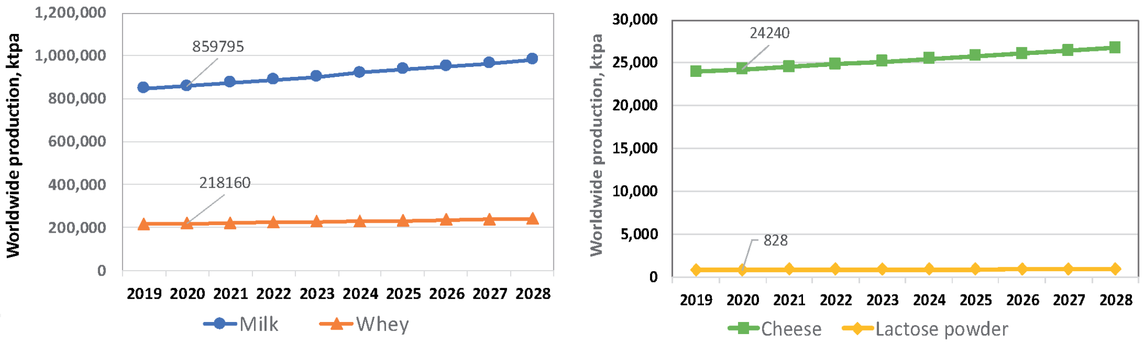

Figure 1.
Worldwide production projections (in metric kilo-tonnes per annum) of milk, cheese, whey, and lactose powder up to 2028 [51].

The most valuable components of whey are, in this order, whey proteins, lactose, and mineral salts. From a conventional process of obtaining lactose from sweet whey, whey powder (on March/2020, 880 EUR/ton), as well as deproteinized whey powder, lactose powder, mineral salts powder, and powder of whey proteins, can be obtained. From the latter, which is the product with the highest added value (on March/2020, 2030EUR/ton), different whey proteins presentations are usually obtained, like whey protein concentrate (WPC), whey protein hydrolysates (WPH), and whey protein isolate (WPI) [49].

As worldwide milk and cheese production has seen a constant increment in recent years, several millions of tons of whey are produced annually as a by-product [50] (**Figure 1**). A significant portion of whey has been used as an animal [51] and human feed supplementation due to its content of value proteins and minerals [52–56]. However, the enormous volumes of whey generated often overcome in many places the capacity of dairy-waste treatment plants [57]. For this reason, have focused the attention of numerous researchers' intent to valorize the whey and diminish the quantity of whey treated as waste [57–61].

Additionally, lactose is the component of whey that most contributes to the high biochemical oxygen demand (BOD) and chemical oxygen demand (COD) values in the dairy wastes [58, 62–64], bringing values around 30–50 and 60–80 kg m^{-3}, respectively [58, 64]. The great volumes of whey generated in the dairy industry could be the main obstacle to the further growth of cheese production in the next years [57]. One of the direct ways to reduce the adverse effects on the environment exerted by whey is using lactose containing the whey [65]. Lactose or "milk sugar" is a disaccharide formed by galactose and glucose, has a sweetening power, slightly lower than sucrose [32, 66]. It is usually used as a food additive [33, 67] or as a starting raw material for other products of agro-industrial interest [68, 69].

3. Organic acid market: overview and perspectives

The citric acid (2415 kilo-tonne per annum (ktpa)), L-ascorbic acid (132 ktpa), tartaric acid (30 ktpa), itaconic acid (43 ktpa), and bio-acetic acid (1830 ktpa) were produced by microbial fermentation, while gluconic acid (50 ktpa, with a 67:33 proportion between fermentative and chemical synthesis way), lactic acid (35 ktpa, 50:50), and malic acid (30 ktpa, 30:70) were produced by both fermentation and chemical synthesis, and, finally, some organic acids, like formic acid (1150 ktpa), butyric acid (80 ktpa), propionic acid (50 ktpa), and fumaric acid (20 ktpa) were chemically synthesized [12, 70–72]. This outlook and its proportions have not changed much today, and the global market of OAs shows a sustainable growth of 5.48% AAGR (average annual growth rate) in the last years and it is expected that it could increase globally up to US$9.29 billion by 2021 and US$11.39 billion by 2022 [3, 73–75].

Biosynthesis of an OA is obtained by the biochemical pathway of cellular metabolism, as the final end product or as an intermediate product of a path [26]. Bacteria and fungi are the most available and suitable living organisms for the industrial production of OAs. The microbial production of organic acids is usually an attractive route for industrial implementation compared to chemical synthesis because the conditions used in microbial bioprocesses tend to be less extreme (in terms of temperature, pressure, extreme pH) and more friendly to the environment [3, 76]. However, this may be effective only if the concentration of these acids in the fermentation broth are high enough (in the order of tens or hundreds of grams per liter), and these are obtained in reasonably short times [77]. Also, the microbial bioconversion of sugars into organic acids is frequently carried out by strict anaerobic microorganisms, with relatively long fermentation, reduced productivity, and low titers of organic acids in the fermentation broth [27]. Those facts conspire with its large-scale implementation, and to turn the biotechnology in an economically attractive choice to the production of organic acids (**Figure 2**) [3, 26, 78].

In this context, the processes of isolation and purification of organic acids become critical [78, 79]. Various alternatives for the isolation and purification of organic acids from fermentation broth or biomass have been used. Among the most used primary purification methods are precipitation with Ca-salt or hydroxide [77], ammonium salt, organic solvents [80], and ionic solutions [81]. Microbial fermentation can produce directly only a few organic acids [74], and even more scarce are the microorganisms that can use lactose to achieve this.

3.1 Acetic acid

Acetic acid ($C_2H_4O_2$, MW 60.052 g mol^{-1}, IUPAC name: Ethanoic acid) is a monocarboxylic acid commonly used as a chemical starting reagent in the production of important chemicals, like cellulose acetate, polyvinyl acetate, and synthetic fibers. Vinegar (near 4% vol. acetic acid) is produced by fermentation of different carbon sources by acetic acid bacteria [82] and is widely employed in food preparation and cooking since ancient times. Currently, three-quarters of the world production is obtained by carbonylation of methanol (by chemical synthesis), basically from nonrenewable sources, while 10% is still obtained from the microbial biotransformation of sugars [83]. By 2014, the global acetic acid market reached 12,100 ktpa, with an average price of US$ 550 per ton and average annual growth of 4–5% [14]. In 2018, world production reached 16,300 ktpa, near to US$ 12.48 billion, forecasting production of 20,300 ktpa by 2024. China with 54% and the US (18%) are the largest producers [84, 85].

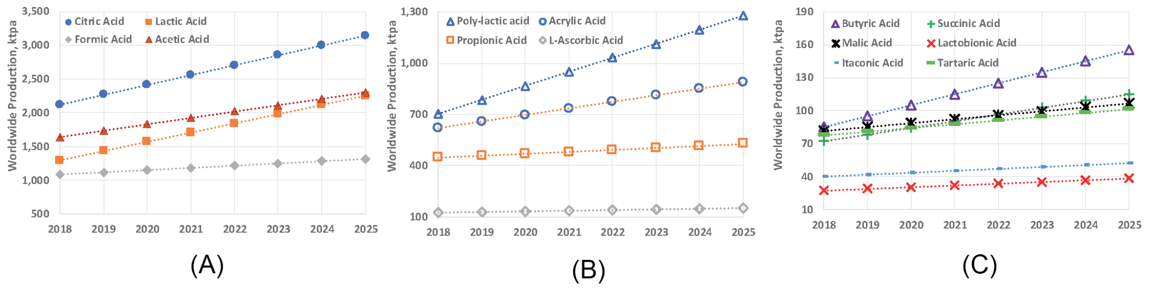

Figure 2.
Worldwide production of some organic acids between 2018 and 2025. (A) High-, (B) medium -, and (C) low-level of global production.

3.2 L-ascorbic acid

A case is the L-ascorbic acid (vitamin C, $C_6H_8O_6$, MW 176.124 g mol^{-1}, IUPAC Name: (5R)-[(1S)-1,2-Dihydroxyethyl]-3,4-dihydroxyfuran-2(5H)-one), one of the organic acids with the highest production and sales volumes today. Vitamin C can be obtained by microbial biosynthesis but from D-sorbitol [86].

Ascorbic acid, previously called hexuronic acid, is a soluble white solid and organic compound that presents itself as two enantiomers: L-ascorbic acid (vitamin C), and D-ascorbic acid, without any biological role found [87, 88]. Vitamin C is an essential nutrient for humans and many animals, and its deficiency can cause scurvy, in the past a common disease among sailors in long sea voyages [89]. It is used in as a food additive and a dietary supplement for its antioxidant properties [87, 88]. There is a report, however, that achieves the synthesis of vitamin C from the lactose present in the cheese whey, but through a defined group of chemical reactions [90]. In 2015 was produced 150.2 ktpa of ascorbic acid with a revenue of US$820.4 million. By 2017, China produced near to 95% of the world supply of vitamin C, having revenue of US$880 million [91].

3.3 Butyric acid

Butyric acid ($C_4H_8O_2$, MW 88.106 g mol^{-1}, IUPAC Name: Butanoic acid) is a mono-carboxylic acid, and it is an oily, colorless liquid that is soluble in water, ethanol, and ether. Salts of butyric acid are known as butyrates. Butyric acid is a chemical, commonly used as a precursor to produces other substances, like biofuel [92, 93], cellulose acetate [94, 95], and methyl butyrates [96], the two last coatings, and flavors compounds, respectively. Chemical synthesis is still the primary way of production of butyric acid due to the availability of raw material [92]. But some research explores the microbial biotransformation from renewable sources like agro-industrial wastes [72]. *Clostridium tyrobutyricum* can produce butyric acid from lactose, present in milk and cheese, along with H_2, CO_2, and acetic acid [97]. By 2016, the butyric acid worldwide market was around 80 ktpa, with a price of US$ 1800 per ton [98]. By 2020, global production of butyric acid is expected to reach 105 ktpa [99].

3.4 Citric acid

Citric acid ($C_6H_8O_7$, MW 192.123 g mol^{-1}, IUPAC Name: 2-Hydroxy-propane-1,2,3-tri-carboxylic acid) is a water-soluble tricarboxylic acid. Citric acid is widely used in the food and pharmaceutical industry due to its antimicrobial, antioxidant, and acidulant properties [100]. Citric acid can be produced from the citrus (like lemon, orange, lime, etc.), by chemical synthesis, or microbial fermentation [101]. Many microorganisms have been used to produce citric acid by microbial fermentation [102–104]. Among others, the fungus *Aspergillus niger* is the preferred choice to produce several useful enzymes and metabolites due to its ease of handling, and it being able to achieve high yields by using different cheaper agricultural by-products and wastes [101, 105]. By 2018, the worldwide citric acid production was more than 2000 ktpa, more than a half was produced in China. The global citric acid market is projected to reach a level of around 3000 ktpa by 2024, growing at a 4% CAGR during this period.

3.5 Propionic acid

Propionic acid ($C_3H_6O_2$, MW 74.079 g mol^{-1}, IUPAC Name: Propanoic acid) is an organic acid, colorless oily liquid with an unpleasant smell. Propionic acid

(PA) is a valuable mono-carboxylic acid used in chemical, pharmaceutical, and food industries, as a mold inhibitor, as a preservative of foods, as a significant element in the vitamin E production, and as a chemical intermediate in the chemical synthesis of cellulose fiber, perfumes, herbicides, etc. [16, 106, 107]. Today, propionate is mainly obtained for two processes. From ethylene, a nonrenewable source synthesized from oil, through the Reppe process [108], or from ethanol and carbon monoxide catalyzed by boron trifluoride (by the Larson process) [109].

Although chemical synthesis is the primary way of its production, the microbial production of PA is gaining attention and importance due to the depletion of petroleum sources and due to pieces of evidence of the more environmentally friendly microbial process [107, 110]. Propionibacterium is the most employed microorganism used for PA large-scale production [107, 111]. In 2020, the worldwide production of PA would reach 470 ktpa. The leading producers remain to be in Germany (BASF SE), USA (Dow Chemical Co. and Eastman Chemical), and Sweden (Perstorp). At the same time, the primary consumers are in the EU, USA, China, and India.

3.6 Lactic acid

Lactic acid ($C_3H_6O_3$, MW 90.078 g mol^{-1}, IUPAC Name: 2-Hydroxypropanoic acid) was the first organic acid commercially produced by microbial fermentation [112]. Bacterial fermentation of carbohydrates had been the main way for the industrial production of lactic acid (LA) with production level between 70 and 90% for 2009 [113]. The rest of production was achieved by chemical synthesis mainly from acetaldehyde coming from crude oil [114]. A racemic mixture of LA commonly is obtained by chemical synthesis, while L-lactic acid can be obtained by homofermentative anaerobic bacteria like *Lactobacillus casei* and *Lactococcus lactis*. Otherwise, heterofermentative bacteria produced carbon dioxide, ethanol, and/or acetic acid in addition to LA [115].

LA is currently used and has been approved as a food additive, preservative, decontaminant, and flavoring agent (with a code E270) [116, 117]. Also, it is used for chemical synthesis [118], mainly to produce poly-lactic acid (PLA), a thermal- and bioplastic polyester with widespread use in many applications [119, 120]. PLA is used, for example, in medical implants [121], as plastic fiber material in 3D-printing [122, 123], and as a decomposable packing material [124, 125].

In 2020, LA and PLA worldwide production will be around 1571 and 800 ktpa, respectively, with China, USA, EU, and Japan being the primary producers [126].

3.7 Succinic acid

Succinic acid ($C_4H_6O_4$, MW 118.088 g mol^{-1}, IUPAC Name: Butanedioic acid) has been widely used in many industries, as a food, detergent, and toner additive, for solders and fluxes, and as an intermediary commodity in the chemical and pharma industry [127]. After the increment of oil prices and diminishing availability of nonrenewable sources, researchers turned their attention over to the renewable feedstocks to produce succinic acid. SA as an intermediate in many biochemical pathways could be produced by many microorganisms and use many carbon sources [127]. For instance, the anaerobic-facultative bacteria *Actinobacillus succinogenes* can produce succinic acid from sugar cane molasses alone [128] or supplement with corn steep liquor powder [129].

Glucose as a carbon source has also been used to produce succinic acid by engineering strains of *Corynebacterium glutamicum* [130], *Escherichia coli* [131], and

Saccharomyces cerevisiae [132]. Succinic acid (SA) is a bulk OA commodity, and by 2010 the bioproduction was between 16 and 30 ktpa, and its expected annual growth was 10% [133], and by 2025, it is expected to exceed 115 ktpa [134].

3.8 Other acids

No reports of microbial obtention of tartaric ($C_4H_6O_6$, dicarboxylic acid), itaconic ($C_5H_6O_4$, dicarboxylic acid), and fumaric acid ($C_4H_4O_4$, dicarboxylic acid) from lactose have been found. Some of those, however, can be obtained indirectly, since there are published studies of the biosynthesis of itaconic acid [135–137], fumaric acid [138, 139] from glucose, and the latter can be obtained from the chemical or enzymatic hydrolysis of lactose.

4. Microbial bioprocesses for obtaining organic acids based on lactose

Like other renewable sources based on residual plant biomass from agricultural productions rich in complex polysaccharides, lactose has been used as a starting raw material to establish bioprocesses to produce different organic acids. Although there are microbial enzymes capable of breaking the bonds of polysaccharides, this would involve energy and time, which in the case of lactose would be less complicated and faster. In the case of lactose, this could become the starting material for

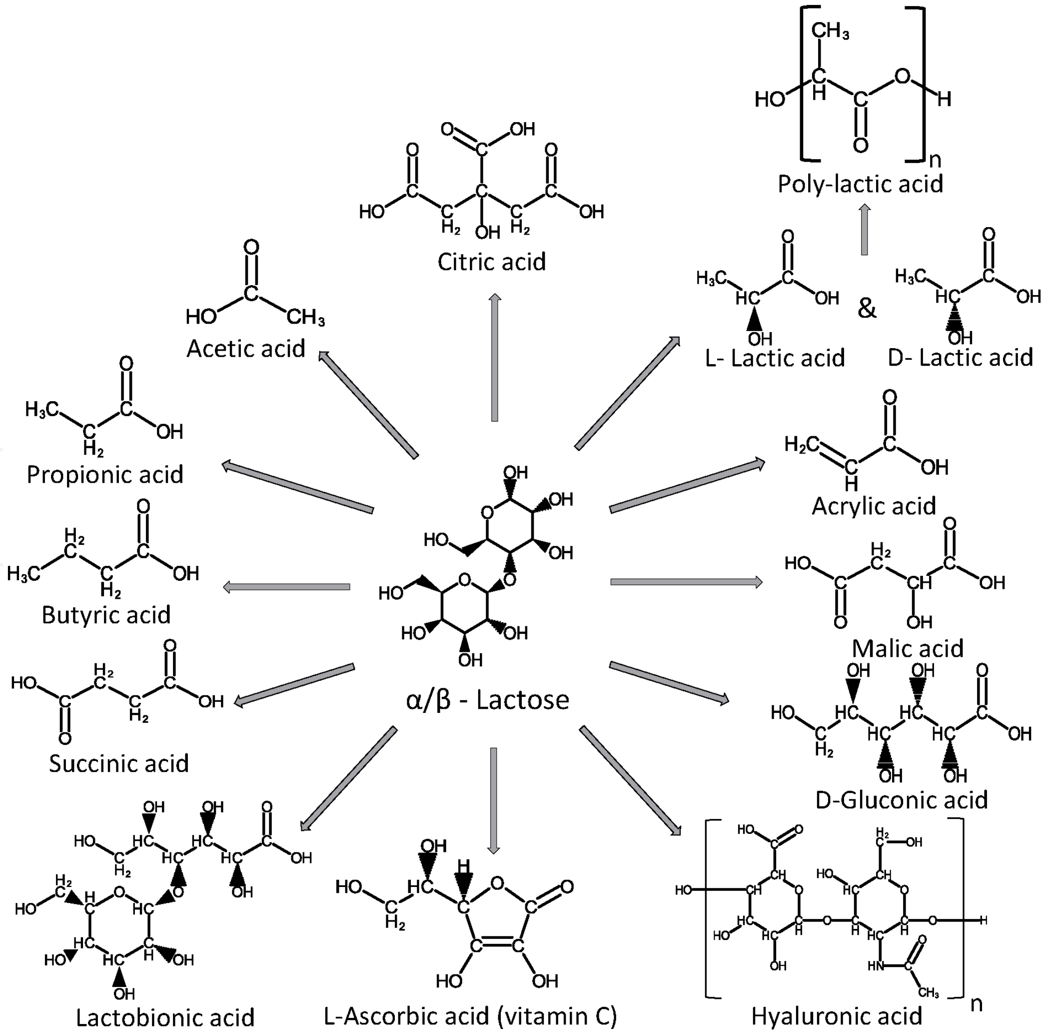

Figure 3.
Some of the organic acids that can be obtained microbially from lactose or whey.

Name	Source	Microorganism(s)	Culture conditions and production results*	Ref.
Acetic acid, $C_2H_4O_2$	WP	*Clostridium thermolacticum* and *Moorella thermoautotrophica*	Anaerobic, batch, 58°C, pH 7.2, 300 h, 0.81 g g^{-1}, 98 mM	[144, 145]
	WP	*Acetobacter aceti*	Aerobic, continuous membrane bioreactor, at 303 K, D = 0.141 h^{-1}, 96.9 g L^{-1}, 0.98 g g^{-1}, 4.82 g L^{-1} h^{-1}	[146–148]
	CW	*Propionibacterium acidipropionici*	Anaerobic, batch, 35°C, pH 6.5, 78 h, 0.11 g L^{-1} acetic acid + 0.33 g L^{-1} propionic acid	[149]
	CW	*Lactobacillus acidophilus*	Anaerobic, 37°C, 72 h, pH 6.5, 7 g L^{-1}	[150]
Acrylic acid, $C_3H_4O_2$	SCW	*Clostridium propionicum*	Anaerobic, +propanoic and acetic acids, 33°C, pH 7.1, 0.133 mmol g^{-1}	[151]
L-Ascorbic acid, $C_6H_8O_6$	CW	*Kluyveromyces lactis*	Aerobic, shake-flask, 48 h, 30°C, 30 mg L^{-1}	[140]
	Gal	*Saccharomyces cerevisiae* *Zygosaccharomyces bailii*	Aerobic, shake-flask,144 h, 30°C,0.40 g g^{-1}, 70 mg L^{-1}	[141]
Propionic acid, $C_3H_6O_2$	SWP	*Propionibacterium acidipropionici*	Anaerobic, fibrous bed bioreactor (immobilized cells), 135 ± 6.5 g L^{-1}	[152]
	CW	*P. acidipropionici*	Anaerobic facultative, 6.1 g L^{-1}	[153]
		Propionibacterium freudenreichii	Anaerobic, 8.2 g L^{-1}	
	CW	*P. acidipropionici*	Anaerobic, 0.33 g L^{-1}	[149]
Lactic acid, $C_3H_6O_3$	SWP	*Lactobacillus casei*	Anaerobic, 36 h, pH 6.5, 37°C, 33.73 g L^{-1}	[154]
	SWP	*Lactobacillus rhamnosus*	Anaerobic, 37°C, pH 6.2, 200 rpm, 50 h, 143.7 g L^{-1}	[155]
	CW	*Lactobacillus acidophilus*	Anaerobic, 37°C, 72 h, pH 6.5, 42.62 g L^{-1}	[150]
	CW	Mixed culture of acetogenic and fermentative bacteria	Dark anaerobic, 35°C, HDT = 1 day, 10.6 g L^{-1} day^{-1}	[156]
Butyric acid, $C_4H_8O_2$	CW	*Clostridium beijerinckii*	Anaerobic, 37°C, pH 5.5, 0.08 g L^{-1} h^{-1}, 12 g L^{-1}	[157]
	CW	*Clostridium butyricum*	Anaerobic, + 5 g L^{-1}YE or + 50 μg L^{-1} biotin, 37°C, pH 6.5, 19 g L^{-1}	[158]
Succinic acid, $C_4H_6O_4$	CW	*Anaerobiospirillum succiniciproducens*	Anaerobic+$CO_{2,}$ + Glu, pH 6.5, 39°C, 36 h, 16.5 g L^{-1}, 0.33 g L^{-1} h^{-1}	[159]
	CW	*Actinobacillus succinogenes*	Anaerobic+CO_2, 38°C, pH 6.8, 48 h,28 g L^{-1}, 0.44 g L^{-1} h^{-1}	[160]
	PWP	*Enterobacter* sp. LU1	Microaerobic, + Gly, 34°C, pH 7, 288 h, 69 g L^{-1}	[161]

Name	Source	Microorganism(s)	Culture conditions and production results*	Ref.
Malic acid, $C_4H_6O_5$	Milk	*Escherichia coli* K-12	Stationary culture for 72 h at 37°C, 168 mg g^{-1} DW	[162]
Gluconic acid, $C_6H_{12}O_7$	CW	*Pseudomonas taetrolens*	Aerobic, + Glu, 30°C, aeration: 1 L min^{-1}, 350–500 rpm, pH 6.5, 8.8 g L^{-1}	[163]
Citric acid, $C_6H_8O_7$	CW	*Aspergillus niger* ATCC9642	Aerobic, +15% sucrose, 30°C, 16 h, 106 g L^{-1}	[164]
Lactobionic acid, $C_{12}H_{22}O_{12}$	CW	*Pseudomonas taetrolens*	Aerobic, 30 °C, + Gly, aeration: 1 L min^{-1}, 350–500 rpm, pH 6.5, 78 g L^{-1}	[163]
	CW		Aerobic, + Lac, 30°C, aeration: 1 L min^{-1}, 350–500 rpm, pH 6.5, 100 g L^{-1}	
Hyaluronic acid, $(C_{14}H_{21}NO_{11})_n$	CCW, HCW	*Streptococcus zooepidemicus*	Aerobic (1 vvm), 37°C, pH 6.7 and 500 rpm	[165]
	Lac	*Lactococcus lactis*	Anaerobic, 1% Lac + 10 ng mL^{-1} nisin, 30°C, 24 h (12 h after induction), 0.6 g L^{-1}	[143]

WP: whey permeate; PWP: powder whey permeate; CW: cheese whey; SCW: sweet cheese whey; SWP: sweet whey powder; CCW: concentrate cheese whey; HCW: hydrolysate cheese whey; Gal: galactose; Gly: glycerol; Glu: glucose; Lac: lactose; YE: yeast extract; HDT: hydraulic detection time.
**In terms of concentration, yield, and/or productivity of the acid.*

Table 1.
Characteristics of some organic acids produced by bioconversion of lactose from commercial products or agro-industrial by-products.

the production by microbial bioprocesses, not only of the most demanded organic acids today but of other less-used ones that still not as highly in demand. However, subsequent studies must be carried out to make these technologies a viable and economically attractive alternative [3, 19].

Nowadays, however, some organic acids can be obtained by microbial bioprocesses directly from lactose (**Figure 3**), cheese whey, or both, using the different routes of their metabolisms (**Table 1**). The most demanded organic acids, like citric, acetic, and lactic acids, have been produced from whey (**Table 1**). Even more complex organic acids like poly-lactic and hyaluronic acids can also be produced from lactose. Another advantage of microbial production is related to the possibility of producing the racemic biological active acids exclusively. L-lactic acid is produced almost exclusively by lactic-acid bacterium *Lactobacillus casei* or L-ascorbic acid (vitamin C) by certain recombinant yeast strains of *Kluyveromyces lactis* or *Saccharomyces cerevisiae* [140, 141]. However, for some of the organic acids, the titers reached are still too low for these bioprocesses to be scaled to industrial production in an economically feasible way, and the chemical synthesis remains the most desired choice. At the industrial scale, to produce organic acids competitively, it would be necessary to have adequate sources of *raw materials* (cheap and renewable) and enhanced *microbial strains* (easy and safe to handle and able to work at high productivity). Also, it would be necessary to dispose of industrial facilities and technical expertise (*technical constrains*) to achieve it (**Figure 4**).

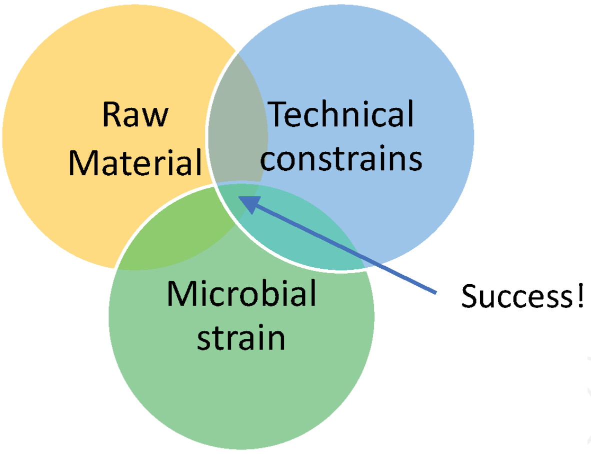

Figure 4.
Successful commercial production of organic acids by microbial biotransformations: keys to success.

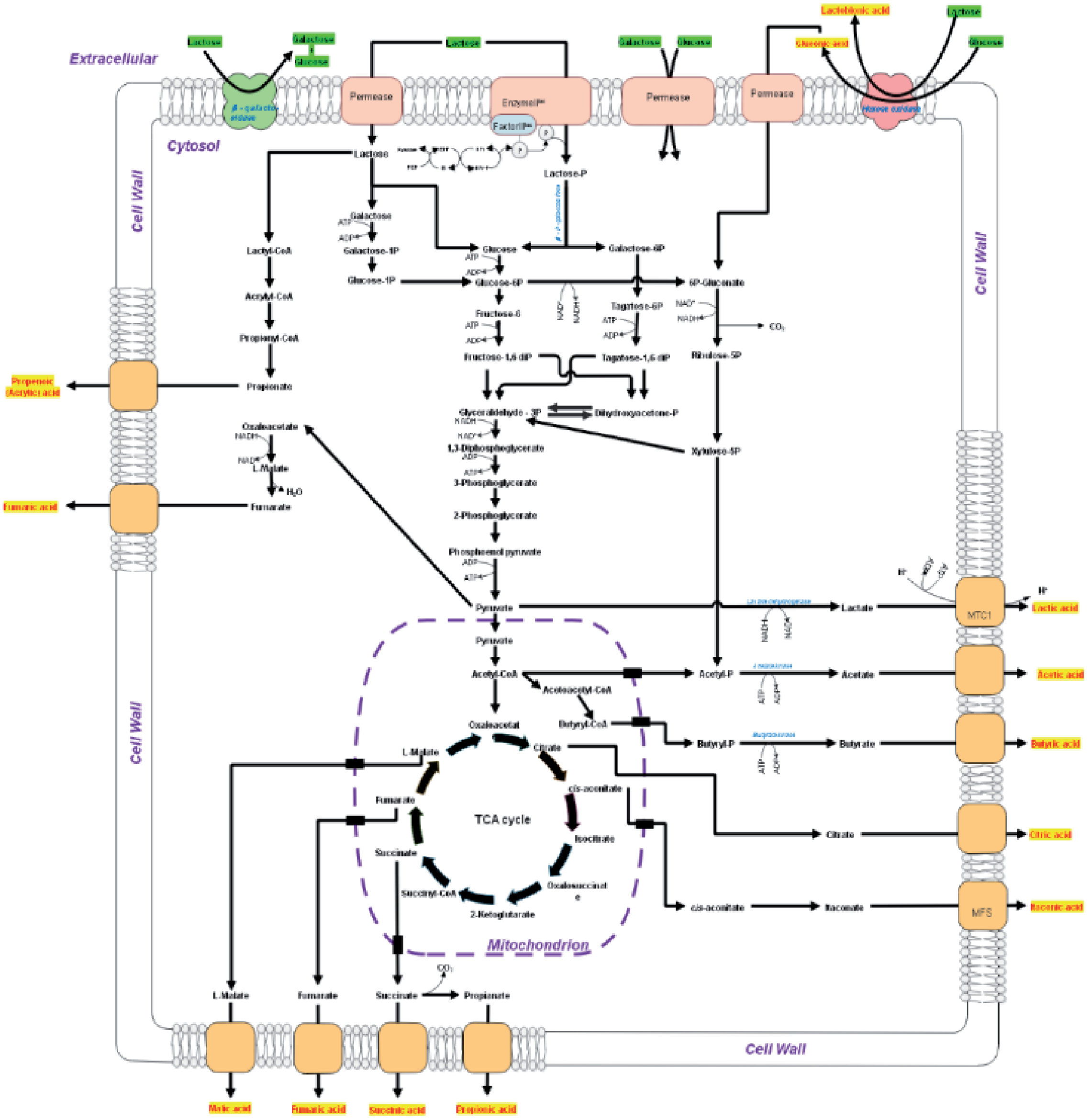

Figure 5.
Some of the microbial metabolic pathways for the synthesis of organic acids.

The microbial bioprocesses could be enhanced through optimization of up- and downstream processes that must be combined with metabolic engineering to increase productivity. Also, genetic engineering techniques could be used to obtain robust industrial strains that raise the expression levels of the genes involved in the metabolic pathways of synthesis of organic acids or repress others that deviate to produce unwanted by-products [142, 143].

Some of the identified metabolic pathways are associated with the tricarboxylic acid (TCA) cycle and demonstrate that most organic acids represent metabolites associated or partially associated with growth (**Figure 5**). A detailed study of these pathways can address the overexpression of some genes or repression of others using genetic engineering techniques.

5. Conclusion

Organic acids constitute a market with a sustained increase at present. Many of them are produced on a large scale by chemical synthesis from petroleum derivatives. Still, more recently, other alternatives, cheap and renewable sources of raw materials, are being intensively studied, among which is whey. This trend will be reinforced soon, which, together with the improvement of microbial processes, will allow more and more bioprocesses to appear at the large scale, which will become the trend of this market in the future. Among the countries whose territories contain the majority of the companies dedicated to supplying the world demand for organic acids, the People's Republic of China stands out, which is expected to continue to be the country that will dominate this market in the coming years.

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