Platform molecule from sustainable raw materials; case study succinic acid

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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.

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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)

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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			(Xue et al. 2016)
Lactic acid		Sugars	(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			(Daorattanachai et al. 2012; Rout et al. 2016)
Levulinic acid		Cellulose or sugars	(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)	

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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

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

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.

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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.

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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-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