



Platform molecule from sustainable raw materials; case study succinic acid

Alaa Salma, Hayet Djelal, Rawa Abdallah, Florence Fourcade, Abdeltif Amrane

► To cite this version:

Alaa Salma, Hayet Djelal, Rawa Abdallah, Florence Fourcade, Abdeltif Amrane. Platform molecule from sustainable raw materials; case study succinic acid. Brazilian Journal of Chemical Engineering, 2021, 38 (2), pp.215-239. 10.1007/s43153-021-00103-8 . hal-03245168

HAL Id: hal-03245168

<https://hal.science/hal-03245168>

Submitted on 18 Jun 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Platform molecule from sustainable raw materials; case study succinic acid

Alaa Salma^{a*}, Hayet Djelal^b, Rawa Abdallah^c, Florence Fourcade^a, Abdeltif Amrane^a

^a Univ Rennes, Ecole Nationale Supérieure de Chimie de Rennes, CNRS, ISCR, UMR6226, F-3500 Rennes, France.

^b UniLaSalle-Ecole des Métiers de l'Environnement, Campus de Ker Lann, 35 170 Rennes, France.

^c Université Libanaise, EDST, Centre Azm pour la Recherche en Biotechnologie et ses Applications, Rue El Mitein, LBA3B Tripoli, Lebanon.

*Corresponding author: Tel.: +33 02 23 23 80 00; Fax: +33 02 23 23 81 99, elaasalma93@gmail.com (A. SALMA)

13

14 **Abstract**

15 Platform molecules were defined by the US Department of Energy, as bio-based or bio-derived
16 chemicals whose constituting elements totally originated from biomass and could be used as
17 building blocks for the production of commodity and refined chemicals. These chemicals can
18 subsequently be converted into a number of high-value bio-based chemicals or materials.
19 Today, there is a growing urge for the discovering of a cheaper and cleaner way for the
20 environment to produce platform molecules from renewable substrate such as carbon. Succinic
21 acid (SA) is considered as a key platform chemical since it is used as a precursor for other
22 valuable chemicals and has aroused interest worldwide with its wide applications. This review
23 aims at highlighting the currently available information about the mechanisms involved in the
24 production of platform molecules, especially the SA production. In this review, the processing
25 technologies used in the production of platform molecules are described, in addition to the
26 information regarding the optimization of key parameters, the mechanisms of genetic
27 engineering and finally the redox potential and purification processes which are known as
28 alternative cost-competitive providers of fossil fuels.

29 **Keywords:** platform molecules; biomass; succinic acid production; fermentation; downstream
30 separation methods; processing technology; redox potential.

31 **Conflict of interest statement**

32 The authors declare that they have no conflicts of interest.

33 **Author contribution**

34 A.S., H.D., R.A., F.F., and A.A, designed and wrote the manuscript. All authors have
35 approved the final form of the manuscript.

36

Background

Early in the 20th century, non-renewable raw materials met our energy needs and provided a broad spectrum of chemicals that enriched our daily lives (Keim 2014). But today, the International Energy Agency (IEA) predicts a significant drop of about 75% of fossil raw materials by 2035. However, the depletion of fossil feedstocks followed by the vigorous demand of consumers for eco-friendly energy sources have made governments as well as the industry interested in the production of chemicals originating from bio-based resources in order to form a sustainable global economy. It represents an unlimited and ubiquitous alternative to the chemical industry, which should replace the current petroleum-based methods producing energy and chemicals (Langeveld et al. 2010). In accordance with the US DOE, the National Renewable Energy Laboratory reports (NREL) and the academic patents available in literature, the United States Department of Energy (US DOE) compiled a list of over 300 chemicals possibly composing an accessible database of a wide assortment of raw materials. In this database, each chemical name is associated to a base product, a structure, a feedstock source, a current potential production process and its propriety in the consumer goods. Feedstocks, the estimated cost of process, the actual sizes of markets and prices were preselection criteria. In the petrochemical industry all products derived from 7 or 8 base chemicals (See Table1). A different approach was developed from the initial list of 300 chemicals ; Indeed, 30 building block chemicals were considered as similar to the petrochemical industry and they were first selected on behalf of the petrochemical criteria as the key selection parameter, then - on behalf of biorefinery - the second strategic fit selection criterion. The direct substitution of a new product with new and improved properties enables the replacement and the use of those chemicals as the only intermediate building blocks; providing the basis of a diversified portfolio of chemicals. However it competes directly against existing products and chemicals deriving from petroleum. These were mostly produced by the petrochemical industry. Twenty years ago, the researchers strove to prove that bio-economy could produce similar products, also known as platform molecules, thanks to inexpensive, simple and eco-friendly chemical building blocks originating from biomass. In the late twentieth century, a new concept of bio-derived platform molecules was considered, as they are simple small molecules basically deriving from biomass and can be used as building blocks for high-value added chemicals and materials. In 2004,

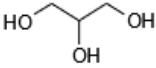
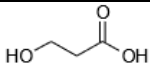
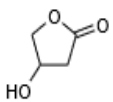
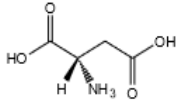
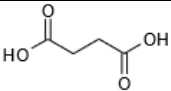
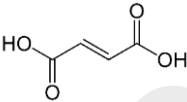
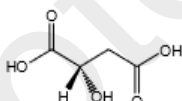
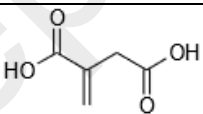
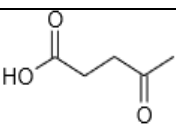
research developed and focused on products deriving from biomass and a report by the US DOE on Top Value Added Chemicals from Biomass was published (Werpy. A et al. 2004). It has been widely claimed that biomass feedstock can replace fossil fuels but it implies a successful integration of biorefineries competitively with oil refineries for the manufacturing of fuels, energy, chemical and material products. The US DOE carried out a critical assessment on the development and the acceleration of a bio-based economy and the implementation of biorefineries technics. They generated a large list of biomass-derived chemicals and, in parallel, the top most promising candidates, thus bringing to light the efforts in universal research. Biorefinery products, which represent $\leq 10\%$ of the fossil resources extracted per year, would be a primary source of money in many operations and more often than not petrochemical route provide a profit margin higher than energy's and fossil fuels'. However, the report released by the US DOE in 2004 interestingly debates the analogy of fossil-derived base chemicals with sugars, lignin, syngas and triglycerides. But it does not cross reference with the 'platform molecule' term (White 2007). The aim of the US DOE report was to significantly list the molecules produced that can be transformed into chemicals and materials with stronger added value (Philp 2014). The second selection round determined 12 sugar-derived building blocks from the top 30 building blocks in competition (See their structures in table 2).

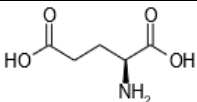
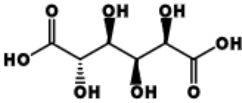
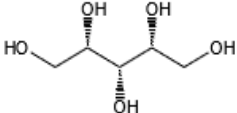
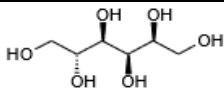
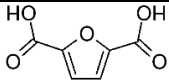
This review highlights the power and the potential capacity of platform molecules, when used as biochemicals, replacing chemicals originating from fossil resources. Furthermore, it also reviews the relevant literature about the main advances of the last years, so as to create the necessary basis for a constructive and supported review. However, bio-economy requires methods to produce the range of familiar chemicals that are crucial in our lives, such as synthetic textiles, surfactants, pharmaceuticals, plastics, pigments, dyes and agrochemicals, and also home and personal care products in order to eventually replace the fossil resources that are depleted. In this review, the status of the industries producing fossil-derived base chemicals is briefly described and the equivalence of chemical building blocks with bio-based chemicals is debated. The notion of platform molecules is now under discussion, leading to the characterization of those small bio-derived chemicals. As a constituent part, the biomass feedstock composition as well as the derived chemicals from each of its component are featured,

96 regarding to the molecules it generates. A vast list of platform molecules is identified and their
 97 processing technologies from fossil and biomass feedstocks are described.

98 **Table 1.** Fossil-derived base chemicals

Feedstocks	Base chemicals	Commodity chemical	Intermediates Chemicals	Consumer goods	References
Naphtha	Ethene	Ethylene oxide	-Polyethylene oxide -Antifreeze -Polyesters	Transportation	(Humans 2008)
		1,2-dichloroethan		Housing	(Stucki and Thueer 1995)
		Polyethylene			(Kasirajan and Ngouajio 2012)
		Vinyl chloride	-Polyvinyl chloride	Health, hygiene	(Guo et al. 2014)
		Ethylbenzene	-Solvents	Housing, safe food supply	(Yang et al. 2016)
		Styrene	-Styrene butadiene rubber	Housing	(Marwa 2017)
	Propene	Propene oxide	-Propandiol	Recreation	(Nijhuis et al. 2006)
		Propene	-Polypropene		
	Butadiene	Propan-2-ol	-Solvents	Housing	(Dilcher et al. 2015)
			Polybutadiene rubber	Recreation, transportation	
	Benzene	Phenol	-Polycarbonates -Bisphenol A	Safe food supply	(Panzella and Napolitano 2017)
		Cyclohexane	-Nylon	Textiles	(Brüschweiler and Merlot 2017)
		Aniline	-Dyes		(Luongo et al. 2016)
	Toluene	Toluene diisocyanate	-Polyurethanes		(Du et al. 2014)
	Xylenes	Terephthalic acid	-Polyethene terephthalate	Housing, transportation	(Collias et al. 2014)
		Isophthalic acid	-Polyethene terephthalate -Adhesives		(Long et al. 2014)
Syngas	Methanol	Acetic acid		Health, hygiene	(Chen et al. 2006)
		Formaldehyde	-Resins	Communications, textiles	(E. Heim et al. 2017)
		Methyl methacrylate	-Latex -Paints		

Carbon number	Building blocks chemical	Structure	Derivatives	Applications and consumer's goods	References
C3	Glycerol		Epichlorohydrin, 1,2-propanediol, 1,3-Propanediol, Mono-, di- and tri-esters, Glyceric acid, Acrolein	Triacetin, food additive, Pharmaceuticals, Personal Care Polyols, Alkyd resins, Tobacco, Explosives, Detergents, Cellophane	
	3-hydroxy propionic acid		1,3-Propanediol, Malonic, Acrylic acid, Acrylamide, Methyl acrylate	Acrylic polymers, Speciality polyesters	(Zhang et al. 2004)
C4	3-hydroxy butyrolactone		Pyrrolidones, γ -butenyl-lactone, acrylate lactone	Intermediate for high value pharma compounds	(Peoples et al. 2014)
	Aspartic acid		Amino- γ -butyrolactone, Aspartic anhydride, 3-Aminotetrahydrofuran, 2-Amino-1,4,-butanediol, Polyaspartic acid	Production of sweetener: aspartame	(Vasiliu et al. 2012)
	1,4 diacids (Succinic acid)		1,4-Butanediol, γ -Butyrolactone, Tetrahydrofuran, N-Methyl-2-pyrrolidone Di-esters, Polyamides, Polyesters	Sweetener in food and beverages	(Kohli et al. 2019)
	Fumaric acid		1,4-Butanediol, γ -Butyrolactone, Tetrahydrofuran, Unsaturated polyesters, L-Aspartic acid, L-Alanine, Succinic acid	Unsaturated polyester resins, Food additive, Animal feed, Dye mordant, Polyhydric alcohols	(Li and Xing 2017a)
	Malic acid		Chlorosuccinic acid	Artificial Sweetener, food additives	(Naude and Nicol 2018)
	Itaconic acid		Methyl-1,4-BDO, 3-Methyl THF, 3-&4-GBL, 2-Methyl-1,4-butanediamine, Pyrrolidones	Copolymer in styrene butadiene polymers (provides dye receptivity for fibers); Nitrile latex	(Okabe et al. 2009)
C5	Levulinic acid		Methyltetrahydrofuran, Esters, γ -Valerolactone, 5-Methyl-2-pyrrolidone, Diphenolic acid	Potential replacement for Bisphenol-A	(Girisuta and Heeres 2017)

	Glutamic acid		Glutaminol, 5-amino-1-butanol, 1,5-pentanediol, Norvoline	Monomers for polyesters and polyamide	(Armstrong et al. 2017)
	Glucaric acid		Polyglucaric esters and amides	Solvents	(Armstrong et al. 2017)
	Xylitol/Arabinitol		Ethylene and propylene glycol, Polyesters, Xylaric, Xylonic, Arabonic, Arabinoic acid	Sweetener, de-icer, Automotive antifreeze	(Linga Venkateswar Rao et al. 2016)
C6	Sorbitol		1,4-Sorbitan, Isosorbide, Polyetherpolyols, Ascorbic acid	Sweetener, Humectant, Thickener, Cryo-stabiliser, Amateur rocket fuel	(Furtwengler and Avérous 2018)
	2,5-furan dicarboxylic Acid		2,5-Dihydroxymethylfuran, 2,5-Dihydroxymethyl tetrahydrofuran, 2,5-Bis(aminomethyl) Tetrahydrofuran	Potential as monomer to replace terephthalic acid	(Rathod and Jadhav 2018)

101

102

103 The definition of Platform molecules

104 The US DOE reports led to the release of research articles on platform molecules even if no
105 accurate definition was set to describe this term. Indeed, a consensus about the knowledge of a
106 platform molecule was difficult to reach. Therefore, many terms were used to refer to platform
107 molecules in articles, reports, patents and books dealing with chemical building-blocks
108 originating from biomass, namely by bio-based platform molecules. For instance, bio-platform
109 molecules (W. Breeden et al. 2012), platform molecules (Martin Alonso et al. 2013), biomass-
110 based platform chemicals (Lai et al. 2017), biomass-derived platform molecules (Serrano-Ruiz
111 et al. 2011), base chemicals from biomass (Sanders et al. 2012), building-block chemicals from
112 biomass (Eckert et al. 2007) and platforms (syngas and triglyceride platform). Some scientists
113 define ‘platforms’ as molecules with multiple functional groups because they can be converted
114 into new families of useful molecules (Wieschalka 2012). Indeed, when numerous building
115 block chemicals aggregate, they produce an extensive range of chemical products. During the
116 biological production of platform molecules through chemical and thermal processing, some

molecules are produced that can also be considered as bio-derived or bio-based platform molecules. Governmental, academic and industrial institutions recently used equivalent terms in European and international projects, when they referred to products originating from biomass also called bio-derived products. Today, according to the European Commission definition, there is no necessity for products or articles to be bio-based, which contradicts with the US Farm Bill that emphasizes that a total or a significant product range should be originating from bio-based materials to be considered as such. Bio-based products are defined as: commercial or industrial non-food products that are largely or completely constituted of renewable biological products, agricultural materials (e.g., plants, animal and forest materials), or marine materials according to the US 2002 Farm Bill. In 2007, the European Commission claimed that the bio-based matrix was considered as a product derived from biomass excepting food or feed (plants, crops, trees, algae, biological waste from households, animals and marine organisms) (Biddy et al. 2007). Bio-based products are products of interest and are considered as fine chemicals with high added value in many fields such as cosmetics, food additives, pharmaceuticals and many others.

The European Committee Standardized (CEN) updated the definition of biomass by explaining that fossil fuels are initially coming from the transformation of biological materials that undergo many natural processes. Geologic formations and fossils are excluded from biomass or from material of biological origin. To define a 'bio-based' product, it is acknowledged that all the terms quoted above, such as bio-derived, are allowed. The term bio-based platform molecule could thus be swapped to bio-derived platform molecule according to its creator. Considering all the terms mentioned to refer to a bio-based platform molecule, the latter could be defined simply as: a chemical compound whose constituent elements totally originate from biomass (material of biological origin excluding fossil carbon sources), and could be used as a building block for the production of another high added value chemical. It may happen that various molecules are identified as platform molecules in the reaction pathway, making it even harder to come up with a correct appellation for a real platform molecule. For example, fructose, as a feedstock, can be converted to hydroxymethylfurfural (HMF) if it is isolated but if it is not isolated, it can also be directly converted to levulinic acid and γ -valerolactone (Yuan et al.

2013). Therefore, these compounds are bio-derived platform molecules directly produced from biomass, depending on their production route.

The source of Platform chemicals

Fossil materials as feedstocks

In the past, a wide range spectrum of chemicals originated from fossil resources that complied with our energy needs. The oil crisis caused severe economic and social impacts in addition to the use of fossil fuels being rightly perceived as a major source of pollution. Most of the products manufactured by the chemical industry using fossil fuels as raw materials usually come from seven simple building-block molecules (mainly natural gas and crude oil) called fossil-derived base chemicals which are produced by distillation and by catalytic reforming (see table 1 (Straathof and Bampouli 2017)). Each year, the production of base chemicals exceeds 10 million tons and in 2010, more than 360 million tons were produced (Gallagher 2012).

From cheap sustainable materials to platform chemicals

In some scientific articles, researchers put forward some alternative renewable feedstocks such as solar, wind, hydropower, thermal, photovoltaic resources (Armaroli and Vincenzo 2010), biomass; energy and chemicals (Andruleit et al. 2016), planet movements; ocean tides, waves, geothermal energy, nuclear energy; fusion and fission, carbon dioxide; hydrogenation to hydrocarbons and oxygenates (Aresta 2010). They were meant to replace non-renewable raw materials and thus impeded the reduction of fossil resources. Therefore, the most common feedstocks used as biomass in biorefinery, such as saccharides, lignin, protein, extracts or any combination of these raw materials, are more advantageous (see fig 1). To these scientists' knowledge, the definition of platform molecules referred to those cheap molecules accessible in large amounts. In table 3, current platform molecules are listed and gathered according to the processing technology used to generate these molecules from biomass. A wide list has been compiled in table 3, relating to the definitions and the diversity given previously, but also the broadest vision considered for any process or bio-derived product. Thanks to the increase of interest in bio-based platform molecules, some chemicals were bound to extend more than others. For instance, every natural amino acid is derived from the fermentation or the protein

depolymerisation of biomass and yet, only glutamic and aspartic acids are mentioned below. A study carried out by (Lammens et al. 2012) figured out a broad range of amino acid sources originating from the fraction of biomass followed by a protein hydrolysis. As a conclusion, these two amino acids may be the most substantial residues to become key platform molecules.

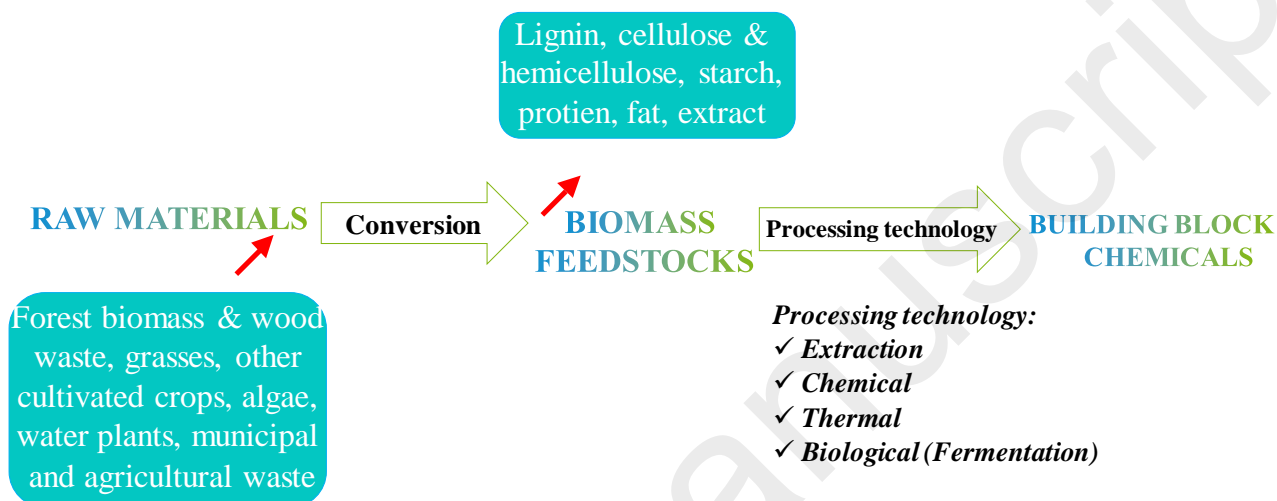


Figure 1. From raw materials to chemicals.

Platform molecule	Processing technology	Derived from	References
Fatty acid alkyl esters	Extraction, chemical-catalytic	Triglyceride	(Taylor et al. 2011),(Ambat et al. 2018)
Triglyceride	Extraction	Oil containing biomass	
Fatty acids (e.g. oleic acid)	Extraction, chemical-catalytic	Triglyceride	
Mannitol		Sugars	
Glycerol		Triglyceride	(Contreras-andrade et al. 2014)
Citric acid Acetic acid Itaconic acid Succinic acid Maleic acid	Biological	Sugars	(Dezam et al. 2017; He et al. 2018; Magalhães Júnior et al. 2018)
Amino acid (glutamic, Aspartic acid)		Sugars or protein	(D'Este et al. 2018)
Ethanol			(Pardo-Planas et al. 2017; Appiah-Nkansah et al. 2018; Orrego et al. 2018)
Butanol		Sugars	(Xue et al. 2016)
Lactic acid			(Li et al. 2018; Andreev et al. 2018; Ho et al. 2018)
Fumaric acid			(Das et al. 2016b; Li and Xing 2017a; Liu et al. 2017b)
3-hydroxy propionic acid			(Jung et al. 2015; Chen et al. 2017c; de Fouchécour et al. 2018)
Xylitol	Chemical catalytic	Hemicellulosic materials or xylose	(Werpy. A et al. 2004; Albuquerque et al. 2014; Linga Venkateswar Rao et al. 2016; Delgado Arcaño et al. 2018)
Sorbitol		Cellulose or sugars	(Xi et al. 2013; Ribeiro et al. 2017a, b)
Glucosamine	Chemical catalytic, Thermal	Chitin	(Shrotri et al. 2017; Park et al. 2018, p.; Duan et al. 2018a)
Oxalic acid	Chemical catalytic	Cellulose or sugars	(Collinson and Thielemans 2010; Tong et al. 2010; Ennaert et al. 2016; Ge et al. 2018)
Furfural		Hemicellulosic materials or sugars	(Luo et al. 2018)
5- Hydroxy methyl furfural		Cellulose or sugars	(Daorattanachai et al. 2012; Rout et al. 2016)
Levulinic acid			(Werpy. A et al. 2004; Thapa et al. 2017; Chen et al. 2017b; Liu et al. 2018; Liang et al. 2018)

Syringol	Thermal	Lignin	(Asmadi et al. 2011; Chua et al. 2017)
Eugenol			(Werpy. A et al. 2004; Brodin et al. 2010; Duan et al. 2018b; Ponnusamy et al. 2018)

A comparison of bio-platform molecule to fossil-derived base chemicals is needed, since bio-economy matures, it is obvious that bio-based chemicals are unlikely fossil-derived base chemical in volumes they are manufactured and used in (table 4).

Table 4. Comparison between base chemical from fossil feedstocks and biomass derived (tons)

Feedstocks	Base chemicals	Annual production from fossils	References	Annual production from biomass	References
Oil, gas	Ethene	≈ 123 300 000	(Davis 2011; Gallagher 2012)	≈ 200000	(Das et al. 2016a)
	Propene	≈ 74900000		Pilot scale	(Gotro and Humphreys 2016)
	Butadiene	≈ 10200000		Pilot scale	(Morse 2015)
Oil	Benzene	≈ 40200000		≥100	(Sikarwar et al. 2017)
	Toluene	≈ 19800000		≥100	
	Xylenes	≈ 42500000		≥ 100	
Syngas	Methanol	≈ 49100000		≈ 340000	(Shamsul et al. 2014)

Pathways to the 12 sugar components

The family of 4-carbon diacids can be combined (succinic, fumaric and malic acids), as they are produced through similar biochemical pathways. Four carbon dicarboxylic acids produced from the Krebs cycle pathway, and from both biotransformation or fermentation, are regarded as key building blocks for the manufacturing of both commodity and specialty chemicals (Fang et al. 2017). The improvement of the microbial biocatalyst is a critical technical challenge aimed to mitigate coproducts yields such as acetic acid and to increase the production of these chemicals. Moreover, cheap recovery processes are needed to remove unwanted salts and the increase of the system integration. These building blocks are transformed into three primary derivative families thanks to three different processes : reduction, reductive amination and direct polymerization (Li and Xing 2017b).

A C3 chemical, 3-Hydroxypropionic acid (3- HPA) is considered as a key building block because it is possible to derive fine chemicals from it. However, one of the major technical challenges is to have 3-HPA converted to a building block through a cheaper fermentation process (Matsakas et al. 2018). The major technical reflections on this fermentation process are the development and scale-up of its integration, by an appropriate organization, in order to generate high production with the improvement of microbial biocatalyst, thus reducing by-products formation, with an efficient cheap recovery process reducing undesirable salts (Kumar et al. 2013).

Glycerol could become an extremely diverse building block in biorefinery. Presently, glycerol is an acknowledged traded item with worldly annual production of $600 - 750 \times 10^3$ tons and the industry expects its consumption to grow above 4 million tons by 2024 (Ahuja and Singh 2018). A lot of chemical industries such as Uniqema, Procter & Gamble and Stepan produce glycerol and its numerous derivatives (such as glycerol stearate, glycerol oleate and glycerol triacetate). Glycerol is manufactured, like natural glycerol by-products, by biodiesel and oleochemical industries, and like synthetic glycerol, derived from propylene. The number one provider and consumer of glycerol worldwide are the USA. Indeed, about 75% of the glycerol supply in the United States is provided by natural sources, and the other synthetic 25% is refined before being used in many ways in markets thus explaining glycerol's comparatively expensive price of \$0.60 – 0.90 per pound. However, since biodiesel was more and more used and since it is a key byproduct in biodiesel manufacturing, cheaper glycerol could be purchased in greater quantities (Quispe et al. 2013). Glycerol prices could fall to \$0.20/lb which is today's industrial average cost for refined and unrefined glycerol. Glycerin could be found at lower cost. Glycerol could become a key building block in biorefinery if its prices dropped into a \$0.20 - \$0.50/lb range. The increase of fatty acid consumption, for fuels and products, may cause the world glycerol output to rise significantly. In the coming years, if the US replaced about 2% of the diesel used for transportation by biodiesel, almost 2 billion pounds of new glycerol would be produced (Muniandy et al. 2016).

Aspartic acid is a 4-carbon amino acid considered as a fundamental part of a metabolism for protein production. Different settings of aspartic acid exist but the L-aspartic, which can be produced in four primary ways (by chemical synthesis, protein extraction, fermentation and

enzymatic conversion), is the most common one and is used to produce a synthetic sweetener, aspartame (Deng et al. 2018). Presently, the favored method of Enzymatic conversion consists in having fumaric acid reacting with ammonia catalyzed by a lyase enzyme because it provides higher production and productivity, generates few byproducts and requires an easy recovery process (crystallization). The main technical impediments of this method are the development of cost-competitive fermentation processes with the existing process (using cheap sugar as substrate), the metabolic engineering of biocatalytic pathway to overexpress oxaloacetate without affecting viability in cells, the operational management in an environmental way, the oxaloacetate enzymatic oxidation and eventually the high cost recovery (Sari 2015). Direct fermentation methods are not yet cost competitive but the use of biotechnological routes seems promising to overcome this obstacle. Another strategy for reducing the cost of aspartic acid is to make improvements to the current process. The first effort to be made should be to reduce the cost of fumaric acid which is currently used as a feedstock for the aspartic acid production (Isikgor and Becer 2015).

3-Hydroxybutyrolactone (3-HBL) - a cyclic chemical with four carbons - is currently used in the pharmaceutical production through chemical transformations and also through fermentation. The chemical synthesis of this building block is considered as “confused” because it requires multiple steps (Martin et al. 2013). One possible way to form 3-HBL starts with malic acid which could be cyclized to give hydroxysuccinic anhydride and then could be reduced to form hydroxybutyrolactone. Still, the primary technical obstacle in the development of this building block requires the development of a cheap fermentation process using a wide range of lignocellulosics biomass as feedstocks that can tolerate its inhibitory components and averting odd oxidants (Dhamankar 2013).

Methyl-SA is a dicarboxylic acid with C5, also known as itaconic acid, considered as a key building block thanks to its capacity to derive fine chemicals. Itaconic acid basic chemistry is similar to maleic acid/anhydride because both are derived from petrochemicals. Itaconic acid used as a specialty monomer is produced through aerobic fungal fermentation (Meena et al. 2010). The main challenge is to reduce the cost of the fermentation process to below \$0.25/pound in order to compete with petrochemical-derived products. However, the development of a process to produce these building block compounds face many technical

barriers including the evolution and scale-up of a cheap fermentation system with an organism using low cost sugars (C5 and C6) and that of a recovery process with high rates, production and productivity, reducing the forming of by-products by improving a microbial biocatalyst to better control the operating environment (Xu et al. 2016b).

Levulinic acid (LA) is one of the most recognized and largest building block family of potential derivatives, formed by the treatment of both 5 and 6 carbon sugar originating from starch, hemicellulosic materials (xylose, arabinose) or lignocellulosics with acid. LA is often used as starting material to produce a large amount of chemicals since it serves as a precious building block available from polysaccharides in biorefinery (Girisuta and Heeres 2017).

When compared to petrochemicals derivatives from maleic anhydride Glutamic acid (GA), the C5 amino acid building block can build five carbon polymers with new functionalities thanks to its by-products. (H. Isikgor and Remzi Becer 2015). The difficulty to develop very cheap fermentation methods is considered as the main technical obstacle to the development of GA as a building block. One of the major challenges is primarily associated with the development of less expensive fermentation processes by a strain that can produce GA as a free acid. To compete with petrochemical-derived products, productivity and final fermentation, the titer should be improved and the fermentation cost needs to be equal to or less than \$0.25/pound (Schouwer et al. 2017).

Sorbitol is produced through the hydrogenation of glucose by several companies and its volume is in the order of 200 million pounds per year. In place of a batch technology, to ensure the complete conversion of glucose, a continuous process using a catalyst such as Raney nickel is used in all commercial processes to reduce the sugars amounts in the sorbitol production. Very strict requirements are necessary because sorbitol is extensively applied in the food industry. Because no technical development is needed for its use as a building block in derivatives, sorbitol is a very inexpensive feedstock (Furtwengler and Avérous 2018). To conclude, if a continuous process is compared to a batch process, the only change is glucose conversion into sorbitol. It makes sorbitol an economical feedstock for producing derivatives (Zhang et al. 2013).

The glucaric acid is an organic compound and member of a large family of materials known as oxidized sugars, representing a significant market opportunity. Glucaric acid can be obtained by the oxidation of glucose with nitric acid and it is considered as a building block. The oxidation of glucose, by using a chemical or biochemical catalysis, entails the production of glucaric acid in high quantity (Armstrong et al. 2017). Therefore, the value of the glucose conversion into glucaric acid in biorefinery can be explained in two ways: the first one is that a broad range of items are produced in high scale markets using glucaric acid as a starting point, and the second one is the development of efficient and robust processes for the production of glucaric acid applicable to the oxidation of other inexpensive sugars such as the xylose or arabinose mentioned in this review (Werpy. A et al. 2004).

Indeed, xylose and arabinose can produce the corresponding sugar alcohols, xylitol and arabinitol, through hydrogenation. At present, xylitol, which is known as a non-nutritive sweetener, is produced in very limited quantity and arabinitol is not produced for commercial purposes, even though there is no obstacle to its production (Rivas et al. 2006). The conversion model of xylose and arabinose into xylitol and arabinitol is based on the conversion model of glucose into sorbitol with a 99% yield range. Nickel, ruthenium and rhodium and hydrogenation catalysts are used in the hydrogenation of C5 sugars into sugar alcohols. There exists no technical development requirements in the production of xylitol used as a building block for derivatives. The production of xylitol could be achieved at a very low cost if the xylose feedstock was not expensive, but it is not the case (H. Isikgor and Remzi Becer 2015).

The oxidative dehydration of glucose using oxygen or electrochemistry leads to the formation of FDCA (2,5-Furandicarboxylic acid), a member of the furan family. It can also be converted by the oxidation of a 5-hydroxymethylfurfural, an intermediate in LA production, one of the top 12 platform molecules from 6-carbon sugars (Rathod and Jadhav 2018). The necessity of developing an effective and specified dehydration process triggers a challenge in the production and use of FDCA. The lack of knowledge in the control limits of sugar dehydration, the innovation of powerful technologies, including the production of new building blocks at a minimum cost, the production of new polymers from FDCA are also challenges while the developing and controlling of esterification reactions and FDCA reactivity will be of great matter (Yan et al. 2018).

Chemical compounds with low molecular weights are characterized by the presence of at least one carboxylic functional group (-COOH) also called organic acids (Porro and Branduardi 2017). Moreover, organic acids were discovered by Scheele in 1784, and humans have used them since early ages because they are broadly produced in nature by all organisms such as micro-organisms, plants, animals and humans. Commercially speaking, lactic acid, citric acid, gluconic acid and itaconic acid are the most important organic acids. They are used in various applications such as flavor enhancers in food, ingredients in pharmaceuticals, cosmetics and beverages and they are also used in the production of biopolymers, coatings, adhesives and others in the chemical industry (Sun et al. 2015). The global market of organic acids was estimated at approximately \$12 billion in 2014 and is expected to reach over \$18 billion by 2023 (Singh et al. 2017). The vision is that these products can replace fossil fuels that in itself is a societal goal.

As mentioned before, various organic acids can serve as platform chemicals for polymers, food, coatings, lubricating oils, pharmaceuticals, cosmetics, solvents and the production of other materials (Cheng et al. 2013; Rogers et al. 2013). They are products of interest due to their prices and in existing highly competitive markets with large quantities used in foods, beverages and chemicals. Currently, acetic, citric, formic, lactic, propionic, and fumaric acids are the highest volumes produced. Organic acids were identified as attractive target molecules derived from sugars or the decomposition of cellulose. It is difficult for the renewable materials originating from the extraction and/or the advanced fermentation technologies to compete with petroleum derived starting materials given their current costs (Rogers et al. 2013). A significant portion of multifunctional organic acids are already produced from renewable sources. Renewable materials could help replace petroleum derived organic acids totally which would acknowledge a good management if costs could be lowered and if integrated large scale processes were developed (Dezam et al. 2017). Significant advances in technology are needed to make renewable organic acids and derived products cost competitive with their petroleum analogs (Li et al. 2016b). Significant investments in developing new strains and enzymes that produce these acids in higher quantities should be continued. Also, of particular interest, the development of fermentation processes using microorganisms that survive to high acid concentrations is crucial. (Bekatorou et al. 2016).

Succinic acid: case study

As mentioned before, 12 building-block or platform chemicals were identified as the most promising candidates out of 300 chemicals. A beneficial shift in their production strategies using renewable feedstocks (eco-friendly) may compete with energy-intensive processes using petroleum based feedstocks (Werpy and Petersen 2004; Saxena et al. 2017). Succinic acid is a high potential candidate as a building block chemical and intermediary for many other chemicals made from renewable resources (Stichnothe et al. 2020; Louasté and Eloutassi 2020). In the meantime, SA is at the top of the list and holds the title for being the only special product with an annual market demand of about 710 kilo tons with a net value of \$115.2 million, and is expected to exceed \$1.1 billion by 2020 (Padman 2014). SA (butanedioic acid) is a dicarboxylic acid that develops naturally in plant and animal tissues as well as microorganisms. This chemical is also known as “Spirit of Amber.” When it was first discovered, it was extracted from amber by pulverizing and distilling it using a sand bath. It was primarily used externally for rheumatic aches and pains. Nowadays the majority of succinic acid produced commercially is made by chemical synthesis. However, attention has been focused on microbial succinic acid production as an alternative to chemical synthesis (Corona-González et al. 2008; Borges and Pereira 2011).

SA is a dicarboxylic acid containing four carbon atoms. In bio-economy, this four-carbon-dicarboxylic acid (SA) progresses to an intermediate platform, as a substitute for maleic anhydride, in order to produce diverse numbers of chemicals considered as bulk/intermediate chemicals. Among them, maleic acid, adipic acid, 1,4- butanediol, γ -butyrolactone, N-methyl-2-pyrrolidone, tetrahydrofuran, 2-pyrrolidone, succinic esters and succinimide are used in green chemistry and in a wide number of industries including polymers (clothing fibres), food, surfactants and detergents, flavors and fragrances and in the pharmaceutical industry (Song and Lee 2006; Li and Xing 2017a). SA applications in industries call for about 9% polybutylene succinate-terephthalate and polybutylene succinate, 6.2% for polyester polyols, 15.1% in pharmaceutical industry, 12.6% in food industry, and 19.3% in resins, coatings and pigments production (Aeschelmann and Carus 2015).

Production methods: an overview

Many bulk substances necessary to our daily lives are obtained through chemical syntheses. These consist in the construction of complex chemical compounds out of simpler ones. This is true for all types of chemical compounds, but most syntheses have to do with organic molecules, enabling their availability in large quantities (Jansen and van Gulik 2014). In the petrochemical process, SA is mostly produced from n-butane through hydrogenation of maleic anhydride followed by hydration (Zhou and Zheng 2013). Other chemical methods were studied but none have so far been able to compete effectively with the production of organic acid by fermentation (Okabe et al. 2009).

The industrial production of organic acids began with the production of citric acid from lemons and the production of malic acid from apples. At the end of the 19th century, studies on microorganisms showed that they could produce organic acids. Since this discovery, researchers and industrialists have turned to the use of microorganisms for the production of platform molecules and it became an important field of study for their various applications (Ke-Ke Cheng et al., 2012). It is estimated that the growth of the chemical industry would reach over 2 trillion \$ per year if bio-based products replace petroleum-based resources, providing an additional income with an amount of over \$500 billion a year according to the U.S. Bio-based Products. Table 5 Compare the advantages and disadvantages of the main processing technologies used for the production of platform molecules.

During the past few decades, bio-based feedstocks have become less expensive and it will remain an added value over the petroleum/gas feedstocks in the future. According to (Kidwell 2008), the SA consumption was of about 25,000 to 30,000 tons annually worldwide with an approximate 10% of increase a year. The SA total capacity is estimated to more than 45–50 million lb/year. The World demand for SA was 51,000 tons in 2013 and is expected to increase to 593,400 tons by 2020 (Padman 2014). In the next few years, these values are expected to augment in parallel with the fast demand rising and the cost-competitiveness of bio-based succinic acid. Many companies are active in the development of bio-based SA at commercial scale and three of them intend to bring more than 140,000 tons per year of capacity online by 2016 (Table 6) (Jansen and van Gulik 2014; Taylor et al. 2015).

Table 5. Advantages and disadvantages of production methods

Process	Advantages	Disadvantages
Conventional process Using petroleum	The product is very pure	Resources of the petroleum are limited
	The production is continuous (no stop)	Like other fossil fuels, petroleum is also non-renewable source of energy
	Fast and efficient	While burning petroleum, greenhouse gases are generated and causes environmental pollution
		Petroleum is also flammable hence it must be handled with care
		Sometimes the waste is dumped into the ocean by many industries, it affects ocean and marine life
Fermentation process Using renewable sources	Temperature conditions are very high	
	Renewable energy is cheaper compared to other sources	Difficult to generate in large amount compared to those produced by conventional process
	Reliable, sustainable and will never run out	Substrates contains undesired compounds (need of pretreatment technics)
	Reduces consumption of fossil fuels such as coal and petroleum	Impure final product
	Reduces production of greenhouse gases	High cost purification technics
	Components are eco-friendly and safe	
	Possibility of using waste materials (valorization)	

408

409

Table 6. World-wide investments in the bio-based chemical SA by the producer's companies

Company	Raw material	Fermentation/ Microorganisms	Start-up	Investment made in	Capacity in thousands per year
BioAmber (DNP/ard)	Wheat glucose Corn glucose	<i>Candida Krusei</i>	2010	Joint venture between Canada and Pomacle, France	30
Reverdia (Roquette & DSM)	Starch/sugars	<i>Saccharomyces cerevisiae</i>	2012	Cassano Spinola, Italy	10
Myriant	Corn glucose	<i>Escherichia coli</i>	2013	Louisiana, USA	14
Succinity (BASF & Corbion – purac)	Glycerol	<i>Basfia succiniciproducens</i>	2013	Montmelo, Spain	10

The metabolism leading to the production of SA is controlled by either aerobic or anaerobic environments. SA is produced by numerous aerobic, facultative and obligate anaerobic microorganisms using C6 sugars, such as glucose and fructose, metabolized by the Embden Meyerhof-Parnas pathway (glycolysis). It provides two moles of pyruvate, ATP (energy) and NADH (reducing power), per mole of sugar (Krishnakumar 2013). In addition to succinic acid, other carboxylic acids (such as lactic acid, formic acid, propionic acid, acetic acid) and alcohols (such as ethanol) are also obtained. The production ratios of these by-product compounds depend on the microorganism strain used, substrate, and on the operation conditions. For example, when glycerol was used as a carbon source in the fermentation of *A. succiniciproducens*, succinic acid was produced with a high yield. Also, the formation of by-product acetic acid was avoided, which resulted in the increased ratio of succinic acid to acetic acid up to 31.7:1. This ratio is 7.9 times higher than that obtained by batch fermentation of glucose as reported by (Lee et al. 2001)

SA producer's microorganisms

A tremendous research is made to develop a biological process for the production of SA, such as a metabolite under aerobic, micro-aerobic and/or anaerobic conditions thanks to the use of microorganisms such as *Aspergillus niger*, *Aspergillus fumigatus*, *Byssoschlamys nivea*, *Lentinus degener*, *Paecilomyces varioti* and *Penicillium viniferum* (Rossi et al. 1964; Taylor et al. 2015). Recently, the topology of the central carbon metabolism by *A. Niger* and the

431 metabolic network were deciphered thanks to the integration of genomic, biochemical and
432 physiological information. Based on this information, a stoichiometric model was designed,
433 suggesting that this organism can produce 1.5 mol/mol (mol of SA produced per mol of glucose
434 consumed) under microaerobic conditions (David et al. 2003). However, the use of fungus was
435 limited to the food and beverages manufactures due to low productivities as well as the
436 difficulties in fermentation, separation and purification methods (Amarasinghe et al. 2018).
437 *Saccharomyces cerevisiae* was studied in order to reach a higher concentration of SA in wine
438 manufacturing (Aponte and Blaiotta 2016). A series of its mutant strains were designed by the
439 overexpression or inactivation of some genes, showing increased levels of SA when compared
440 to wild type strains, from 0.96 g/L to 2.25 g/L (Arikawa et al. 1999; Ahn et al. 2016). SA is not
441 accumulated intracellularly which makes it a suitable and promising strain for the
442 biotechnological production of SA on an industrial scale (Raab et al. 2010). Few Gram-positive
443 bacteria such as *Corynebacterium glutamicum* and *Enterococcus faecalis* were used for the
444 production of SA. Several engineered *C. glutamicum* strains were designed by gene
445 modifications, and their optimal culture conditions were developed (Inui et al. 2004). However,
446 the SA rate was increased seven times, while the glucose consumption rate was increased five
447 times under deprived oxygen conditions. The SA metabolic pathways syntheses are diverse.
448 However, the main one in a bacterium is the phosphoenolpyruvate (PEP) carboxylation
449 reaction, whereas other microorganisms use multiple pathways. *Actinobacillus succinogenes*,
450 *Mannheimia succiniciproducens*, *Anaerobiospirillum succiniciproducens* and recombinant
451 *Escherichia coli* are gram-negative bacteria which produce SA in various forms (Herselman et
452 al. 2017). Table 7 represents the best applicants as they produce SA as a major fermentation
453 product. A wild type of *E. coli* ferments, primarily glucose into ethanol, formic, acetic and lactic
454 acids with small detectable amounts of SA under anaerobic conditions as stated by (Clark
455 1989). The quantity of SA on glucose achievable is no more than 0.13 g/g. It is known that the
456 metabolic pathway used by *E. coli* to form SA differs from that of the three bacteria mentioned
457 above. The PEP carboxykinase plays a minor role. *E. coli* produces succinate naturally through
458 a TCA cycle reductive branch. However, the quantity is limited and this route is not applicable
459 for a large scale commercial production. Therefore, to achieve a high SA production and to
460 inhibit any formation of by-products, there was considerable interest in *E. coli* engineering that

is several gene disruptions (Li et al. 2016a). The enzymatic pathway technology used to produce succinate (SA ionized form) as explained by (Vaswani 2010).

In his paper, the metabolic pathway of wild-type *E. coli* with gene alterations (or gene editing) are studied. To enhance and improve the succinate overall performance, a number of genes were knocked out in the pathway. In the first step, the deletion of phosphotransferase synthase (PTS) genes leads to the end of the metabolic pathway, which converts phosphoenolpyruvate (PEP) into pyruvate, ensuring the inhibition of PEP and hence, the whole reaction is introduced in the TCA cycle to produce succinates without the formation of any by-products. In the next stage, the deletion of lactose-dehydrogenase (*LDH* genes) and pyruvate formate lyase (*PFL*) prevents the conversion of pyruvate into lactate and acetyl-CoA, as by-products. Furthermore, pyruvate is recycled into a TCA cycle, which globally improves the formation of succinates (Guarnieri et al. 2017).

474

475 **Table 7.** SA producer's bacteria.

Microorganisms	Fermentation strategy	Substrate	Concentration	Yield (SA produced /Sugars consumed)	References
<i>A. succinogenes</i> 130Z	Batch	Glucose	10 g/L	0.56 g/g	(Almqvist et al. 2016)
		Xylose	10 g/L	0.42 g/g	
		Mannose	10 g/L	0.38 g/g	
		Arabinose	10 g/L	0.44 /g	
<i>A. succinogenes</i> 130Z	Continuous	Glucose	26.5 g/L	0.74 g/g	(Brink and Nicol 2014a)
<i>A. succinogenes</i> 130Z	Batch	Xylose	80 g/L	0.74 g/g	(Salvachúa et al. 2016a)
		Glucose	5.4 g/L	0.80 g/g	(Ferone et al. 2017)
		Mannose	5.7 g/L	0.85 g/g	
		Arabinose	5 g/L	0.96 g/g	
		Xylose	5.2 g/L	0.84 g/g	
<i>A. succinogenes</i> NJ113	Batch	Cellobiose	50 g/L	0.67 g/g	(Jiang et al. 2013)
<i>A. succinogenes</i> CGMCC1593	Batch	Straw hydrolaste	58 g/L	0.80 g/g	(Zheng et al. 2009)
<i>M. succiniciproducens</i> LPK7	Fed batch	Glucose	20 g/L	0.76 g/g	(Lee et al. 2006)
	Continuous	Glucose	18 g/L	0.25 g/g	(Oh et al. 2008)
Recombinant <i>E. coli</i> AFPP11	Dual phase Fed batch	Glucose	40 g/L	1.1 g/g	(Vemuri et al. 2002a)
Recombinant <i>E. coli</i> HL27659k	Fed batch	Glucose	Not reported	0.61 g/g	(Lin et al. 2005)
<i>B. succinioproducens</i> BPP7	Batch	Arundo donax hydrolysate	17 g/L	0.75 mol/mol	(Cimini et al. 2016)

476

477 Table 7 presents the data relating to the conditions and fermentation efficiency using different
 478 microbial strains producing succinic acid.

479 The production of SA by a fermentative way has been achieved by nature and mutant strains.
480 According to the American type culture collection (ATCC) and Deutsche Sammlung von
481 Mikroorganismen und Zellkulturen (DSMZ), three facultative anaerobes bacteria isolated from
482 the rumen, *Actinobacillus succinogenes*, *Basfia succiniciproducens* and *Mannheimia*
483 *succiniciproducens*, are classified as biosafety level 1 microorganisms. They are considered as
484 the top promising wild -type bacterial stems, due to their potential for consuming various
485 sources of carbon and therefore for achieving high fermentation efficiency. A better
486 concentration of succinate (105.8 g/L) was achieved in fermentation of glucose (carbon source)
487 by *A. succinogenes* FZ53 mutant, leading to a yield and productivity of 0.82 g SA/g glucose
488 and 1.36 g/L/h, respectively (Guettler et al. 1996). *B. succiniciproducens* metabolic fluxes were
489 investigated and two engineered strains were evolved, but unfortunately its use for SA
490 production was not investigated to a great extent (Becker et al. 2013).

491 A genetically modified *E. coli* strain was designed to produce highly efficient succinic acid,
492 such as in a dual phase fermentation. The strain, *E. coli* AFP111/pTrc99A–pyc, gave a
493 concentration of 99.2 g/L of SA, with a top yield of 1.1 g of SA/g of glucose and a productivity
494 of 1.3 g/L/h. (Vemuri et al. 2002b). *Corynebacterium glutamicum* Δ ldhA pCRA717 could also
495 be a promising candidate to produce SA referring to its high volumetric productivity (3.17
496 g/L/h) and yield (0.92 g SA/g glucose) achieved with a final concentration of (146 g/L) (Okino
497 et al. 2008). Research emphasized on the evolving of some modified yeast strains which could
498 be considered to produce SA at low pH, which should be helpful in view of the reduction of the
499 costs of operations downstream (purification and separation) of SA (Graaf et al. 2012; Jansen
500 and van Gulik 2014).

501 In order to produce SA, the main features of *A. succinogenes* 130Z are used as a wide variety
502 of feedstocks containing carbon sources, with suitable tolerance to inhibitors, sufficient as well
503 as an efficient fermentative pathway even with sustainable raw materials (Brink and Nicol
504 2014b). Whereas the principal drawback is the demanding nature of this strain for nitrogen
505 sources (corn steep liquor, yeast extract or NH_4Cl), vitamins such as biotin, the optimal pH
506 demanded (nearly neutral), besides the tools for genetic modification handling are restricted (Li
507 et al. 2011). SA bio-production using *A. succinogenes* 130Z is implemented in biorefineries
508 employing cheap and complex renewable raw materials, which enrich a fermentation medium
509 at less expensive cost compared to commercial nutrient sources. The use of pH neutralizers in

fermentation broth, which result from the decrease of pH during *A. succinogenes* 130Z cultivations, affects upstream and downstream separation costs (Bradfield et al. 2015). The low pH values attained in the fermentation broth led to minimizing the cost of the downstream separation, as it affects the SA dissociation level ($pK_{a1} = 4.16$ and $pK_{a2} = 5.6$) (Jansen and van Gulik 2014).

Metabolic network towards SA production in *A. succinogenes*

A. succinogenes 130Z have been isolated from bovine rumen. It is a fermentative Gram-negative, facultative anaerobic, non-motile, non-spore forming, capnophilic, pleomorphic rod and taxonomically referred to as the Pasteurellaceae family, as follows: Bacteria; Proteobacteria; Gammaproteobacteria; Pasteurellales; Pasteurellaceae. *A. succinogenes*, based on the 16S rRNA amplification (Guettler et al. 1999; Zhu et al. 2012), is mesophilic and grows well at 30-37 °C in a chemically defined medium. It can consume a broad range of C5 and C6 sugars as well as various disaccharides and other carbon sources, such as glucose, xylose, arabinose, mannose, galactose, fructose, sucrose, lactose, cellobiose, mannitol, maltose and glycerol (Wan et al. 2008; Zheng et al. 2009; Carvalho et al. 2014). Besides sugarcane bagasse hemicellulose hydrolysate, many others substrates have been used for produce succinate by *A. succinogenes* as sake lees, cane molasses, corn stover, corn fiber, wheat flour, corncob hydrolysates, corn stalk and cotton stalk and whey (Louasté and Eloutassi 2020). Higher SA yields were achieved when reduced carbon resources were used as feedstocks, such as glycerol, sorbitol and mannitol, while the use of C5 sugars, such as arabinose and xylose, led to lower succinate yields (Li et al. 2010a). As a rule, glucose is transported through the cell membrane into the cell by means of a permeable action. Hence, glucose phosphorylation occurs through a phosphoenolpyruvate dependent phosphotransferase system (PTS) (McKinlay et al. 2007), and also through the action of hexokinase forming glucose-6-phosphate, which is converted to phosphoenolpyruvate (PEP) through a glycolytic pathway. The interference of the oxidative pentose phosphate pathway (OPPP) has a limited contribution in the glucose metabolism. Thus, NADH is generated through the activity of pyruvate and forms dehydrogenase, while NADPH results from a transhydrogenase and/or from the combination of two enzyme activities of NADH-oxidizing malate dehydrogenase and NADP-reducing malic (McKinlay et al. 2007). Additionally, the flux distribution between the C3 and C4 pathways is affected by the NADPH

requirements, mainly referring to pyruvate and the formation of dehydrogenase activities (figure 2). Both, the glyoxylate and Entner-Doudoroff pathways are absent in the *A. succinogenes* 130Z fermentative metabolism. Four nodes are essential to the flux distribution to produce succinate. These are phosphoenolpyruvate (PEP), oxaloacetate (OAA), malate and pyruvate (McKinlay et al. 2005; Pereira et al. 2018). The metabolic flux analysis has shown that the main SA pathway is from PEP to oxaloacetate, malate, fumarate ending into succinate catalyzed by key enzymes, which are PEP carboxykinases, malate dehydrogenase, fumarase and fumarate reductase (McKinlay et al. 2007; Nag et al. 2018). Nevertheless, via the C3 pathway, PEP could be transformed into formate, acetate and ethanol, and via the C4 network, it is converted to succinate by malic and OAA decarboxylase enzyme which hold the roles of pyruvate bio-conversion, making therefore a reversible shunt between the C3 and C4 pathways (McKinlay and Vieille 2008).

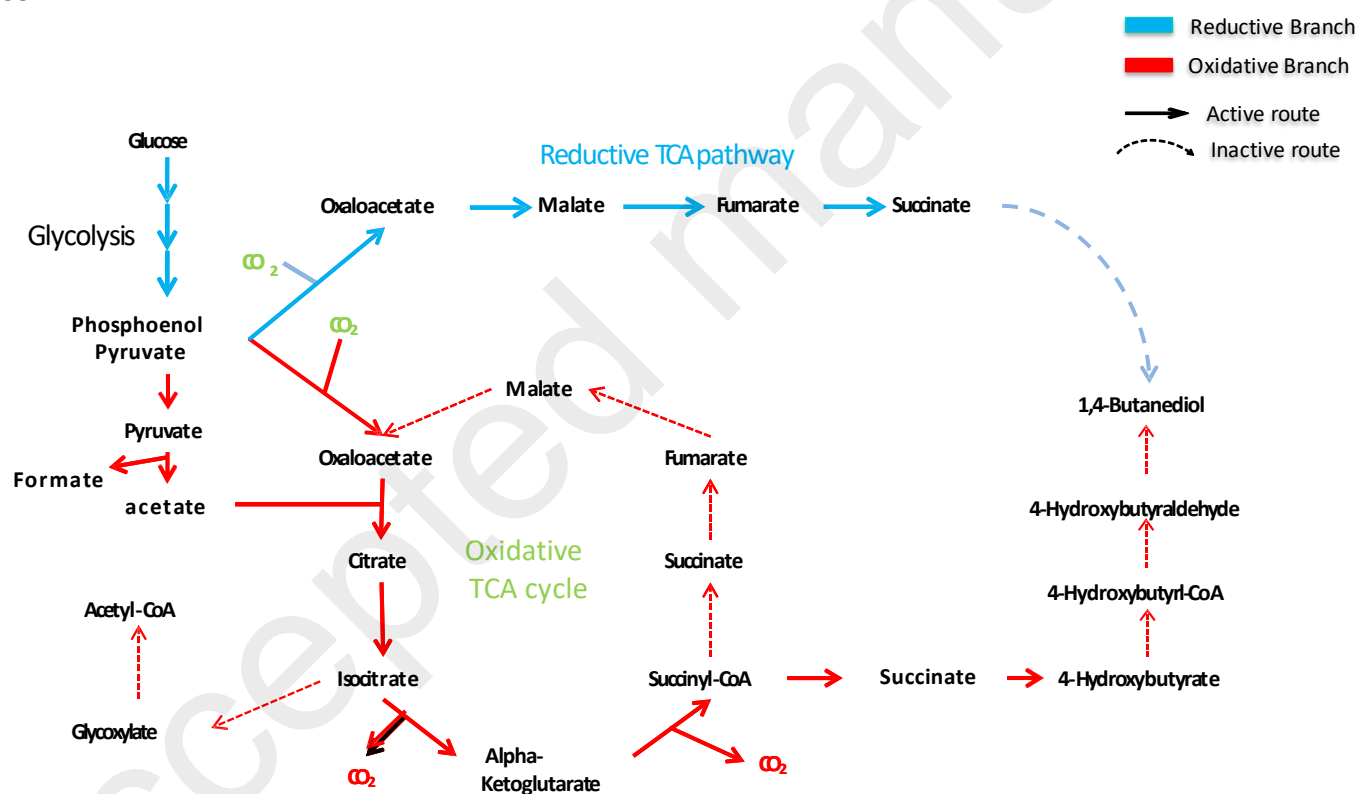


Figure 2. Metabolic pathway occurs in *Actinobacillus succinogenes*

Key factors requirements

pH regulators

Frequently, pH is considered as a major key factor in fermentation processes. For optimal performances, almost microbial cultures require near neutral pH values. The SA fermentation also leads to the production of organic acids (formic and acetic acids) which provokes the acidification of the medium, therefore necessitating the addition of neutralizing agents. During fermentation, when pH values are near neutral, these by-products are in their dissociated shapes leading to the formation of salts by neutralization. A study done by (Zhu et al. 2012) reviewed that the highest SA production occurs in the fermentation of *A. succinogenes* ATCC 55618 at optimum pH value of 7.5. While individual neutralizing agents are added, such as NaOH or KOH, results make the SA production fall down, which may be related to the acute cell flocculation. When ammonium hydroxide (NH₄OH) or calcium hydroxide are used as neutralizing agents, a growth inhibition is observed. To prevent cell flocculation, 5 M of NaOH and 0.47 M of MgCO₃ were combined, achieving a 28 % higher SA concentration (59.2 g/L) in fermentation than when NaOH was used as only neutralizing agent (Bazaes et al. 2007). A stable production of SA occurs at a pH range of 6 to 7.2 as reported in another paper (Liu Yu-Peng et al. 2008), while magnesium carbonate (MgCO₃) was considered as the most promising neutralizing agent when compared to Na₂CO₃, NaOH, CaCO₃ and NH₄OH in the *A. succinogenes* CGMCC1593 fermentation, using glucose as the sole carbon source. When NaOH or Na₂CO₃ are used, cell flocculation occurs after 12 hours, whereas cell flocculation is not observed when MgCO₃ is used. (Li et al. 2011) demonstrated that among many neutralizer agents, such as CaCO₃, NaHCO₃, NaOH, Na₂CO₃, Ca(OH)₂, Mg(OH)₂, and NH₃·H₂O, MgCO₃ was the most efficient regarding SA production, glucose utilization and growth of *A. succinogenes* NJ113, reaching a conversion yield of 0.73 g/g of glucose into SA and decreasing fermentation cost by 55.9%. The use of CaCO₃, Ca(OH)₂ and NH₃·H₂O as neutralizers, results in decreasing cell growth, and thus low production of SA; while the supply of mixed neutralizers of Mg(OH)₂ and NaOH at a ratio of 1:1 led to the same efficiency for SA production as using only MgCO₃ as neutralizer. This could be referred to NaOH solubility and strong alkalinity, and the lack of Mg²⁺ as cofactor for PEP carboxykinase (Liu Yu-Peng et al. 2008). In the studies mentioned above (Liu Yu-Peng et al. 2008), MgCO₃ was considered as the most

efficient regulator of the pH, providing both CO₂ and Mg²⁺ ions serving as cofactors in the TCA cycle reductive branch for the first enzyme, PEP carboxykinase.

CO₂ Feed in

In fermentation, while gaseous CO₂ is sparged, the dissolved CO₂ concentration relies on the fermentation broth components, temperature, agitation, CO₂ flow rate and partial pressure. During the *A. succinogenes* 130Z fermentation, when carbonate (e.g. MgCO₃) or bicarbonate salts are added, higher dissolved CO₂ concentrations can be reached, regardless a gaseous CO₂ supply. During fermentation, CO₂ availability results in carbonates and bicarbonates ions conversion into HCO₃⁻, and diffusion through cell membranes, which demands ATP consumption so as to maintain reaction equilibrium. A study by (Zou et al. 2011) on the SA production by *A. succinogenes* ATCC 55618 explored the action of dissolved concentration of CO₂, partial pressure of gaseous CO₂ as well as the MgCO₃ supply on SA production. The CO₂ dissolved concentration was not sufficient, when only gaseous CO₂ was sparged. To maximize SA production; consequently 0.47 M of MgCO₃ and CO₂ partial pressure of 101.33 kPa (100% CO₂ gas) was supplied, resulting in higher concentration (60.4 g/L), productivity (0.84 g/L.h) and yield (0.58 g of SA/g of glucose) of succinic acid.

(Xi et al. 2011) investigated the effect of agitation and other parameters on SA production. Maximum SA production was obtained when *A. succinogenes* NJ113 was grown in the following conditions: 200 rpm stirring speed, pH 6.8, 0.1 MPa CO₂ partial pressure, 37°C and 150 mM NaHCO₃. These conditions led to a CO₂ optimal fixation rate of 0.57 g/L.h, with a concentration of 51.6 g/L and 0.76 g/g yield.

The CO₂ availability could raise owing to its market price of around 60 \$/t with an annual assessed carbon capture and storage of 90% (Quadrelli Elsje Alessandra et al. 2011). An analogue solution could be the MgCO₃ production by precipitating CO₂ and Mg²⁺ ions that could be used in SA fermentation.

Redox potential

Redox state of the cells is known to affect metabolites profiles. More and more microbes are figured out with a process having the capacity of using extracellular electron transfer, in which they use either electron donors or acceptors for metabolic reactions (Li et al. 2010b). This

feature can be used to overcome cellular redox limitations and hence optimizing microbial production. Redox potential, also known as oxido-reduction potential (ORP), reflects overall electron transfer and redox balance involved in metabolic activity of microorganisms. ORP is identified by a ratio of oxidative to reductive redox couple in fermentation operation (Liu et al. 2013). The majority of fermentation products achieved under microaerobic or anaerobic conditions are considered as bulk commodities. Although many fermentation processes have been well developed with long-term operability, cost saving is an endless effort, particularly for biofuels and bio-based chemicals production at bulk quantity such as ethanol and butanol to address global concern on sustainable development (Kracke et al. 2018). Since redox reactions and homeostasis are basis for intracellular metabolism, ORP status controls metabolites profiles, which subsequently offers a strategy to direct the pathway for efficient production of more and more materials and energy (Liu et al. 2017a). With advanced technologies that can detect ORP levels and its intracellular influence on gene expression, protein biosynthesis and metabolites caused by ORP shifts, mechanism underlying this phenomenon can be elucidated. More robust strains and optimized processes can be developed by redox potential which can be controlled by metabolic modifications and bioprocess engineering levels, which have been highlighted in ethanol and butanol fermentations under microaerobic and anaerobic conditions (Liu et al. 2017a). Figure 3 shows the standard ORP of some redox pairs in an intracellular metabolism and it is affected by temperature, aerobic or anaerobic conditions. Therefore, strategies have been implemented to regulate redox potential, including gene modification, energy input, reagents supplementation and sparging gases. A study carried out by (Park and Zeikus 1999) showed the impact of redox potential regulation on succinate formation which is enhanced by 20% when using *A. succinogenes* 130Z in bioelectrical reactors, and its efficiency depends on the interactions between microorganisms and the working electrode. In batch fermentation, optical cell density and metabolites formation were shifted with respect to redox potential levels in the range of -100 to -450 mV, recording an optimal ORP level of -350 mV, which result in higher SA yield (1.28 mol/mol), productivity (1.18 g/ L/h) and higher mole ratio of SA to acetic acid (2.02) as reported in literature (Li et al. 2010b). Another study revealed that the use of redox mediators has the potential to improve fermentation end-products, such as the case of *Corynebacterium crenatum*, and more reduced environment benefited SA production when using reagent supplements such as $K_3Fe(CN)_6$, Na_2S (Chen et al. 2012).

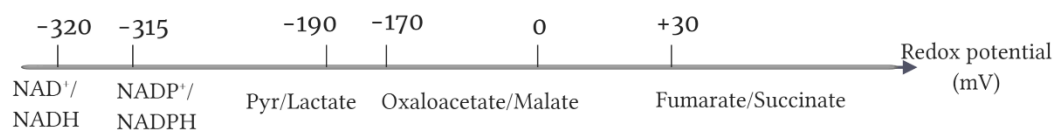


Figure 3. Standard potential redox E° (mv) at 25°C of some redox pair involved in intracellular metabolism (Moscoviz 2017). This photo was done by the authors themselves.

Current fermentation limitations

Carbohydrate fermentation is considered as an interesting alternative process to produce chemicals, simply referring to feedstocks nature which is renewable; however, it has many limitations. Biochemicals production by fermentation presents a number of challenges in terms of overcoming the product-mediated toxicities for microorganisms, by-products formation, low yield and productivity, fermentation and purification costs, in order to achieve efficient and economical recovery of a product.

First, a whole fermentation occurs in a defined pH range, between 6.0 and 7.2 with an optimal pH at 6.8 for *A. succinogenes* 130Z (Wan et al. 2008). A higher cell growth results from higher pH, however increasing by-products formation; while under a pH of 6.0, bacterial growth is limited maybe due to an increase of cell maintenance requirements (Lee et al. 2002). Many researches indicate that as cells cease to ferment glucose, pH decreases and the major product formed is succinate (Isar et al. 2006) as a dissociated molecule, unfortunately referring to its pKa values, which are 4.20 and 5.61, and leading to the main problem of most downstream separation methods that entail the undissociated form of SA (Carvalho 2015). During fermentation, formic and acetic acids are produced as well as succinic acid. It is therefore necessary to regulate the pH by the addition of alkaline solution to stand the process at its optimal pH and hence leading to the equivalent salt succinate. Otherwise, cell flocculation occurs and the osmolarity is affected; cell productivity is dwindled as energy is consumed for cell maintenance (Liu et al. 2008). Another bottleneck in fermentation processes is that when more energy is required to maintain cells. Production increases and hence product inhibition takes place, leading to the cessation of cell growth and synthesis (Kim et al. 2009). Another

limitation occurs in the media when the end product becomes toxic for cell due to its accumulation such as in the fermentation of carvone from carveol (L.E. Morrish et al. 2008). The inhibition of the end product is considered as a limitation in SA production using *A. succinogenes* 130Z, as shown in some studies (E Urbance et al. 2004; Lin et al. 2008; Yan et al. 2014). The target suggested by the US Department of Energy (2.5 g/L·h) is not reachable yet, since the highest productivity seen from this organism is around 1.7 g/L.h in batch mode (Werpy and Petersen 2004; Alcantara et al. 2017). More recently, the continuous and repeat-batch biofilm fermentation of *A. succinogenes* 130Z made it possible for a significant increase in succinic acid productivity to take place (22 g/L.h) (Ferone et al. 2018). By solving the inhibition of the end product, it increased the production of SA. The formation of by-products has a similar effect to the inhibition of the product. Indeed, it prohibits the product formation at high concentrations, as is the case in SA fermentation; by-products, mainly formate and acetate, can minimize SA production by taking away the carbon dedicated to the main product, decreasing its yield and affecting downstream process (Lee et al. 2001; Xu et al. 2016a). A study carried out in 2008 (Lin et al. 2008) revealed that formic acid is the most important inhibitor of both, cell growth and SA production. One solution could be the application of genetic engineering. Indeed, specific genes are expressed, enabling to reduce or eliminate unwanted products. However, the idea of altering organisms can result in decreasing growth and production rates, as it has been shown in the case of genetically engineered *E. coli* (Ma et al. 2010; Thakker et al. 2013). Because of these limitations, the applications of these genetically modified strains in fermentation at large-scale are not feasible. Taking into consideration substrate concentration levels, neither a high concentrations of glucose (over 100 g/L), nor a low one (20 g/L) could lead to high cell growth and succinate production (Lee et al. 2017). Many studies were achieved on optimal substrate and its concentration showing that the optimal initial concentration of glucose as substrate was between 50 g/L and 60 g/L (Lin et al. 2008). To ensure that there is an optimum production of such substrate, fermentation should be monitored steadily; knowing that with time, the concentration of glucose decreases and should be renewed, this situation creates a challenge. Some studies reveal that there is an increase of the production of succinic acid, even if they worked with a constant glucose concentration, showing that the monitoring of glucose at constant concentration is not a crucial issue. Actually, SA production from butane remains still economically efficient and can compete with these

fermentation technologies (Li and Xing 2017a). Another challenge rises concerning the fermentation cost and the budget dedicated for the improvement of the considered process as declared by the US DOE (Werpy. A et al. 2004). To be competitive with petrochemical production, a target productivity should be 2.5 g/L·h or more. Downstream process also stands as the largest expense in SA production (can account for up to 60% to 70%) and considered as a major area for improvement (Carvalho et al. 2016).

Challenges and future perspectives of SA production by *A. succinogenes*

The rumen bacterium *A. succinogenes* possesses various significant advantageous features for SA biosynthesis, however, fermentative production remains restricted at laboratory scale. As discussed above, several attempts have been executed to mitigate some of the challenges, however, they are not sufficiently enough to have a credible process for the production of SA. To date, there is no commercial production of SA by *A. succinogenes* at industrial scale. Industrially, limiting factors for production of SA using *A. succinogenes* begin from upstream to downstream processing steps. The major challenges are byproduct formation and accumulation, product inhibition, NADH limitation and poverty of efficient genetic tools. These problems are related to one another as they have cumulatively effect on downstream processing, medium cost, and SA yield. Typically, the accumulation of products and by-product results in product inhibition and by which impact substrate consumption and biomass formation (Lin et al. 2008), makes complication in the downstream process, subsequently. As reported by (Guarnieri et al. 2017), attempt to delete by-product formation pathways and to overexpress of pathways leading to SA production could not improve the production of SA and could not eliminate completely by-products. This might be referring to the disruption of energy generating C3 pathway that affects biomass and SA yield. Therefore, knockout strategies should be performed with different energy compensation mechanisms (NADH and ATP). SA fermentation using carbohydrate substrates is possible in microorganisms that contains a complete TCA cycle or a glyoxylate shunt (Bradfield and Nicol 2016a), as they produce SA in NADH limited conditions. Therefore, the coupling of a such engineered pathways with the knockout of by-products formation pathways could lead to a powerful fermentation as a results. As concluding remark, the final goal of overcoming all these challenges is to upgrade a competitive industrial bio-based process for SA production. Apparently, the key to achieve this

successful goal is relying on strain improvement via genetic and metabolic engineering. The powerful technologies of genetics tools such as CRISPR/Cas9 along with other genome-editing tools will assist to ease the current challenges. In addition, the utilisation of a bioelectrochemical system (insert of an electrode into the reactors) could also enhance the production of succinic acid in electro-fermentation process. With the recent developments in electro-fermentation technology, succinic acid production using various electrodes seems to be a new attractive option. Finally, the efforts that have been in this field gives the chance in the future to industrialize SA production using *A. succinogenes*.

SA downstream separation methods

SA production can be divided in two key steps; fermentation of substrate (carbohydrates) into SA and its recuperation (Thuy et al. 2017). As mentioned before, as an input, SA is required in its non-dissociated form, and this where expenses took place (Efe et al. 2013). The major challenge posed in the overall process is the step of separation and purification due to the problems with fermentation mentioned above. However, it is the major way to enhance the process from an economic point of view (Khunnonkwao et al. 2018). Till now, no single approach meets all requirements (product recovery, concentration, acidification and purification) to get SA from succinate in the fermentation media (Bekatorou et al. 2016; Prochaska et al. 2018). Up to now, there are few methods converting the dissociated form of succinate to its undissociated form, removing impurities and increasing product purity, that are used at the laboratory scale, including ion exchange, reactive extraction, electrodialysis, crystallization and nanofiltration (Figure 4) (Alexandri et al. 2019).

Currently, extraction including liquid-liquid extraction, reactive extraction, salting-out extraction, ionic liquids/salts extraction and sugaring-out extraction are evaluated to recuperate SA from the fermentation broth media (Sun et al. 2019). Based on pKa values, amine-based extraction is a promising method that separates organic acids, as it removes undissociated acids in-situ at mild conditions; thus, in this method, no pre-treatment is needed to act properly (Cheng et al. 2012). Previous studies have shown that the reactive extraction of succinate when using tri-n-octylamine (ToA) extracts SA very efficiently and appears as an excellent separation method. However, complications remain to be solved before this method can be adopted. Only

undissociated acids can be extracted using ToA; it is toxic to cells, affecting that way biomass and products formation. However, ToA is sensitive to pH fluctuation; so when pH increases, there is a decline of ToA uptake. Consequently, pH should be kept low to make sure that acid is removed from the solution. However, there is no selectivity and acetic acid is removed first; and hence an extra processing of fermentation broth is needed after the removal of acetic acid. It is therefore considered as a pre-treatment step more than a process for SA removal from media (Antony and Wasewar 2018). Other methods of downstream extraction and separation of SA need to be inspected. An additional step was evolved to separate and purify SA, such as crystallization and vacuum distillation, since that by-product has been eliminated, making it simpler and reaching a 99.8% final purity (Li et al. 2016b).

Ion-exchange technology using resins have been demonstrated to be promising technology when used to recuperate from supernatant, lactic acid without altering the pH of the system (Luongo et al. 2018). It involves the captures of cations with an ionic resin; a cationic resin is used to capture lactate. (Chen et al. 2017a) suggested to use this method with SA as a prior step to crystallization. Nevertheless, few publications discuss the purification of SA using ion-exchange resins. According to Chen et al. (2017 a), the use of highly acidic followed by a weak basic ion exchange resin, can eliminate impurities, cations and anions, enabling a purified flow with very low concentrations of sulphate, nitrogenous and impurities. However, ion exchange resins process requires an additional purification step to remove cells and acid due to the low selectivity of the resins.

(Glassner et al. 1995) suggest to use electrodialysis, a process involving an electric potential difference incorporated with membranes to separate molecules that are anionic or weakly ionic from those that are ionized. In the fermentation broth, electrodialysis targets the succinate ion in its dissociated form, and leaving behind other components either non-ionic or very weakly ionic, such as proteins, amino acids and carbohydrates. When fermentation occurs, through the electrodialysis system, liquid from the reactor could be run, the succinate ions are removed and the residual fluid including cells can be recycled back into the bioreactor (Fu et al. 2014). Electrodialysis could be combined with other separation methods as stated by (Szczygiel et al. 2017). Electrodialysis is a method having a significant potential, with some glaring shortcomings in this system in industrial scale. One of the main electrodialysis bottlenecks is

the energy requirement, which seems to be a bit counterintuitive to use since the SA production in fermentation goal as an eco-environmentally friendly process, was to reduce and substitute fossil fuels relying on non-renewable resources (Bunani et al. 2017). Also, electrodialysis selectivity raises an issue because acetate residues still remain in succinate stream and should be removed for a high purity of the SA product.

Another separation process suggested by (Glassner et al. 1995) is precipitating SA out of solution. After the completion of fermentation, solids are centrifuged and separated from broth; then broth is processed with calcium hydroxide, creating a solid that precipitates out of solution, calcium succinate which is removed from broth and washed with reverse osmosis (RO) water (Cheng et al. 2012). The commonly and simplest method for SA separation is precipitation; however, it is the most inefficient from an eco-environmental standpoint. As an example, the pH of the system is neutralized and buffered in fermentation by supplying chemicals such as calcium hydroxide, and to recuperate SA, large amounts of sulphuric acid are added to the solution, creating SA from calcium succinate, which needs to be washed by a huge quantity of water (raising an environmental issue and making precipitation as an unwanted choice for SA separation); an acidification step to remove contaminants slurry and solid waste and producing calcium sulphate, makes this process expensive and unfit for commercial applications (Salvachúa et al. 2016b).

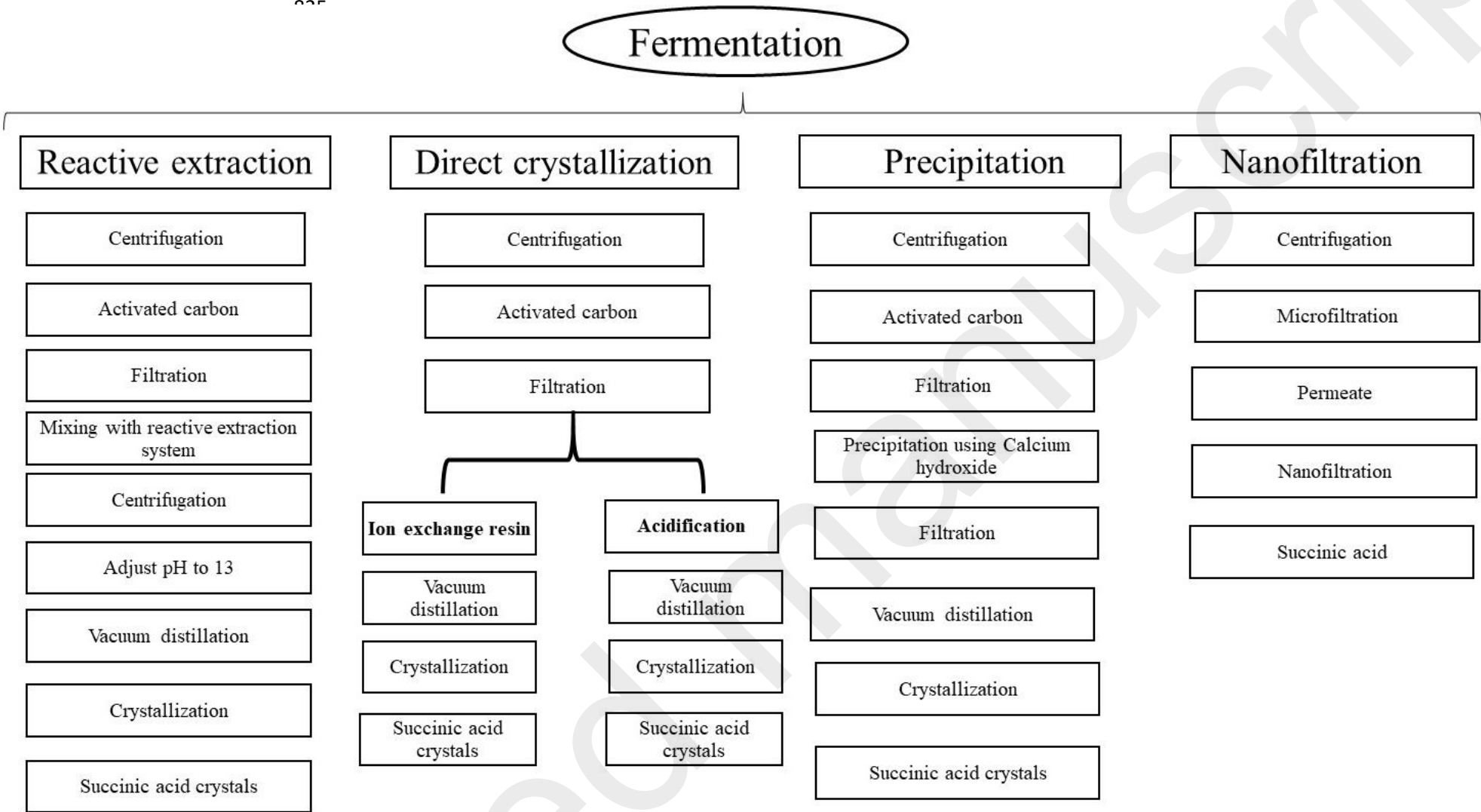
A relatively recent development in the separation process is nanofiltration, a new method for separating out the different byproducts of the fermentation broth from succinate. A study carried out by (Kang and Chang 2005) shows how nanofiltration membranes can separate succinate, formate and acetate; the products of glucose fermentation by *A. succinogenes* 130Z. First, tests on individual components were completed, with increasing components up to a quaternary ion solution, and highest retention of succinate was seen in final test. Nanofiltration is a promising method, but still there are some issues that are not addressed, like the prices of membranes, the membrane fouling and the separation method application in real fermented broth (Thuy and Boontawan 2017; Law and Wahab Mohammad 2017).

Each of these five separation processes have a positive side which can be composed of integrating steps for a higher SA recovery rather than individual methods. However, some defects remain, requiring a new process to resolve the issue mentioned above. A perfect process

821 should prevent cells destruction, could be done in-situ and requires a minimal chemicals
822 supplement.

Accepted manuscript

823
824
825



844
845
846

Figure 4. Representative downstream separation process for succinic acid purification

847

848 **Conclusions**

849 At present, platform chemicals are mainly produced from petroleum-based raw materials and
850 they have an undeniable commercial importance. However, with the decline of these resources
851 and the looming dangers of dramatic CO₂ emissions, the sustainable production of platform
852 chemicals using biomass-based feedstocks is becoming inevitable. In this context, present
853 questions on the design of platform molecules are discussed in this survey review. The
854 screening of bio platform molecules, native and mutant microorganisms, integrated upstream
855 and downstream processing technology are the major areas of platform chemicals discussed in
856 the literature, that also need further research. A future perspective to control redox potential
857 fermentation profiles is attractive, using genetically modified strains featuring tailor-made
858 redox potential balance, that is subjected to tight regulation through a precise redox potential
859 level. At different levels of redox potentials, metabolic flux profiles will be quantified to locate
860 potential bottlenecks for strain improvement and to reach a maximum production of various
861 desired metabolites. Succinic acid production using electro-fermentation process is a new
862 attractive option that should be addressed in the future.

863 **Acknowledgment**

864 The authors would like to thank the municipality of Bebnine, North-Lebanon for financial
865 support through the Education Program of Lebanese students. The authors thank Marie-Anne
866 Hairan (UniLasalle-EME) for her critical reading of the manuscript and helpful comments for
867 improving the English.

868

References

- A. Glassner D, Elankovan P, R. Beacom D, Berglund K (1995) Purification process for succinic acid produced by fermentation. *Appl Biochem Biotechnol* 51–52:73–82
- Aeschelmann F, Carus M (2015) Biobased Building Blocks and Polymers in the World: Capacities, Production, and Applications–Status Quo and Trends Towards 2020. *Ind Biotechnol* 11:154–159. <https://doi.org/10.1089/ind.2015.28999.fae>
- Ahn JH, Jang Y-S, Lee SY (2016) Production of succinic acid by metabolically engineered microorganisms. *Curr Opin Biotechnol* 42:54–66. <https://doi.org/10.1016/j.copbio.2016.02.034>
- Ahuja K, Singh S (2018) Glycerol Market Trends Analysis 2018-2024 World Industry Report. <https://www.gminsights.com/industry-analysis/glycerol-market-size>. Accessed 25 Jun 2019
- Albuquerque TL de, da Silva IJ, de Macedo GR, Rocha MVP (2014) Biotechnological production of xylitol from lignocellulosic wastes: A review. *Process Biochem* 49:1779–1789. <https://doi.org/10.1016/j.procbio.2014.07.010>
- Alcantara J, Mondala A, Hughey L, Shield shaun (2017) Direct Succinic Acid Production from Minimally Pretreated Biomass Using Sequential Solid-State and Slurry Fermentation with Mixed Fungal Cultures
- Alexandri M, Vlysidis A, Papapostolou H, et al (2019) Downstream separation and purification of succinic acid from fermentation broths using spent sulphite liquor as feedstock. *Sep Purif Technol* 209:666–675. <https://doi.org/10.1016/j.seppur.2018.08.061>
- Almqvist H, Pateraki C, Alexandri M, et al (2016) Succinic acid production by *Actinobacillus succinogenes* from batch fermentation of mixed sugars. *J Ind Microbiol Biotechnol* 43:1117–1130. <https://doi.org/10.1007/s10295-016-1787-x>
- Amarasinghe H, Weerakkody NS, Waisundara VY (2018) Evaluation of physicochemical properties and antioxidant activities of kombucha “Tea Fungus” during extended periods of fermentation. *Food Sci Nutr* 6:659–665. <https://doi.org/10.1002/fsn3.605>

- 894 Ambat I, Srivastava V, Sillanpää M (2018) Recent advancement in biodiesel production methodologies
895 using various feedstock: A review. *Renew Sustain Energy Rev* 90:356–369.
896 <https://doi.org/10.1016/j.rser.2018.03.069>
- 897 Andreev N, Ronteltap M, Boincean B, Lens PNL (2018) Lactic acid fermentation of human excreta for
898 agricultural application. *J Environ Manage* 206:890–900.
899 <https://doi.org/10.1016/j.jenvman.2017.11.072>
- 900 Andruleit H, Babies HG, Fleig S, et al (2016) Reserves, Resources and Availability of Energy Resources
- 901 Antony FM, Wasewar KL (2018) Reactive separation of protocatechuic acid using Tri-n-octyl amine
902 and Di-(2-ethylhexyl) phosphoric acid in Methyl isobutyl ketone. *Sep Purif Technol* 207:99–
903 107. <https://doi.org/10.1016/j.seppur.2018.06.037>
- 904 Aponte M, Blaiotta G (2016) Potential Role of Yeast Strains Isolated from Grapes in the Production of
905 Taurasi DOCG. *Front Microbiol* 7:. <https://doi.org/10.3389/fmicb.2016.00809>
- 906 Appiah-Nkansah NB, Zhang K, Rooney W, Wang D (2018) Ethanol production from mixtures of sweet
907 sorghum juice and sorghum starch using very high gravity fermentation with urea
908 supplementation. *Ind Crops Prod* 111:247–253. <https://doi.org/10.1016/j.indcrop.2017.10.028>
- 909 Aresta M (2010) Carbon Dioxide as Chemical Feedstock
- 910 Arikawa Y, Kuroyanagi T, Shimosaka M, et al (1999) Effect of gene disruptions of the TCA cycle on
911 production of succinic acid in *Saccharomyces cerevisiae*. *J Biosci Bioeng* 87:28–36
- 912 Armaroli N, Vincenzo B (2010) Energy for a Sustainable World: From the Oil Age to a Sun-Powered
913 Future
- 914 Armstrong RD, Kariuki BM, Knight DW, Hutchings GJ (2017) How to Synthesise High Purity,
915 Crystalline d-Glucaric Acid Selectively. *Eur J Org Chem* 2017:6811–6814.
916 <https://doi.org/10.1002/ejoc.201701343>
- 917 Asmadi M, Kawamoto H, Saka S (2011) Thermal reactions of guaiacol and syringol as lignin model
918 aromatic nuclei. *J Anal Appl Pyrolysis* 92:88–98. <https://doi.org/10.1016/j.jaap.2011.04.011>
- 919 Bazaes S, Toncio M, Laivenieks M, et al (2007) Comparative kinetic effects of Mn (II), Mg (II) and the
920 ATP/ADP ratio on phosphoenolpyruvate carboxykinases from *Anaerobiospirillum*

921 *succiniciproducens* and *Saccharomyces cerevisiae*. Protein J 26:265–269.
 922 <https://doi.org/10.1007/s10930-006-9068-6>

923 Becker J, Reinefeld J, Stellmacher R, et al (2013) Systems-wide analysis and engineering of metabolic
 924 pathway fluxes in bio-succinate producing *Basfia succiniciproducens*. Biotechnol Bioeng
 925 110:3013–3023. <https://doi.org/10.1002/bit.24963>

926 Bekatorou A, Dima A, Tsafrakidou P, et al (2016) Downstream extraction process development for
 927 recovery of organic acids from a fermentation broth. Bioresour Technol 220:34–37.
 928 <https://doi.org/10.1016/j.biortech.2016.08.039>

929 Biddy MJ, Scarlata C, Kinchin C (2007) Chemicals from Biomass: A Market Assessment of Bioproducts
 930 with Near-Term Potential

931 Borges ER, Pereira N (2011) Succinic acid production from sugarcane bagasse hemicellulose
 932 hydrolysate by *Actinobacillus succinogenes*. J Ind Microbiol Biotechnol 38:1001–1011.
 933 <https://doi.org/10.1007/s10295-010-0874-7>

934 Bradfield MFA, Mohagheghi A, Salvachúa D, et al (2015) Continuous succinic acid production by
 935 *Actinobacillus succinogenes* on xylose-enriched hydrolysate. Biotechnol Biofuels 8:.
 936 <https://doi.org/10.1186/s13068-015-0363-3>

937 Brink HG, Nicol W (2014a) Succinic acid production with *Actinobacillus succinogenes*: rate and yield
 938 analysis of chemostat and biofilm cultures. Microb Cell Factories 13:111.
 939 <https://doi.org/10.1186/s12934-014-0111-6>

940 Brink HG, Nicol W (2014b) Succinic acid production with *Actinobacillus succinogenes*: rate and yield
 941 analysis of chemostat and biofilm cultures. Microb Cell Factories 13:.
 942 <https://doi.org/10.1186/s12934-014-0111-6>

943 Brodin I, Sjöholm E, Gellerstedt G (2010) The behavior of kraft lignin during thermal treatment. J Anal
 944 Appl Pyrolysis 87:70–77. <https://doi.org/10.1016/j.jaap.2009.10.005>

945 Brüscheiler BJ, Merlot C (2017) Azo dyes in clothing textiles can be cleaved into a series of mutagenic
 946 aromatic amines which are not regulated yet. Regul Toxicol Pharmacol 88:214–226.
 947 <https://doi.org/10.1016/j.yrtph.2017.06.012>

- 948 Bunani S, Yoshizuka K, Nishihama S, et al (2017) Application of bipolar membrane electrodialysis
949 (BMED) for simultaneous separation and recovery of boron and lithium from aqueous solutions.
950 Desalination 424:37–44. <https://doi.org/10.1016/j.desal.2017.09.029>
- 951 Carvalho M (2015) Bioproduction of succinic acid from renewable feedstocks by *Actinobacillus*
952 *succinogenes* 130Z
- 953 Carvalho M, Roca C, Reis MAM (2014) Carob pod water extracts as feedstock for succinic acid
954 production by *Actinobacillus succinogenes* 130Z. Bioresour Technol 170:491–498.
955 <https://doi.org/10.1016/j.biortech.2014.07.117>
- 956 Carvalho M, Roca C, Reis MAM (2016) Improving succinic acid production by *Actinobacillus*
957 *succinogenes* from raw industrial carob pods. Bioresour Technol 218:491–497.
958 <https://doi.org/10.1016/j.biortech.2016.06.140>
- 959 Chen K, Hao S, Lyu H, et al (2017a) Ion exchange separation for recovery of monosaccharides, organic
960 acids and phenolic compounds from hydrolysates of lignocellulosic biomass. Sep Purif Technol
961 172:100–106. <https://doi.org/10.1016/j.seppur.2016.08.004>
- 962 Chen SS, Yu IKM, Tsang DCW, et al (2017b) Valorization of cellulosic food waste into levulinic acid
963 catalyzed by heterogeneous Brønsted acids: Temperature and solvent effects. Chem Eng J
964 327:328–335. <https://doi.org/10.1016/j.cej.2017.06.108>
- 965 Chen W-M, Ding Y-J, Jiang D-H, et al (2006) A selective synthesis of acetic acid from syngas over a
966 novel Rh nanoparticles/nanosized SiO₂ catalysts. Catal Commun 7:559–562.
967 <https://doi.org/10.1016/j.catcom.2006.01.018>
- 968 Chen X, Jiang S, Zheng Z, et al (2012) Effects of culture redox potential on succinic acid production by
969 *Corynebacterium crenatum* under anaerobic conditions. Process Biochem 47:1250–1255.
970 <https://doi.org/10.1016/j.procbio.2012.04.026>
- 971 Chen Z, Huang J, Wu Y, et al (2017c) Metabolic engineering of *Corynebacterium glutamicum* for the
972 production of 3-hydroxypropionic acid from glucose and xylose. Metab Eng 39:151–158.
973 <https://doi.org/10.1016/j.ymben.2016.11.009>

974 Cheng K-K, Wang G-Y, Zeng J, Zhang J-A (2013) Improved Succinate Production by Metabolic
 975 Engineering. In: BioMed Res. Int. <https://www.hindawi.com/journals/bmri/2013/538790/>.
 976 Accessed 28 Jan 2019

977 Cheng K-K, Zhao X-B, Zeng J, et al (2012) Downstream processing of biotechnological produced
 978 succinic acid. Appl Microbiol Biotechnol 95:841–850. [https://doi.org/10.1007/s00253-012-](https://doi.org/10.1007/s00253-012-4214-x)
 979 4214-x

980 Chua YW, Yu Y, Wu H (2017) Thermal decomposition of pyrolytic lignin under inert conditions at low
 981 temperatures. Fuel 200:70–75. <https://doi.org/10.1016/j.fuel.2017.03.035>

982 Cimini D, Argenzio O, D'Ambrosio S, et al (2016) Production of succinic acid from *Basfia*
 983 *succiniciproducens* up to the pilot scale from Arundo donax hydrolysate. Bioresour Technol
 984 222:355–360. <https://doi.org/10.1016/j.biortech.2016.10.004>

985 Clark DP (1989) The fermentation pathways of Escherichia coli. FEMS Microbiol Lett 63:223–234.
 986 [https://doi.org/10.1016/0378-1097\(89\)90132-8](https://doi.org/10.1016/0378-1097(89)90132-8)

987 Collias DI, Harris AM, Nagpal V, et al (2014) Biobased Terephthalic Acid Technologies: A Literature
 988 Review. Ind Biotechnol 10:91–105. <https://doi.org/10.1089/ind.2014.0002>

989 Collinson SR, Thielemans W (2010) The catalytic oxidation of biomass to new materials focusing on
 990 starch, cellulose and lignin. Coord Chem Rev 254:1854–1870.
 991 <https://doi.org/10.1016/j.ccr.2010.04.007>

992 Contreras-andrade I, Martínez-González M, Figueroa Casallas L, et al (2014) Modeling of Liquid-
 993 Liquid Extraction Process for Glycerol Purification from Biodiesel Production. J Chem Chem
 994 Eng 8:971–977. <https://doi.org/10.17265/1934-7375/2014.10.006>

995 Corona-González RI, Bories A, González-Álvarez V, Pelayo-Ortiz C (2008) Kinetic study of succinic
 996 acid production by *Actinobacillus succinogenes* ZT-130. Process Biochem 43:1047–1053.
 997 <https://doi.org/10.1016/j.procbio.2008.05.011>

998 Daorattanachai P, Namuangruk S, Viriya-empikul N, et al (2012) 5-Hydroxymethylfurfural production
 999 from sugars and cellulose in acid- and base-catalyzed conditions under hot compressed water. J
 1000 Ind Eng Chem 18:1893–1901. <https://doi.org/10.1016/j.jiec.2012.04.019>

1001 Das BK, Kalita P, Chakraborty M (2016a) Chapter 21 - Integrated Biorefinery for Food, Feed, and
1002 Platform Chemicals. In: Brar SK, Sarma SJ, Pakshirajan K (eds) Platform Chemical
1003 Biorefinery. Elsevier, Amsterdam, pp 393–416

1004 Das RK, Brar SK, Verma M (2016b) Potential use of pulp and paper solid waste for the bio-production
1005 of fumaric acid through submerged and solid state fermentation. J Clean Prod 112:4435–4444.
1006 <https://doi.org/10.1016/j.jclepro.2015.08.108>

1007 David H, Akesson M, Nielsen J (2003) Reconstruction of the central carbon metabolism of *Aspergillus*
1008 *niger*. Eur J Biochem 270:4243–4253

1009 Davis sean (2011) Chemical Economics Handbook Product Review: Petrochemical Industry Overview.
1010 SRI Consulting, Englewood, CO, USA.

1011 de Fouchécour F, Sánchez-Castañeda A-K, Saulou-Bérion C, Spinnler HÉ (2018) Process engineering
1012 for microbial production of 3-hydroxypropionic acid. Biotechnol Adv 36:1207–1222.
1013 <https://doi.org/10.1016/j.biotechadv.2018.03.020>

1014 Delgado Arcaño Y, Valmaña García OD, Mandelli D, et al (2018) Xylitol: A review on the progress and
1015 challenges of its production by chemical route. Catal Today.
1016 <https://doi.org/10.1016/j.cattod.2018.07.060>

1017 Deng W, Wang Y, Zhang S, et al (2018) Catalytic amino acid production from biomass-derived
1018 intermediates. Proc Natl Acad Sci U S A 115:5093–5098.
1019 <https://doi.org/10.1073/pnas.1800272115>

1020 D’Este M, Alvarado-Morales M, Angelidaki I (2018) Amino acids production focusing on fermentation
1021 technologies – A review. Biotechnol Adv 36:14–25.
1022 <https://doi.org/10.1016/j.biotechadv.2017.09.001>

1023 Dezam APG, Vasconcellos VM, Lacava PT, Farinas CS (2017) Microbial production of organic acids
1024 by endophytic fungi. Biocatal Agric Biotechnol 11:282–287.
1025 <https://doi.org/10.1016/j.bcab.2017.08.001>

1026 Dhamankar HH (2013) Microbial synthesis of 3,4-dihydroxybutyric acid, 3-hydroxybutyrolactone and
1027 other 3-hydroxyalkanoic acids. Thesis, Massachusetts Institute of Technology

- 1028 Dilcher J-P, Jürgens H, Luinstra GA (2015) Sequential Post-modifications of Polybutadiene for
1029 Industrial Applications. In: Theato P (ed) Multi-Component and Sequential Reactions in
1030 Polymer Synthesis. Springer International Publishing, Cham, pp 163–201
- 1031 Du Z, Mo J, Zhang Y, Xu Q (2014) Benzene, toluene and xylenes in newly renovated homes and
1032 associated health risk in Guangzhou, China. *Build Environ* 72:75–81.
1033 <https://doi.org/10.1016/j.buildenv.2013.10.013>
- 1034 Duan B, Huang Y, Lu A, Zhang L (2018a) Recent advances in chitin based materials constructed via
1035 physical methods. *Prog Polym Sci* 82:1–33.
1036 <https://doi.org/10.1016/j.progpolymsci.2018.04.001>
- 1037 Duan D, Ruan R, Wang Y, et al (2018b) Microwave-assisted acid pretreatment of alkali lignin: Effect
1038 on characteristics and pyrolysis behavior. *Bioresour Technol* 251:57–62.
1039 <https://doi.org/10.1016/j.biortech.2017.12.022>
- 1040 E Urbance S, Pometto III A, Dispirito A, Denli Y (2004) Evaluation of succinic acid continuous and
1041 repeat-batch biofilm fermentation by *Actinobacillus succinogenes* using plastic composite
1042 support bioreactors. *Appl Microbiol Biotechnol* 65:664–70
- 1043 Eckert C, Ragauskas A, Hallett J, et al (2007) Tunable solvents for fine chemicals from the biorefinery.
1044 *Green Chem - GREEN CHEM* 9:
- 1045 Efe Ç, Wielen LAM van der, Straathof AJJ (2013) Techno-economic analysis of succinic acid
1046 production using adsorption from fermentation medium. *Biomass Bioenergy* 56:479–492
- 1047 E. Heim L, Konnerth H, G. Precht MH (2017) Future perspectives for formaldehyde: pathways for
1048 reductive synthesis and energy storage. *Green Chem* 19:2347–2355.
1049 <https://doi.org/10.1039/C6GC03093A>
- 1050 Ennaert T, Schutyser W, Dijkmans J, et al (2016) Chapter 9 - Conversion of Biomass to Chemicals:
1051 The Catalytic Role of Zeolites. In: Sels BF, Kustov LM (eds) *Zeolites and Zeolite-Like*
1052 *Materials*. Elsevier, Amsterdam, pp 371–431
- 1053 Fang Z, Jr RLS, Qi X (2017) *Production of Platform Chemicals from Sustainable Resources*. Springer

- 1054 Ferone M, Raganati F, Ercole A, et al (2018) Continuous succinic acid fermentation by *Actinobacillus*
 1055 *succinogenes* in a packed-bed biofilm reactor. *Biotechnol Biofuels* 11:.
 1056 <https://doi.org/10.1186/s13068-018-1143-7>
- 1057 Ferone M, Raganati F, Olivieri G, et al (2017) Biosuccinic Acid from Lignocellulosic-Based Hexoses
 1058 and Pentoses by *Actinobacillus succinogenes*: Characterization of the Conversion Process. *Appl*
 1059 *Biochem Biotechnol*. <https://doi.org/10.1007/s12010-017-2514-4>
- 1060 Fu L, Gao X, Yang Y, et al (2014) Preparation of succinic acid using bipolar membrane electrodialysis.
 1061 *Sep Purif Technol* 127:212–218. <https://doi.org/10.1016/j.seppur.2014.02.028>
- 1062 Furtwengler P, Avérous L (2018) From D-sorbitol to five-membered bis(cyclo-carbonate) as a platform
 1063 molecule for the synthesis of different original biobased chemicals and polymers. *Sci Rep*
 1064 8:9134. <https://doi.org/10.1038/s41598-018-27450-w>
- 1065 Gallagher L (2012) Global Chemicals Outlook Towards Sound Management of Chemicals
- 1066 Ge X, Chang C, Zhang L, et al (2018) Chapter Five - Conversion of Lignocellulosic Biomass Into
 1067 Platform Chemicals for Biobased Polyurethane Application. In: Li Y, Ge X (eds) *Advances in*
 1068 *Bioenergy*. Elsevier, pp 161–213
- 1069 Girisuta B, Heeres HJ (2017) Levulinic Acid from Biomass: Synthesis and Applications. In: Fang Z,
 1070 Smith Jr Richard L, Qi X (eds) *Production of Platform Chemicals from Sustainable Resources*.
 1071 Springer Singapore, Singapore, pp 143–169
- 1072 Gotro J, Humphreys R (2016) Introduction to Biopolymers and Bioplastics
- 1073 Graaf MJVD, Vallianpoer F, Fiey G, et al (2012) Process for the crystallization of succinic acid
- 1074 Guarnieri MT, Chou Y-C, Salvachúa D, et al (2017) Metabolic Engineering of *Actinobacillus*
 1075 *succinogenes* Provides Insights into Succinic Acid Biosynthesis. *Appl Environ Microbiol*
 1076 83:e00996-17. <https://doi.org/10.1128/AEM.00996-17>
- 1077 Guettler MV, Jain MK, Rumler D (1996) Method for making succinic acid, bacterial variants for use in
 1078 the process, and methods for obtaining variants

1079 Guettler MV, Rumler D, Jain MK (1999) *Actinobacillus succinogenes* sp. nov., a novel succinic-acid-
1080 producing strain from the bovine rumen. *Int J Syst Bacteriol* 49 Pt 1:207–216.
1081 <https://doi.org/10.1099/00207713-49-1-207>

1082 Guo NN, Zhang QG, Li HM, et al (2014) Facile Fabrication, Structure, and Applications of Polyvinyl
1083 Chloride Mesoporous Membranes. *Ind Eng Chem Res* 53:20068–20073.
1084 <https://doi.org/10.1021/ie503986h>

1085 He X, Yin J, Liu J, et al (2018) Characteristics of acidogenic fermentation for volatile fatty acid
1086 production from food waste at high concentrations of NaCl. *Bioresour Technol*.
1087 <https://doi.org/10.1016/j.biortech.2018.09.116>

1088 Herselman J, Bradfield MFA, Vijayan U, Nicol W (2017) The effect of carbon dioxide availability on
1089 succinic acid production with biofilms of *Actinobacillus succinogenes*. *Biochem Eng J*
1090 117:218–225. <https://doi.org/10.1016/j.bej.2016.10.018>

1091 H. Isikgor F, Remzi Becer C (2015) Lignocellulosic biomass: a sustainable platform for the production
1092 of bio-based chemicals and polymers. *Polym Chem* 6:4497–4559.
1093 <https://doi.org/10.1039/C5PY00263J>

1094 Ho VTT, Fleet GH, Zhao J (2018) Unravelling the contribution of lactic acid bacteria and acetic acid
1095 bacteria to cocoa fermentation using inoculated organisms. *Int J Food Microbiol* 279:43–56.
1096 <https://doi.org/10.1016/j.ijfoodmicro.2018.04.040>

1097 Humans IWG on the E of CR to (2008) Ethylene Oxide. International Agency for Research on Cancer

1098 Inui M, Kawaguchi H, Murakami S, et al (2004) Metabolic engineering of *Corynebacterium glutamicum*
1099 for fuel ethanol production under oxygen-deprivation conditions. *J Mol Microbiol Biotechnol*
1100 8:243–254. <https://doi.org/10.1159/000086705>

1101 Isar J, Agarwal L, Saran S, et al (2006) Effect of process parameters on succinic acid production in
1102 *Escherichia coli* W3110 and enzymes involved in the reductive tricarboxylic acid cycle. *Can J*
1103 *Microbiol* 52:893–902

1104 Isikgor FH, Becer CR (2015) Lignocellulosic biomass: a sustainable platform for the production of bio-
1105 based chemicals and polymers. *Polym Chem* 6:4497–4559.
1106 <https://doi.org/10.1039/C5PY00263J>

- 1107 Jansen MLA, van Gulik WM (2014) Towards large scale fermentative production of succinic acid. *Curr*
1108 *Opin Biotechnol* 30:190–197
- 1109 Jiang M, Xu R, Xi Y-L, et al (2013) Succinic acid production from cellobiose by *Actinobacillus*
1110 *succinogenes*. *Biorefineries* 135:469–474. <https://doi.org/10.1016/j.biortech.2012.10.019>
- 1111 Jung I-Y, Lee J-W, Min W-K, et al (2015) Simultaneous conversion of glucose and xylose to 3-
1112 hydroxypropionic acid in engineered *Escherichia coli* by modulation of sugar transport and
1113 glycerol synthesis. *Bioresour Technol* 198:709–716.
1114 <https://doi.org/10.1016/j.biortech.2015.09.079>
- 1115 Kang SH, Chang YK (2005) Removal of organic acid salts from simulated fermentation broth containing
1116 succinate by nanofiltration. *J Membr Sci* 246:49–57.
1117 <https://doi.org/10.1016/j.memsci.2004.08.014>
- 1118 Kasirajan S, Ngouajio M (2012) Polyethylene and biodegradable mulches for agricultural applications:
1119 a review. *Agron Sustain Dev* 32:501–529. <https://doi.org/10.1007/s13593-011-0068-3>
- 1120 Keim W (2014) Fossil Feedstocks—What Comes After? In: Bertau M, Offermanns H, Plass L, et al. (eds)
1121 Methanol: The Basic Chemical and Energy Feedstock of the Future: Asinger's Vision Today.
1122 Springer Berlin Heidelberg, Berlin, Heidelberg, pp 23–37
- 1123 Ke-Ke Cheng, Xue-Bing Zhao, Jing Zeng and Jian-An Zhang (2012) Biotechnological production of
1124 succinic acid: current state and perspectives. *Biofuels Bioprod Bioref* 6:302–318
- 1125 Khunnonkwao P, Jantama K, Kanchanatawee S, et al (2018) A two steps membrane process for the
1126 recovery of succinic acid from fermentation broth. *Sep Purif Technol* 207:451–460.
1127 <https://doi.org/10.1016/j.seppur.2018.06.056>
- 1128 Kidwell H (2008) Bio-succinic acid to go commercial. In: -Pharmatechnologistcom. [https://www.in-](https://www.in-pharmatechnologist.com/Article/2008/01/24/Bio-succinic-acid-to-go-commercial)
1129 [pharmatechnologist.com/Article/2008/01/24/Bio-succinic-acid-to-go-commercial](https://www.in-pharmatechnologist.com/Article/2008/01/24/Bio-succinic-acid-to-go-commercial). Accessed 6
1130 Feb 2019
- 1131 Kim MI, Jong Kim N, Shang L, et al (2009) Continuous Production of Succinic Acid Using an External
1132 Membrane Cell Recycle System. *J Microbiol Biotechnol* 19:1369–73

- 1133 Kohli K, Prajapati R, Sharma BK (2019) Bio-Based Chemicals from Renewable Biomass for Integrated
1134 Biorefineries. *Energies* 12:233. <https://doi.org/10.3390/en12020233>
- 1135 Kracke F, Lai B, Yu S, Krömer JO (2018) Balancing cellular redox metabolism in microbial
1136 electrosynthesis and electro fermentation – A chance for metabolic engineering. *Metab Eng*
1137 45:109–120. <https://doi.org/10.1016/j.ymben.2017.12.003>
- 1138 Krishnakumar J (2013) Biological Production of Succinic Acid Using a Cull Peach Medium. 67
- 1139 Kumar V, Ashok S, Park S (2013) Recent advances in biological production of 3-hydroxypropionic
1140 acid. *Biotechnol Adv* 31:945–961. <https://doi.org/10.1016/j.biotechadv.2013.02.008>
- 1141 Lai YY, Yik KCH, Hau HP, et al (2017) Systematic decision making methodology for chemical product
1142 design in integrated biorefineries. In: Espuña A, Graells M, Puigjaner L (eds) 27th European
1143 Symposium on Computer Aided Process Engineering. Elsevier, pp 1771–1776
- 1144 Lammens TM, Franssen MCR, Scott EL, Sanders JPM (2012) Availability of protein-derived amino
1145 acids as feedstock for the production of bio-based chemicals. *Biomass Bioenergy* 44:168–181.
1146 <https://doi.org/10.1016/j.biombioe.2012.04.021>
- 1147 Langeveld H, Dixon J, F. Jaworski J (2010) Development Perspectives Of The Biobased Economy: A
1148 Review. *Crop Sci* S-1–S
- 1149 Law JY, Wahab Mohammad A (2017) Separation of Succinate from Organic Acid Salts Using
1150 Nanofiltration Membranes. *Chem Eng Trans* 56:1705–1710.
1151 <https://doi.org/10.3303/CET1756285>
- 1152 L.E. Morrish J, T Brennan E, C Dry H, Daugulis A (2008) Enhanced Bioproduction of Carvone in a
1153 Two-Liquid-Phase Partitioning Bioreactor With a Highly Hydrophobic Biocatalyst. *Biotechnol*
1154 *Bioeng* 101:768–75
- 1155 Lee G-E, Loveridge S, Joshi S (2017) Local acceptance and heterogeneous externalities of biorefineries.
1156 *Energy Econ* 67:328–336. <https://doi.org/10.1016/j.eneco.2017.08.013>
- 1157 Lee P, G Lee W, Lee S-Y, Chang H (2001) Succinic acid production with reduced by-product formation
1158 in the fermentation of *Anaerobiospirillum succiniciproducens* using glycerol as a carbon source.
1159 *Biotechnol Bioeng* 72:41–8

- 1160 Lee P, Lee S, Hong S, Chang H (2002) Isolation and characterization of a new succinic acid-producing
1161 bacterium, *Mannheimia succiniciproducens* MBEL55E, from bovine rumen. Appl Microbiol
1162 Biotechnol 58:663–668. <https://doi.org/10.1007/s00253-002-0935-6>
- 1163 Lee SJ, Song H, Lee SY (2006) Genome-based metabolic engineering of *Mannheimia*
1164 *succiniciproducens* for succinic acid production. Appl Environ Microbiol 72:1939–1948.
1165 <https://doi.org/10.1128/AEM.72.3.1939-1948.2006>
- 1166 Li J, Jiang M, Chen K, et al (2010a) Enhanced production of succinic acid by *Actinobacillus*
1167 *succinogenes* with reductive carbon source. Process Biochem 45:980–985
- 1168 Li J, Jiang M, Chen K-Q, et al (2010b) Effect of redox potential regulation on succinic acid production
1169 by *Actinobacillus succinogenes*. Bioprocess Biosyst Eng 33:911–920.
1170 <https://doi.org/10.1007/s00449-010-0414-x>
- 1171 Li J, Zhang W, Li X, et al (2018) Production of lactic acid from thermal pretreated food waste through
1172 the fermentation of waste activated sludge: Effects of substrate and thermal pretreatment
1173 temperature. Bioresour Technol 247:890–896. <https://doi.org/10.1016/j.biortech.2017.09.186>
- 1174 Li J, Zheng X-Y, Fang X-J, et al (2011) A complete industrial system for economical succinic acid
1175 production by *Actinobacillus succinogenes*. Bioresour Technol 102:6147–6152.
1176 <https://doi.org/10.1016/j.biortech.2011.02.093>
- 1177 Li Q, Wu H, Li Z, Ye Q (2016a) Enhanced succinate production from glycerol by engineered
1178 *Escherichia coli* strains. Bioresour Technol 218:217–223.
1179 <https://doi.org/10.1016/j.biortech.2016.06.090>
- 1180 Li Q, Xing J (2017a) Production of 1,4-Diacids (Succinic, Fumaric, and Malic) from Biomass. In: Fang
1181 Z, Smith RL Jr, Qi X (eds) Production of Platform Chemicals from Sustainable Resources.
1182 Springer Singapore, Singapore, pp 231–262
- 1183 Li Q, Xing J (2017b) Production of 1,4-Diacids (Succinic, Fumaric, and Malic) from Biomass. In: Fang
1184 Z, Smith Jr Richard L, Qi X (eds) Production of Platform Chemicals from Sustainable
1185 Resources. Springer Singapore, Singapore, pp 231–262

- 1186 Li Q-Z, Jiang X-L, Feng X-J, et al (2016b) Recovery Processes of Organic Acids from Fermentation
1187 Broths in the Biomass-Based Industry. J Microbiol Biotechnol 26:1–8.
1188 <https://doi.org/10.4014/jmb.1505.05049>
- 1189 Liang C, Hu Y, Wang Y, et al (2018) Production of levulinic acid from corn cob residue in a fed-batch
1190 acid hydrolysis process. Process Biochem 73:124–131.
1191 <https://doi.org/10.1016/j.procbio.2018.08.002>
- 1192 Lin H, Bennett GN, San K-Y (2005) Fed-batch culture of a metabolically engineered *Escherichia coli*
1193 strain designed for high-level succinate production and yield under aerobic conditions.
1194 Biotechnol Bioeng 90:775–779. <https://doi.org/10.1002/bit.20458>
- 1195 Lin SKC, Du C, Koutinas A, et al (2008) Substrate and product inhibition kinetics in succinic acid
1196 production by *Actinobacillus succinogenes*. Biochem Eng J 41:128–135.
1197 <https://doi.org/10.1016/j.bej.2008.03.013>
- 1198 Linga Venkateswar Rao, Goli JK, Gentela J, Koti S (2016) Bioconversion of lignocellulosic biomass to
1199 xylitol: An overview. Bioresour Technol 213:299–310.
1200 <https://doi.org/10.1016/j.biortech.2016.04.092>
- 1201 Liu C-G, Qin J-C, Lin Y-H (2017a) Fermentation and Redox Potential. In: Jozala AF (ed) Fermentation
1202 Processes. InTech
- 1203 Liu C-G, Xue C, Lin Y-H, Bai F-W (2013) Redox potential control and applications in microaerobic
1204 and anaerobic fermentations. Biotechnol Adv 31:257–265.
1205 <https://doi.org/10.1016/j.biotechadv.2012.11.005>
- 1206 Liu H, Hu H, Jin Y, et al (2017b) Co-fermentation of a mixture of glucose and xylose to fumaric acid
1207 by *Rhizopus arrhizus* RH 7-13-9#. Bioresour Technol 233:30–33.
1208 <https://doi.org/10.1016/j.biortech.2017.02.035>
- 1209 Liu L, Li Z, Hou W, Shen H (2018) Direct conversion of lignocellulose to levulinic acid catalyzed by
1210 ionic liquid. Carbohydr Polym 181:778–784. <https://doi.org/10.1016/j.carbpol.2017.11.078>
- 1211 Liu Y-P, Zheng P, Sun Z-H, et al (2008) Economical succinic acid production from cane molasses by
1212 *Actinobacillus succinogenes*. Bioresour Technol 99:1736–1742.
1213 <https://doi.org/10.1016/j.biortech.2007.03.044>

- 1214 Liu Yu-Peng, Zheng Pu, Sun Zhi-Hao, et al (2008) Strategies of pH control and glucose-fed batch
1215 fermentation for production of succinic acid by *Actinobacillus succinogenes* CGMCC1593. J
1216 Chem Technol Biotechnol 83:722–729. <https://doi.org/10.1002/jctb.1862>
- 1217 Long X, Wang Z, Wu S, et al (2014) Production of isophthalic acid from m-xylene oxidation under the
1218 catalysis of the H3PW12O40/carbon and cobalt catalytic system. J Ind Eng Chem 20:100–107.
1219 <https://doi.org/10.1016/j.jiec.2013.04.020>
- 1220 Louasté B, Eloutassi N (2020) Succinic acid production from whey and lactose by *Actinobacillus*
1221 *succinogenes* 130Z in batch fermentation. Biotechnol Rep e00481.
1222 <https://doi.org/10.1016/j.btre.2020.e00481>
- 1223 Luo Y, Li Z, Li X, et al (2018) The production of furfural directly from hemicellulose in lignocellulosic
1224 biomass: A review. Catal Today. <https://doi.org/10.1016/j.cattod.2018.06.042>
- 1225 Luongo G, Iadaresta F, Moccia E, et al (2016) Determination of aniline and quinoline compounds in
1226 textiles. J Chromatogr A 1471:11–18. <https://doi.org/10.1016/j.chroma.2016.09.068>
- 1227 Luongo V, Palma A, Eldon RR, Fontana A (2018) (PDF) Lactic acid recovery from a simplified mimic
1228 of *Thermotoga neapolitana* fermentation broth using ion exchange resins in batch and fixed-
1229 bed reactors. ResearchGate 17. <https://doi.org/10.1080/01496395.2018.1520727>
- 1230 Ma J-F, Jiang M, Chen K-Q, et al (2010) Succinic acid production with metabolically engineered *E. coli*
1231 recovered from two-stage fermentation. Biotechnol Lett 32:1413–1418.
1232 <https://doi.org/10.1007/s10529-010-0313-x>
- 1233 Magalhães Júnior AI, de Carvalho JC, Thoms JF, et al (2018) Techno-economic Analysis of
1234 Downstream Processes in Itaconic Acid Production from Fermentation Broth. J Clean Prod.
1235 <https://doi.org/10.1016/j.jclepro.2018.09.204>
- 1236 Martin Alonso D, G. Wettstein S, A. Dumesic J (2013) Gamma-valerolactone, a sustainable platform
1237 molecule derived from lignocellulosic biomass. Green Chem 15:584–595
- 1238 Martin CH, Dhamankar H, Tseng H-C, et al (2013) A platform pathway for production of 3-
1239 hydroxyacids provides a biosynthetic route to 3-hydroxy- γ -butyrolactone. Nat Commun 4:1414.
1240 <https://doi.org/10.1038/ncomms2418>

1241 Marwa S (2017) Global Styrene Isoprene Styrene (SIS) Market: By Key Players, Application, Type,
1242 Region and Forecast to 2023. In: eMarketResearch. [https://emarketresearch.us/global-styrene-](https://emarketresearch.us/global-styrene-isoprene-styrene-market/)
1243 [isoprene-styrene-market/](https://emarketresearch.us/global-styrene-isoprene-styrene-market/). Accessed 28 Nov 2018

1244 Matsakas L, Hružová K, Rova U, Christakopoulos P (2018) Biological Production of 3-
1245 Hydroxypropionic Acid: An Update on the Current Status. *Fermentation* 4:13.
1246 <https://doi.org/10.3390/fermentation4010013>

1247 McKinlay JB, Shachar-Hill Y, Zeikus JG, Vieille C (2007) Determining *Actinobacillus succinogenes*
1248 metabolic pathways and fluxes by NMR and GC-MS analyses of ¹³C-labeled metabolic product
1249 isotopomers. *Metab Eng* 9:177–192. <https://doi.org/10.1016/j.ymben.2006.10.006>

1250 McKinlay JB, Vieille C (2008) ¹³C-metabolic flux analysis of *Actinobacillus succinogenes*
1251 fermentative metabolism at different NaHCO₃ and H₂ concentrations. *Metab Eng* 10:55–68

1252 McKinlay JB, Zeikus JG, Vieille C (2005) Insights into *Actinobacillus succinogenes* Fermentative
1253 Metabolism in a Chemically Defined Growth Medium. *Appl Environ Microbiol* 71:6651–6656.
1254 <https://doi.org/10.1128/AEM.71.11.6651-6656.2005>

1255 Meena V, Sumanjali A, Dwarka K, et al (2010) Production of Itaconic Acid through Submerged
1256 Fermentation Employing Different Species of *Aspergillus*

1257 Morse M (2015) Genomatica and Braskem now producing renewable butadiene at lab scale.

1258 Moscoviz R (2017) Electrochemical control of a biological process : glycerol electro-fermentation.
1259 Phdthesis, Montpellier SupAgro

1260 Muniandy A, Kamarudin SK, Kofli N (2016) The potential of glycerol as a value-added commodity.
1261 *Chem Eng J* 295:. <https://doi.org/10.1016/j.cej.2016.03.012>

1262 Nag A, John PCS, Crowley MF, Bomble YJ (2018) Prediction of reaction knockouts to maximize
1263 succinate production by *Actinobacillus succinogenes*. *PLOS ONE* 13:e0189144.
1264 <https://doi.org/10.1371/journal.pone.0189144>

1265 Naude A, Nicol W (2018) Malic acid production through the whole-cell hydration of fumaric acid with
1266 immobilised *Rhizopus oryzae*. *Biochem Eng J* 137:152–161.
1267 <https://doi.org/10.1016/j.bej.2018.05.022>

1268 Nijhuis TA, Makkee M, Moulijn JA, Weckhuysen BM (2006) The Production of Propene Oxide:
 1269 Catalytic Processes and Recent Developments. *Ind Eng Chem Res* 45:3447–3459.
 1270 <https://doi.org/10.1021/ie0513090>

1271 Oh IJ, Lee HW, Park CH, et al (2008) Succinic acid production from continuous fermentation process
 1272 using *Mannheimia succiniciproducens* LPK7. *J Microbiol Biotechnol* 18:908–912

1273 Okabe M, Lies D, Kanamasa S, Park EY (2009) Biotechnological production of itaconic acid and its
 1274 biosynthesis in *Aspergillus terreus*. *Appl Microbiol Biotechnol* 84:597–606.
 1275 <https://doi.org/10.1007/s00253-009-2132-3>

1276 Okino S, Noburyu R, Suda M, et al (2008) An efficient succinic acid production process in a
 1277 metabolically engineered *Corynebacterium glutamicum* strain. *Appl Microbiol Biotechnol*
 1278 81:459–464. <https://doi.org/10.1007/s00253-008-1668-y>

1279 Orrego D, Zapata-Zapata AD, Kim D (2018) Ethanol production from coffee mucilage fermentation by
 1280 *S. cerevisiae* immobilized in calcium-alginate beads. *Bioresour Technol Rep* 3:200–204.
 1281 <https://doi.org/10.1016/j.biteb.2018.08.006>

1282 Padman S (2014) Bio-Succinic Acid Market Volume is Expected to Reach 710 Kilo Tons with
 1283 Corresponding Revenue of \$1.1 billion Globally in 2020 - Allied Market Research. In: Allied
 1284 Mark. Res. <https://www.alliedmarketresearch.com/bio-succinic-acid-market>. Accessed 29 Jan
 1285 2019

1286 Panzella L, Napolitano A (2017) Natural Phenol Polymers: Recent Advances in Food and Health
 1287 Applications. *Antioxidants* 6:. <https://doi.org/10.3390/antiox6020030>

1288 Pardo-Planas O, Atiyeh HK, Phillips JR, et al (2017) Process simulation of ethanol production from
 1289 biomass gasification and syngas fermentation. *Bioresour Technol* 245:925–932.
 1290 <https://doi.org/10.1016/j.biortech.2017.08.193>

1291 Park DH, Zeikus JG (1999) Utilization of Electrically Reduced Neutral Red by *Actinobacillus*
 1292 *succinogenes*: Physiological Function of Neutral Red in Membrane-Driven Fumarate
 1293 Reduction and Energy Conservation. *J Bacteriol* 181:2403–2410

1294 Park M-R, Kim HS, Kim S-K, Jeong G-T (2018) Thermo-chemical conversion for production of
 1295 levulinic and formic acids from glucosamine. *Fuel Process Technol* 172:115–124.
 1296 <https://doi.org/10.1016/j.fuproc.2017.12.016>

1297 Peoples O, Samuleson D, Senechal M, et al (2014) Production of salts of 4-hydroxybutyrate using
 1298 biobased raw materials

1299 Pereira B, Miguel J, Vilaça P, et al (2018) Reconstruction of a genome-scale metabolic model for
 1300 *Actinobacillus succinogenes* 130Z. *BMC Syst Biol* 12:. [https://doi.org/10.1186/s12918-018-](https://doi.org/10.1186/s12918-018-0585-7)
 1301 0585-7

1302 Philp J (2014) Biobased Chemicals and Bioplastics: Finding the Right Policy Balance. *OECD Sci*
 1303 *Technol Ind Policy Pap* 17:

1304 Ponnusamy VK, Nguyen DD, Dharmaraja J, et al (2018) A review on lignin structure, pretreatments,
 1305 fermentation reactions and biorefinery potential. *Bioresour Technol*.
 1306 <https://doi.org/10.1016/j.biortech.2018.09.070>

1307 Porro D, Branduardi P (2017) Production of Organic Acids by Yeasts and Filamentous Fungi. In: Sibirny
 1308 AA (ed) *Biotechnology of Yeasts and Filamentous Fungi*. Springer International Publishing,
 1309 Cham, pp 205–223

1310 Prochaska K, Antczak J, Regel-Rosocka M, Szczygiełda M (2018) Removal of succinic acid from
 1311 fermentation broth by multistage process (membrane separation and reactive extraction). *Sep*
 1312 *Purif Technol* 192:360–368. <https://doi.org/10.1016/j.seppur.2017.10.043>

1313 Quadrelli Elsje Alessandra, Centi Gabriele, Duplan Jean-Luc, Perathoner Siglinda (2011) Carbon
 1314 Dioxide Recycling: Emerging Large-Scale Technologies with Industrial Potential.
 1315 *ChemSusChem* 4:1194–1215

1316 Quispe CAG, Coronado CJR, Carvalho Jr. JA (2013) Glycerol: Production, consumption, prices,
 1317 characterization and new trends in combustion. *Renew Sustain Energy Rev* 27:475–493.
 1318 <https://doi.org/10.1016/j.rser.2013.06.017>

1319 Raab AM, Gebhardt G, Bolotina N, et al (2010) Metabolic engineering of *Saccharomyces cerevisiae* for
 1320 the biotechnological production of succinic acid. *Metab Eng* 12:518–525.
 1321 <https://doi.org/10.1016/j.ymben.2010.08.005>

- 1322 Rathod PV, Jadhav VH (2018) Efficient Method for Synthesis of 2,5-Furandicarboxylic Acid from 5-
1323 Hydroxymethylfurfural and Fructose Using Pd/CC Catalyst under Aqueous Conditions. ACS
1324 Sustain Chem Eng 6:5766–5771. <https://doi.org/10.1021/acssuschemeng.7b03124>
- 1325 Ribeiro LS, Delgado JJ, de Melo Órfão JJ, Pereira MFR (2017a) Direct conversion of cellulose to
1326 sorbitol over ruthenium catalysts: Influence of the support. Catal Today 279:244–251.
1327 <https://doi.org/10.1016/j.cattod.2016.05.028>
- 1328 Ribeiro LS, Órfão JJ de M, Pereira MFR (2017b) Direct catalytic production of sorbitol from waste
1329 cellulosic materials. Bioresour Technol 232:152–158.
1330 <https://doi.org/10.1016/j.biortech.2017.02.008>
- 1331 Rivas B, Torre P, Domínguez JM, et al (2006) Purification of Xylitol Obtained by Fermentation of
1332 Corncob Hydrolysates. J Agric Food Chem 54:4430–4435. <https://doi.org/10.1021/jf053156x>
- 1333 Rogers* P, Chen J-S, Zidwick MJ (2013) Organic Acid and Solvent Production: Acetic, Lactic,
1334 Gluconic, Succinic, and Polyhydroxyalkanoic Acids. In: Rosenberg E, DeLong EF, Lory S, et
1335 al. (eds) The Prokaryotes: Applied Bacteriology and Biotechnology. Springer Berlin
1336 Heidelberg, Berlin, Heidelberg, pp 3–75
- 1337 Rossi C, Hauber J, Singer TP (1964) Mitochondrial and Cytoplasmic Enzymes for the Reduction of
1338 Fumarate to Succinate in Yeast. Nature 204:167–170. <https://doi.org/10.1038/204167a0>
- 1339 Rout PK, Nannaware AD, Prakash O, et al (2016) Synthesis of hydroxymethylfurfural from cellulose
1340 using green processes: A promising biochemical and biofuel feedstock. Chem Eng Sci 142:318–
1341 346. <https://doi.org/10.1016/j.ces.2015.12.002>
- 1342 Salvachúa D, Mohagheghi A, Smith H, et al (2016a) Succinic acid production on xylose-enriched
1343 biorefinery streams by *Actinobacillus succinogenes* in batch fermentation. Biotechnol Biofuels
1344 9:28. <https://doi.org/10.1186/s13068-016-0425-1>
- 1345 Salvachúa D, Smith H, St. John PC, et al (2016b) Succinic acid production from lignocellulosic
1346 hydrolysate by *Basfia succiniciproducens*. Bioresour Technol 214:558–566.
1347 <https://doi.org/10.1016/j.biortech.2016.05.018>

- 1348 Sanders JPM, Clark JH, Harmsen GJ, et al (2012) Process intensification in the future production of
1349 base chemicals from biomass. *Chem Eng Process Process Intensif* 51:117–136.
1350 <https://doi.org/10.1016/j.cep.2011.08.007>
- 1351 Sari YW (2015) Biomass and its potential for protein and amino acids : valorizing agricultural by-
1352 products. Wageningen University
- 1353 Saxena RK, Saran S, Isar J, Kaushik R (2017) 27 - Production and Applications of Succinic Acid. In:
1354 Pandey A, Negi S, Soccol CR (eds) *Current Developments in Biotechnology and*
1355 *Bioengineering*. Elsevier, pp 601–630
- 1356 Schouwer FD, Cuypers T, Claes L, Vos DED (2017) Metal-catalyzed reductive deamination of glutamic
1357 acid to bio-based dimethyl glutarate and methylamines. *Green Chem* 19:1866–1876.
1358 <https://doi.org/10.1039/C6GC03222B>
- 1359 Serrano-Ruiz JC, Luque R, Sepúlveda-Escribano A (2011) Transformations of biomass-derived
1360 platform molecules: from high added-value chemicals to fuels via aqueous-phase processing.
1361 *Chem Soc Rev* 40:5266–5281. <https://doi.org/10.1039/C1CS15131B>
- 1362 Shamsul NS, Kamarudin SK, Rahman NA, Kofli NT (2014) An overview on the production of bio-
1363 methanol as potential renewable energy. *Renew Sustain Energy Rev* 33:578–588.
1364 <https://doi.org/10.1016/j.rser.2014.02.024>
- 1365 Shrotri A, Kobayashi H, Fukuoka A (2017) Chapter Two - Catalytic Conversion of Structural
1366 Carbohydrates and Lignin to Chemicals. In: Song C (ed) *Advances in Catalysis*. Academic
1367 Press, pp 59–123
- 1368 Sikarwar VS, Zhao M, Fennell PS, et al (2017) Progress in biofuel production from gasification. *Prog*
1369 *Energy Combust Sci* 61:189–248. <https://doi.org/10.1016/j.pecs.2017.04.001>
- 1370 Singh R, Kumar M, Mittal A, Mehta PK (2017) Microbial metabolites in nutrition, healthcare and
1371 agriculture. *3 Biotech* 7:15. <https://doi.org/10.1007/s13205-016-0586-4>
- 1372 Song H, Lee SY (2006) Production of succinic acid by bacterial fermentation. *Enzyme Microb Technol*
1373 39:352–361

- 1374 Stichnothe H, Bell G, Jørgensen H, et al (2020) Bio-Based Chemicals A 2020 Update Bio-Based
1375 Chemicals A 2020 Update With input from: Published by IEA Bioenergy
- 1376 Straathof A, Bampouli A (2017) Potential of commodity chemicals to become bio-based according to
1377 maximum yields and petrochemical prices. *Biofuels Bioprod Biorefining*
- 1378 Stucki Gerhard, Thueer Markus (1995) Experiences of a Large-Scale Application of 1,2-Dichloroethane
1379 Degrading Microorganisms for Groundwater Treatment. *Environ Sci Technol* 29:2339–2345.
1380 <https://doi.org/10.1021/es00009a028>
- 1381 Sun X, Shen X, Jain R, et al (2015) Synthesis of chemicals by metabolic engineering of microbes. *Chem*
1382 *Soc Rev* 44:3760–3785. <https://doi.org/10.1039/C5CS00159E>
- 1383 Sun Y, Zhang X, Zheng Y, et al (2019) Sugaring-out extraction combining crystallization for recovery
1384 of succinic acid. *Sep Purif Technol* 209:972–983. <https://doi.org/10.1016/j.seppur.2018.09.049>
- 1385 Szczygiel M, Antczak J, Prochaska K (2017) Separation and concentration of succinic acid from post-
1386 fermentation broth by bipolar membrane electrodialysis (EDBM). *Sep Purif Technol* 181:53–
1387 59. <https://doi.org/10.1016/j.seppur.2017.03.018>
- 1388 Taylor DC, Smith MA, Fobert P, et al (2011) 4.06 - Metabolic Engineering of Higher Plants to Produce
1389 Bio-Industrial Oils. In: Moo-Young M (ed) *Comprehensive Biotechnology* (Second Edition),
1390 Second Edition. Academic Press, Burlington, pp 67–85
- 1391 Taylor R, Natrass L, Alberts G, et al (2015) From the Sugar Platform to biofuels and biochemicals
- 1392 Thakker C, San K-Y, Bennett GN (2013) Production of succinic acid by engineered *E. coli* strains using
1393 soybean carbohydrates as feedstock under aerobic fermentation conditions. *Bioresour Technol*
1394 130:398–405. <https://doi.org/10.1016/j.biortech.2012.10.154>
- 1395 Thapa I, Mullen B, Saleem A, et al (2017) Efficient green catalysis for the conversion of fructose to
1396 levulinic acid. *Appl Catal Gen* 539:70–79. <https://doi.org/10.1016/j.apcata.2017.03.016>
- 1397 Thuy NTH, Boontawan A (2017) Production of very-high purity succinic acid from fermentation broth
1398 using microfiltration and nanofiltration-assisted crystallization. *J Membr Sci* 524:470–481.
1399 <https://doi.org/10.1016/j.memsci.2016.11.073>

1400 Thuy NTH, Kongkaew A, Flood A, Boontawan A (2017) Fermentation and crystallization of succinic
 1401 acid from *Actinobacillus succinogenes* ATCC55618 using fresh cassava root as the main
 1402 substrate. *Bioresour Technol* 233:342–352. <https://doi.org/10.1016/j.biortech.2017.02.114>

1403 Tong X, Ma Y, Li Y (2010) Biomass into chemicals: Conversion of sugars to furan derivatives by
 1404 catalytic processes. *Appl Catal Gen* 385:1–13. <https://doi.org/10.1016/j.apcata.2010.06.049>

1405 Vasiliu M, Jones AJ, Guynn K, Dixon DA (2012) Prediction of the Thermodynamic Properties of Key
 1406 Products and Intermediates from Biomass. II. *J Phys Chem C* 116:20738–20754.
 1407 <https://doi.org/10.1021/jp306596d>

1408 Vaswani S (2010) Bio-Based Succinic Acid.

1409 Vemuri GN, Eiteman MA, Altman E (2002a) Succinate production in dual-phase *Escherichia coli*
 1410 fermentations depends on the time of transition from aerobic to anaerobic conditions. *J Ind*
 1411 *Microbiol Biotechnol* 28:325–332. <https://doi.org/10.1038/sj/jim/7000250>

1412 Vemuri GN, Eiteman MA, Altman E (2002b) Succinate production in dual-phase *Escherichia coli*
 1413 fermentations depends on the time of transition from aerobic to anaerobic conditions. *J Ind*
 1414 *Microbiol Biotechnol* 28:325–332. <https://doi.org/10.1038/sj/jim/7000250>

1415 W. Breeden S, Clark J, Farmer T, et al (2012) ChemInform Abstract: Microwave Heating for Rapid
 1416 Conversion of Sugars and Polysaccharides to 5-Chloromethyl Furfural. *Green Chem* 15:72

1417 Wan C, Li Y, Shahbazi G, Xiu S (2008) Succinic Acid Production from Cheese Whey using
 1418 *Actinobacillus succinogenes* 130 Z. *Appl Biochem Biotechnol* 145:111–9

1419 Werpy. A T, Holladay J, White J (2004) Top Value Added Chemicals From Biomass: I. Results of
 1420 Screening for Potential Candidates from Sugars and Synthesis Gas

1421 Werpy T, Petersen G (2004) Top Value Added Chemicals from Biomass: Volume I -- Results of
 1422 Screening for Potential Candidates from Sugars and Synthesis Gas

1423 White J (2007) Top Value-Added Chemicals from Biomass Volume II—Results of Screening for
 1424 Potential Candidates from Biorefinery Lignin. *Biomass Fuels* 2:

1425 Wieschalka S (2012) Engineering *Corynebacterium glutamicum* as a designer-bug for the bio-based
 1426 production of chemical building blocks and biofuel. Dissertation, Universität Ulm

- 1427 Xi J, Zhang Y, Xia Q, et al (2013) Direct conversion of cellulose into sorbitol with high yield by a novel
1428 mesoporous niobium phosphate supported Ruthenium bifunctional catalyst. Appl Catal Gen
1429 459:52–58. <https://doi.org/10.1016/j.apcata.2013.03.047>
- 1430 Xi Y, Chen K, Li J, et al (2011) Optimization of culture conditions in CO₂ fixation for succinic acid
1431 production using *Actinobacillus succinogenes*. J Ind Microbiol Biotechnol 38:1605–1612.
1432 <https://doi.org/10.1007/s10295-011-0952-5>
- 1433 Xu H, Zhou Z, Wang C, et al (2016a) Enhanced succinic acid production in *Corynebacterium*
1434 *glutamicum* with increasing the available NADH supply and glucose consumption rate by
1435 decreasing H⁺-ATPase activity. Biotechnol Lett 38:1181–1186.
1436 <https://doi.org/10.1007/s10529-016-2093-4>
- 1437 Xu J, Cao F, Li T, et al (2016b) Itaconic Acid Based Surfactants: I. Synthesis and Characterization of
1438 Sodium n-Octyl Sulfoitaconate Diester Anionic Surfactant. J Surfactants Deterg 19:373–379.
1439 <https://doi.org/10.1007/s11743-015-1769-4>
- 1440 Xue C, Liu F, Xu M, et al (2016) Butanol production in acetone-butanol-ethanol fermentation with in
1441 situ product recovery by adsorption. Bioresour Technol 219:158–168.
1442 <https://doi.org/10.1016/j.biortech.2016.07.111>
- 1443 Yan D, Wang G, Gao K, et al (2018) One-Pot Synthesis of 2,5-Furandicarboxylic Acid from Fructose
1444 in Ionic Liquids. Ind Eng Chem Res 57:1851–1858. <https://doi.org/10.1021/acs.iecr.7b04947>
- 1445 Yan Q, Zheng P, Tao S-T, Dong J-J (2014) Fermentation process for continuous production of succinic
1446 acid in a fibrous bed bioreactor. Biochem Eng J 91:92–98.
1447 <https://doi.org/10.1016/j.bej.2014.08.002>
- 1448 Yang W, Wang Z, Sun H, Zhang B (2016) Advances in development and industrial applications of
1449 ethylbenzene processes. Chin J Catal 37:16–26. [https://doi.org/10.1016/S1872-2067\(15\)60965-](https://doi.org/10.1016/S1872-2067(15)60965-2)
1450 2
- 1451 Yuan J, Li S-S, Yu L, et al (2013) Copper-based catalysts for the efficient conversion of carbohydrate
1452 biomass into valerolactone in the absence of externally added hydrogen. Energy Environ Sci
1453 6:3308

1454 Zhang D, A. Hillmyer M, B. Tolman W (2004) A New Synthetic Route to Poly[3-hydroxypropionic
 1455 acid] (P[3-HP]): Ring-Opening Polymerization of 3-HP Macrocyclic Esters. *Macromolecules*
 1456 37:.. <https://doi.org/10.1021/ma048092q>

1457 Zhang J, Li J, Wu S-B, Liu Y (2013) Advances in the Catalytic Production and Utilization of Sorbitol.
 1458 *Ind Eng Chem Res* 52:11799–11815. <https://doi.org/10.1021/ie4011854>

1459 Zheng P, Dong J-J, Sun Z-H, et al (2009) Fermentative production of succinic acid from straw
 1460 hydrolysate by *Actinobacillus succinogenes*. *Bioresour Technol* 100:2425–2429.
 1461 <https://doi.org/10.1016/j.biortech.2008.11.043>

1462 Zhou X, Zheng P (2013) Spirit-based distillers' grain as a promising raw material for succinic acid
 1463 production. *Biotechnol Lett* 35:679–684. <https://doi.org/10.1007/s10529-013-1147-0>

1464 Zhu L-W, Wang C-C, Liu R-S, et al (2012) *Actinobacillus succinogenes* ATCC 55618 Fermentation
 1465 Medium Optimization for the Production of Succinic Acid by Response Surface Methodology.
 1466 *J Biomed Biotechnol* 2012:.. <https://doi.org/10.1155/2012/626137>

1467 Zou W, Zhu L-W, Li H-M, Tang Y-J (2011) Significance of CO₂ donor on the production of succinic
 1468 acid by *Actinobacillus succinogenes* ATCC 55618. *Microb Cell Factories* 10:87.
 1469 <https://doi.org/10.1186/1475-2859-10-87>

1470 Synthesis of acrylates and methacrylates from coal-derived syngas. Quarterly report, October--
 1471 December 1996 - Digital Library. <https://digital.library.unt.edu/ark:/67531/metadc691706/>.
 1472 Accessed 29 Nov 2018

1473

1474

1475

1476 **Glossary :**

1477 5K4DG: 5dehydro-4-deoxy-D-glucarate

1478 5KG: 5-ketogluconate

1479 A6P: Ascorbate-6-phosphate

1480 AcCoA: Acetyl-CoA

1481 AcP: acetyl-phosphate

1482 Ald: Aldehyde

1483 Ara: Arabinose

1484 DHAP: dihydroxyacetone phosphate

1485 E4P: Erythrose-4-phosphate

1486 F1,6P: Fructose-1,6-biphosphate

1487 F1P: Fructose-1-phosphshate

1488 F6P: Fructose-6-phosphate

1489 G1P: Glucose-1-phosphate

1490 Gal: Galactose

1491 Gal1P: Galactose-1-phosphate

1492 Galte: Galactarate

1493 Glc: Glucose

1494 Glcte: Glucarate

1495 Gly: Glycerol

1496 Gt6P: Gluconate-6-phosphate

1497 Gte: Gluconate

1498 Ido:Idonate

1499 KDPG: 2-keto-3deoxy-6-phosphogluconate

1500 Lac: Lactose

1501 Mal: Maltose

1502 Man6P: Mannose-6-phosphate

1503 MOH1P: Mannitol-1-phosphate
 1504 Pec: Pectin
 1505 R5P: Ribose-5-phosphate
 1506 Rib: Ribose
 1507 Ribu: Ribulose
 1508 Ru5P: Ribulose-5-phosphate
 1509 S6P: Sucrose-6-phosphate
 1510 S7P: Sedoheptulose-7phosphate
 1511 SOH6P: Sorbitol-6-phosphate
 1512 SucCoA: Succinyl-CoA
 1513 Xu5P: Xylulose-5phosphate
 1514 Xyl: Xylose
 1515 Xylu: Xylulose
 1516 β G6P: β -Glucoside-6-phosphate.
 1517 SA: succinic acid
 1518 GA: Glutamic acid
 1519 ORP: oxydoreduction potential
 1520 US DOE: The United State Department of energy
 1521 NREL: National Renewable Energy Laboratory reports
 1522 CEN: European Committee Standardized
 1523 HMF: hydroxymethylfurfural
 1524 FDCA: 2,5-Furandicarboxylic acid
 1525 ATP: Adenosine triphosphate
 1526 NAD⁺: Nicotinamide adenine dinucleotide
 1527 (PEP) phosphoenolpyruvate
 1528 TCA: Tricarboxylic cycle acid
 1529 *LDH*: lactose-dehydrogenase
 1530 *PFL*: pyruvate formate lyase

- 1531 CSL: corn steep liquor
- 1532 OPPP: oxidative pentose phosphate pathway
- 1533 OAA: oxaloacetate
- 1534 RO : Reverse osmosis
- 1535 PTS: phosphotransferase synthase