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1 **Platform molecule from sustainable raw materials; case study succinic acid**

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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

## 37 **Background**

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

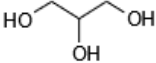
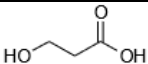
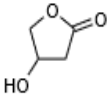
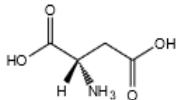
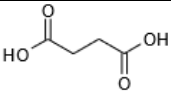
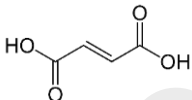
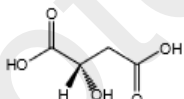
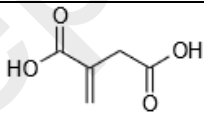
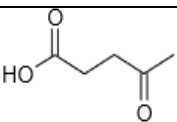
67 research developed and focused on products deriving from biomass and a report by the US DOE  
68 on Top Value Added Chemicals from Biomass was published (Werpy, A et al. 2004). It has  
69 been widely claimed that biomass feedstock can replace fossil fuels but it implies a successful  
70 integration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

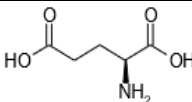
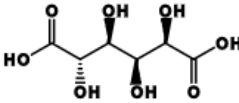
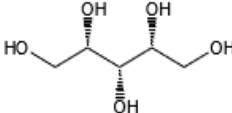
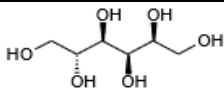
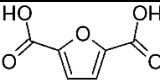
84 This review highlights the power and the potential capacity of platform molecules, when used  
85 as biochemicals, replacing chemicals originating from fossil resources. Furthermore, it also  
86 reviews the relevant literature about the main advances of the last years, so as to create the  
87 necessary basis for a constructive and supported review. However, bio-economy requires  
88 methods to produce the range of familiar chemicals that are crucial in our lives, such as synthetic  
89 textiles, surfactants, pharmaceuticals, plastics, pigments, dyes and agrochemicals, and also  
90 home and personal care products in order to eventually replace the fossil resources that are  
91 depleted. In this review, the status of the industries producing fossil-derived base chemicals is  
92 briefly described and the equivalence of chemical building blocks with bio-based chemicals is  
93 debated. The notion of platform molecules is now under discussion, leading to the  
94 characterization of those small bio-derived chemicals. As a constituent part, the biomass  
95 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) (Kasirajan and Ngouajio 2012)
		Polyethylene			
		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			
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, $\gamma$ -butenyl-lactone, acrylatelactone	Intermediate for high value pharma compounds	(Peoples et al. 2014)
	Aspartic acid		Amino- $\gamma$ -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, $\gamma$ -Butyrolactone, Tetrahydrofuran, N-Methyl-2-pyrrolidone Di-esters, Polyamides, Polyesters	Sweetener in food and beverages	(Kohli et al. 2019)
	Fumaric acid		1,4-Butanediol, $\gamma$ -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)
C5	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)
	Levulinic acid		Methyltetrahydrofuran, Esters, $\gamma$ -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-pentandiol, 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, Arabinic 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



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

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

146 2013). Therefore, these compounds are bio-derived platform molecules directly produced from  
147 biomass, depending on their production route.

## 148 **The source of Platform chemicals**

### 149 **Fossil materials as feedstocks**

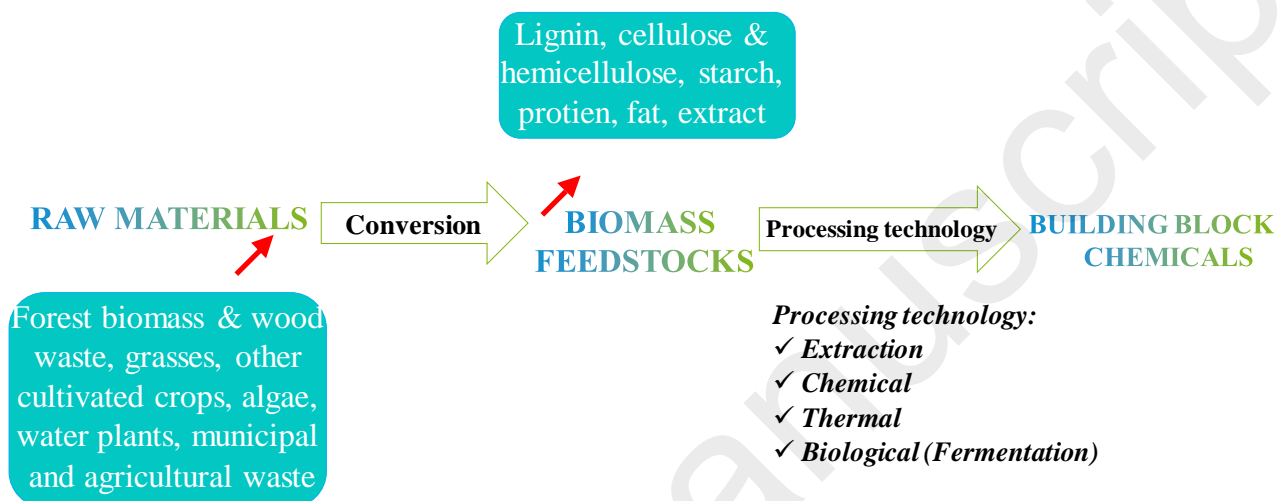
150 In the past, a wide range spectrum of chemicals originated from fossil resources that complied  
151 with our energy needs. The oil crisis caused severe economic and social impacts in addition to  
152 the use of fossil fuels being rightly perceived as a major source of pollution. Most of the  
153 products manufactured by the chemical industry using fossil fuels as raw materials usually  
154 come from seven simple building-block molecules (mainly natural gas and crude oil) called  
155 fossil-derived base chemicals which are produced by distillation and by catalytic reforming  
156 view table 1 (Straathof and Bampouli 2017). Each year, the production of base chemicals  
157 exceeds 10 million tons and in 2010, more than 360 million tons were produced (Gallagher  
158 2012).

### 159 **From cheap sustainable materials to platform chemicals**

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

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

179



180

181

Figure 1. From raw materials to chemicals.

182

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 Actonic 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 Lactic acid		Sugars	(Xue et al. 2016)	
Fumaric acid			(Li et al. 2018; Andreev et al. 2018; Ho et al. 2018)	
3-hydroxy propionic acid			(Das et al. 2016b; Li and Xing 2017a; Liu et al. 2017b)	
			(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)

185

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

189 **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)

190

### 191 **Pathways to the 12 sugar components**

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

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

210 Glycerol could become an extremely diverse building block in biorefinery. Presently, glycerol  
211 is an acknowledged traded item with worldly annual production of  $600 - 750 \times 10^3$  tons and the  
212 industry expects its consumption to grow above 4 million tons by 2024 (Ahuja and Singh 2018).  
213 A lot of chemical industries such as Uniqema, Procter & Gamble and Stepan produce glycerol  
214 and its numerous derivatives (such as glycerol stearate, glycerol oleate and glycerol triacetate).  
215 Glycerol is manufactured, like natural glycerol by-products, by biodiesel and oleochemical  
216 industries, and like synthetic glycerol, derived from propylene. The number one provider and  
217 consumer of glycerol worldwide are the USA. Indeed, about 75% of the glycerol supply in the  
218 United States is provided by natural sources, and the other synthetic 25% is refined before being  
219 used in many ways in markets thus explaining glycerol's comparatively expensive price of  
220 \$0.60 – 0.90 per pound. However, since biodiesel was more and more used and since it is a key  
221 byproduct in biodiesel manufacturing, cheaper glycerol could be purchased in greater quantities  
222 (Quispe et al. 2013). Glycerol prices could fall to \$0.20/lb which is today's industrial average  
223 cost for refined and unrefined glycerol. Glycerin could be found at lower cost. Glycerol could  
224 become a key building block in biorefinery if its prices dropped into a \$0.20 - \$0.50/lb range.  
225 The increase of fatty acid consumption, for fuels and products, may cause the world glycerol  
226 output to rise significantly. In the coming years, if the US replaced about 2% of the diesel used  
227 for transportation by biodiesel, almost 2 billion pounds of new glycerol would be produced  
228 (Muniandy et al. 2016).

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

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

246 3-Hydroxybutyrolactone (3-HBL) - a cyclic chemical with four carbons - is currently used in  
247 the pharmaceutical production through chemical transformations and also through  
248 fermentation. The chemical synthesis of this building block is considered as “confused” because  
249 it requires multiple steps (Martin et al. 2013). One possible way to form 3-HBL starts with  
250 malic acid which could be cyclized to give hydroxysuccinic anhydride and then could be  
251 reduced to form hydroxybutyrolactone. Still, the primary technical obstacle in the development  
252 of this building block requires the development of a cheap fermentation process using a wide  
253 range of lignocellulosics biomass as feedstocks that can tolerate its inhibitory components and  
254 averting odd oxidants (Dhamankar 2013).

255 Methyl-SA is a dicarboxylic acid with C5, also known as itaconic acid, considered as a key  
256 building block thanks to its capacity to derive fine chemicals. Itaconic acid basic chemistry is  
257 similar to maleic acid/anhydride because both are derived from petrochemicals. Itaconic acid  
258 used as a specialty monomer is produced through aerobic fungal fermentation (Meena et al.  
259 2010). The main challenge is to reduce the cost of the fermentation process to below  
260 \$0.25/pound in order to compete with petrochemical-derived products. However, the  
261 development of a process to produce these building block compounds face many technical

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

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

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

280 Sorbitol is produced through the hydrogenation of glucose by several companies and its volume  
281 is in the order of 200 million pounds per year. In place of a batch technology, to ensure the  
282 complete conversion of glucose, a continuous process using a catalyst such as Raney nickel is  
283 used in all commercial processes to reduce the sugars amounts in the sorbitol production. Very  
284 strict requirements are necessary because sorbitol is extensively applied in the food industry.  
285 Because no technical development is needed for its use as a building block in derivatives,  
286 sorbitol is a very inexpensive feedstock (Furtwengler and Avérous 2018). To conclude, if a  
287 continuous process is compared to a batch process, the only change is glucose conversion into  
288 sorbitol. It makes sorbitol an economical feedstock for producing derivatives (Zhang et al.  
289 2013).



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

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

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

320 Chemical compounds with low molecular weights are characterized by the presence of at least  
321 one carboxylic functional group (-COOH) also called organic acids (Porro and Branduardi  
322 2017). Moreover, organic acids were discovered by Scheele in 1784, and humans have used  
323 them since early ages because they are broadly produced in nature by all organisms such as  
324 micro-organisms, plants, animals and humans. Commercially speaking, lactic acid, citric acid,  
325 gluconic acid and itaconic acid are the most important organic acids. They are used in various  
326 applications such as flavor enhancers in food, ingredients in pharmaceuticals, cosmetics and  
327 beverages and they are also used in the production of biopolymers, coatings, adhesives and  
328 others in the chemical industry (Sun et al. 2015). The global market of organic acids was  
329 estimated at approximately \$12 billion in 2014 and is expected to reach over \$18 billion by  
330 2023 (Singh et al. 2017). The vision is that these products can replace fossil fuels that in itself  
331 is a societal goal.

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

## 350 **Succinic acid: case study**

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

367 SA is a dicarboxylic acid containing four carbon atoms. In bio-economy, this four-carbon-  
368 dicarboxylic acid (SA) progresses to an intermediate platform, as a substitute for maleic  
369 anhydride, in order to produce diverse numbers of chemicals considered as bulk/intermediate  
370 chemicals. Among them, maleic acid, adipic acid, 1,4- butanediol,  $\gamma$ -butyrolactone, N-methyl-  
371 2-pyrrolidone, tetrahydrofuran, 2-pyrrolidone, succinic esters and succinimide are used in green  
372 chemistry and in a wide number of industries including polymers (clothing fibres), food,  
373 surfactants and detergents, flavors and fragrances and in the pharmaceutical industry (Song and  
374 Lee 2006; Li and Xing 2017a). SA applications in industries call for about 9% polybutylene  
375 succinate-terephthalate and polybutylene succinate, 6.2% for polyester polyols, 15.1% in  
376 pharmaceutical industry, 12.6% in food industry, and 19.3% in resins, coatings and pigments  
377 production (Aeschelmann and Carus 2015).

## 378 **Production methods: an overview**

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

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

397 During the past few decades, bio-based feedstocks have become less expensive and it will  
398 remain an added value over the petroleum/gas feedstocks in the future. According to (Kidwell  
399 2008), the SA consumption was of about 25,000 to 30,000 tons annually worldwide with an  
400 approximate 10% of increase a year. The SA total capacity is estimated to more than 45–50  
401 million lb/year. The World demand for SA was 51,000 tons in 2013 and is expected to increase  
402 to 593,400 tons by 2020 (Padman 2014). In the next few years, these values are expected to  
403 augment in parallel with the fast demand rising and the cost-competitiveness of bio-based  
404 succinic acid. Many companies are active in the development of bio-based SA at commercial  
405 scale and three of them intend to bring more than 140,000 tons per year of capacity online by  
406 2016 (Table 6) (Jansen and van Gulik 2014; Taylor et al. 2015).

407 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	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

410 **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

411  
 412 The metabolism leading to the production of SA is controlled by either aerobic or anaerobic  
 413 environments. SA is produced by numerous aerobic, facultative and obligate anaerobic  
 414 microorganisms using C6 sugars, such as glucose and fructose, metabolized by the Embden  
 415 Meyerhof-Parnas pathway (glycolysis). It provides two moles of pyruvate, ATP (energy) and  
 416 NADH (reducing power), per mole of sugar (Krishnakumar 2013). In addition to succinic acid,  
 417 other carboxylic acids (such as lactic acid, formic acid, propionic acid, acetic acid) and alcohols  
 418 (such as ethanol) are also obtained. The production ratios of these by-product compounds  
 419 depend on the microorganism strain used, substrate, and on the operation conditions. For  
 420 example, when glycerol was used as a carbon source in the fermentation of *A.*  
 421 *succiniciproducens*, succinic acid was produced with a high yield. Also, the formation of by-  
 422 product acetic acid was avoided, which resulted in the increased ratio of succinic acid to acetic  
 423 acid up to 31.7:1. This ratio is 7.9 times higher than that obtained by batch fermentation of  
 424 glucose as reported by (Lee et al. 2001)

#### 425 **SA producer's microorganisms**

426 A tremendous research is made to develop a biological process for the production of SA, such  
 427 as a metabolite under aerobic, micro-aerobic and/or anaerobic conditions thanks to the use of  
 428 microorganisms such as *Aspergillus niger*, *Aspergillus fumigatus*, *Byssoschlamys nivea*,  
 429 *Lentinus degener*, *Paecilomyces varioti* and *Penicillium viniferum* (Rossi et al. 1964; Taylor et  
 430 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

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

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

473



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) (Ferone et al. 2017)
		Glucose	5.4 g/L	0.80 g/g	
		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*  $\Delta$ 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).

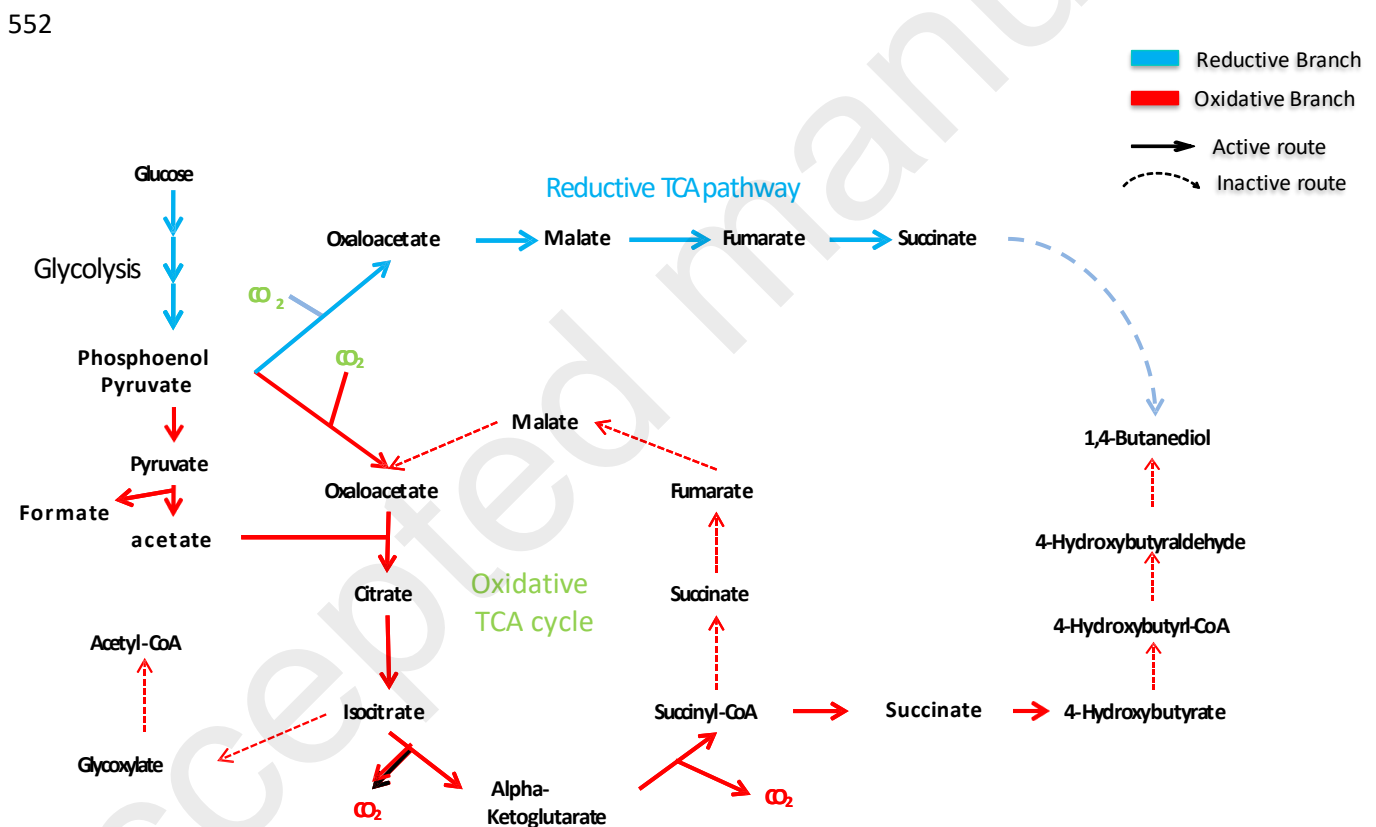
501 In order to produce SA, the main features of *A. succinogenes* 130Z are used as a wide variety  
502 of feedstocks containing carbon sources, with suitable tolerance to inhibitors, sufficient as well  
503 as an efficient fermentative pathway even with sustainable raw materials (Brink and Nicol  
504 2014b). Whereas the principal drawback is the demanding nature of this strain for nitrogen  
505 sources (corn steep liquor, yeast extract or  $\text{NH}_4\text{Cl}$ ), 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

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

#### 515 **Metabolic network towards SA production in *A. succinogenes***

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

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



553 Figure 2. Metabolic pathway occurs in *Actinobacillus succinogenes*

## 554 **Key factors requirements**

### 555 *pH regulators*

556 Frequently, pH is considered as a major key factor in fermentation processes. For optimal  
557 performances, almost microbial cultures require near neutral pH values. The SA fermentation  
558 also leads to the production of organic acids (formic and acetic acids) which provokes the  
559 acidification of the medium, therefore necessitating the addition of neutralizing agents. During  
560 fermentation, when pH values are near neutral, these by-products are in their dissociated shapes  
561 leading to the formation of salts by neutralization. A study done by (Zhu et al. 2012) reviewed  
562 that the highest SA production occurs in the fermentation of *A. succinogenes* ATCC 55618 at  
563 optimum pH value of 7.5. While individual neutralizing agents are added, such as NaOH or  
564 KOH, results make the SA production fall down, which may be related to the acute cell  
565 flocculation. When ammonium hydroxide (NH<sub>4</sub>OH) or calcium hydroxide are used as  
566 neutralizing agents, a growth inhibition is observed. To prevent cell flocculation, 5 M of NaOH  
567 and 0.47 M of MgCO<sub>3</sub> were combined, achieving a 28 % higher SA concentration (59.2 g/L)  
568 in fermentation than when NaOH was used as only neutralizing agent (Bazaes et al. 2007). A  
569 stable production of SA occurs at a pH range of 6 to 7.2 as reported in another paper (Liu Yu-  
570 Peng et al. 2008), while magnesium carbonate (MgCO<sub>3</sub>) was considered as the most promising  
571 neutralizing agent when compared to Na<sub>2</sub>CO<sub>3</sub>, NaOH, CaCO<sub>3</sub> and NH<sub>4</sub>OH in the *A.*  
572 *succinogenes* CGMCC1593 fermentation, using glucose as the sole carbon source. When  
573 NaOH or Na<sub>2</sub>CO<sub>3</sub> are used, cell flocculation occurs after 12 hours, whereas cell flocculation is  
574 not observed when MgCO<sub>3</sub> is used. (Li et al. 2011) demonstrated that among many neutralizer  
575 agents, such as CaCO<sub>3</sub>, NaHCO<sub>3</sub>, NaOH, Na<sub>2</sub>CO<sub>3</sub>, Ca(OH)<sub>2</sub>, Mg(OH)<sub>2</sub>, and NH<sub>3</sub>·H<sub>2</sub>O, MgCO<sub>3</sub>  
576 was the most efficient regarding SA production, glucose utilization and growth of *A.*  
577 *succinogenes* NJ113, reaching a conversion yield of 0.73 g/g of glucose into SA and decreasing  
578 fermentation cost by 55.9%. The use of CaCO<sub>3</sub>, Ca(OH)<sub>2</sub> and NH<sub>3</sub>·H<sub>2</sub>O as neutralizers, results  
579 in decreasing cell growth, and thus low production of SA; while the supply of mixed  
580 neutralizers of Mg(OH)<sub>2</sub> and NaOH at a ratio of 1:1 led to the same efficiency for SA production  
581 as using only MgCO<sub>3</sub> as neutralizer. This could be referred to NaOH solubility and strong  
582 alkalinity, and the lack of Mg<sup>2+</sup> as cofactor for PEP carboxykinase (Liu Yu-Peng et al. 2008).  
583 In the studies mentioned above (Liu Yu-Peng et al. 2008), MgCO<sub>3</sub> was considered as the most

584 efficient regulator of the pH, providing both CO<sub>2</sub> and Mg<sup>2+</sup> ions serving as cofactors in the  
585 TCA cycle reductive branch for the first enzyme, PEP carboxykinase.

### 586 ***CO<sub>2</sub> Feed in***

587 In fermentation, while gaseous CO<sub>2</sub> is sparged, the dissolved CO<sub>2</sub> concentration relies on the  
588 fermentation broth components, temperature, agitation, CO<sub>2</sub> flow rate and partial pressure.  
589 During the *A. succinogenes* 130Z fermentation, when carbonate (e.g. MgCO<sub>3</sub>) or bicarbonate  
590 salts are added, higher dissolved CO<sub>2</sub> concentrations can be reached, regardless a gaseous CO<sub>2</sub>  
591 supply. During fermentation, CO<sub>2</sub> availability results in carbonates and bicarbonates ions  
592 conversion into HCO<sub>3</sub><sup>-</sup>, and diffusion through cell membranes, which demands ATP  
593 consumption so as to maintain reaction equilibrium. A study by (Zou et al. 2011) on the SA  
594 production by *A. succinogenes* ATCC 55618 explored the action of dissolved concentration of  
595 CO<sub>2</sub>, partial pressure of gaseous CO<sub>2</sub> as well as the MgCO<sub>3</sub> supply on SA production. The CO<sub>2</sub>  
596 dissolved concentration was not sufficient, when only gaseous CO<sub>2</sub> was sparged. To maximize  
597 SA production; consequently 0.47 M of MgCO<sub>3</sub> and CO<sub>2</sub> partial pressure of 101.33 kPa (100%  
598 CO<sub>2</sub> gas) was supplied, resulting in higher concentration (60.4 g/L), productivity (0.84 g/L.h)  
599 and yield (0.58 g of SA/g of glucose) of succinic acid.

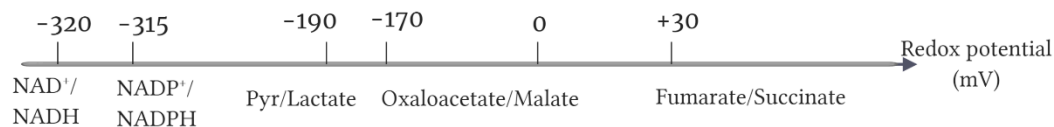
600 (Xi et al. 2011) investigated the effect of agitation and other parameters on SA production.  
601 Maximum SA production was obtained when *A. succinogenes* NJ113 was grown in the  
602 following conditions: 200 rpm stirring speed, pH 6.8, 0.1 MPa CO<sub>2</sub> partial pressure, 37°C and  
603 150 mM NaHCO<sub>3</sub>. These conditions led to a CO<sub>2</sub> optimal fixation rate of 0.57 g/L.h, with a  
604 concentration of 51.6 g/L and 0.76 g/g yield.

605 The CO<sub>2</sub> availability could raise owing to its market price of around 60 \$/t with an annual  
606 assessed carbon capture and storage of 90% (Quadrelli Elsje Alessandra et al. 2011). An  
607 analogue solution could be the MgCO<sub>3</sub> production by precipitating CO<sub>2</sub> and Mg<sup>2+</sup> ions that  
608 could be used in SA fermentation.

### 609 ***Redox potential***

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

613 feature can be used to overcome cellular redox limitations and hence optimizing microbial  
614 production. Redox potential, also known as oxido-reduction potential (ORP), reflects overall  
615 electron transfer and redox balance involved in metabolic activity of microorganisms. ORP is  
616 identified by a ratio of oxidative to reductive redox couple in fermentation operation (Liu et al.  
617 2013). The majority of fermentation products achieved under microaerobic or anaerobic  
618 conditions are considered as bulk commodities. Although many fermentation processes have  
619 been well developed with long-term operability, cost saving is an endless effort, particularly for  
620 biofuels and bio-based chemicals production at bulk quantity such as ethanol and butanol to  
621 address global concern on sustainable development (Kracke et al. 2018). Since redox reactions  
622 and homeostasis are basis for intracellular metabolism, ORP status controls metabolites  
623 profiles, which subsequently offers a strategy to direct the pathway for efficient production of  
624 more and more materials and energy (Liu et al. 2017a). With advanced technologies that can  
625 detect ORP levels and its intracellular influence on gene expression, protein biosynthesis and  
626 metabolites caused by ORP shifts, mechanism underlying this phenomenon can be elucidated.  
627 More robust strains and optimized processes can be developed by redox potential which can be  
628 controlled by metabolic modifications and bioprocess engineering levels, which have been  
629 highlighted in ethanol and butanol fermentations under microaerobic and anaerobic conditions  
630 (Liu et al. 2017a). Figure 3 shows the standard ORP of some redox pairs in an intracellular  
631 metabolism and it is affected by temperature, aerobic or anaerobic conditions. Therefore,  
632 strategies have been implemented to regulate redox potential, including gene modification,  
633 energy input, reagents supplementation and sparging gases. A study carried out by (Park and  
634 Zeikus 1999) showed the impact of redox potential regulation on succinate formation which is  
635 enhanced by 20% when using *A. succinogenes* 130Z in bioelectrical reactors, and its efficiency  
636 depends on the interactions between microorganisms and the working electrode. In batch  
637 fermentation, optical cell density and metabolites formation were shifted with respect to redox  
638 potential levels in the range of -100 to -450 mV, recording an optimal ORP level of -350 mV,  
639 which result in higher SA yield (1.28 mol/mol), productivity (1.18 g/ L/h) and higher mole ratio  
640 of SA to acetic acid (2.02) as reported in literature (Li et al. 2010b). Another study revealed  
641 that the use of redox mediators has the potential to improve fermentation end-products, such as  
642 the case of *Corynebacterium crenatum*, and more reduced environment benefited SA  
643 production when using reagent supplements such as  $K_3Fe(CN)_6$ ,  $Na_2S$  (Chen et al. 2012).



645

646 Figure 3. Standard potential redox  $E^{\circ}$  (mv) at 25°C of some redox pair involved in intracellular metabolism  
 647 (Moscoviz 2017). This photo was done by the authors themselves.

648

### 649 **Current fermentation limitations**

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

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



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

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

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

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

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

#### 740 **SA downstream separation methods**

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

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

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

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

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

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

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

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

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

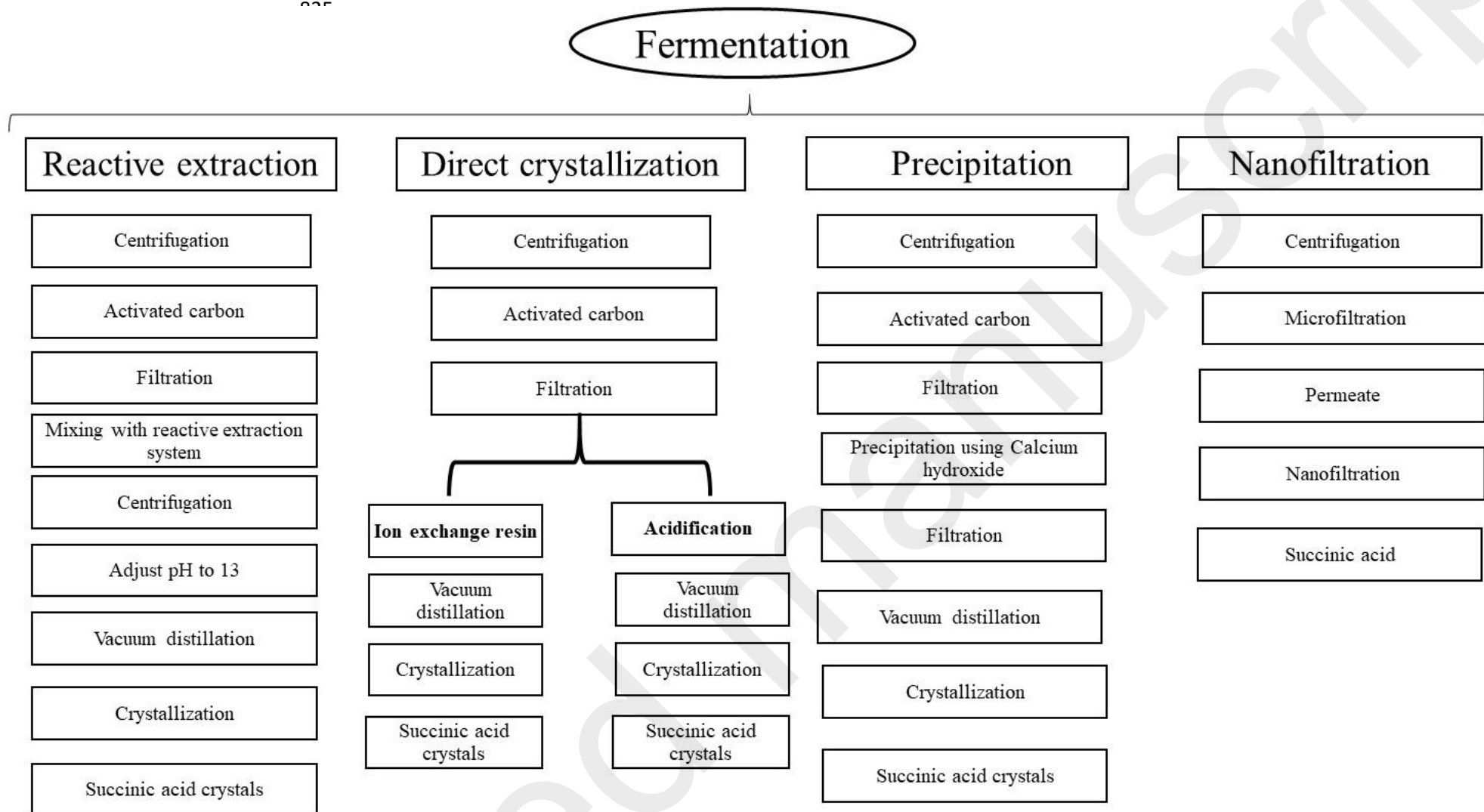
821 should prevent cells destruction, could be done in-situ and requires a minimal chemicals  
822 supplement.

Accepted manuscript

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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 CO<sub>2</sub> 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.

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868



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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-phospshate

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  $\beta$ G6P:  $\beta$ -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<sup>+</sup>: 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

Accepted manuscript