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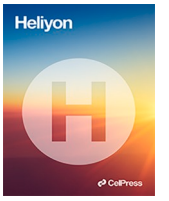

Review article

Succinic acid – A run-through of the latest perspectives of production from renewable biomass

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ABSTRACT

Succinic acid (SA) production is continuously rising, as its applications in diverse end-product generation are getting broader and more expansive. SA is an eco-friendly bulk product that acts as a valuable intermediate in different processes and might substitute other petrochemical-based products due to the inner capacity of microbes to biosynthesize it. Moreover, large amounts of SA can be obtained through biotechnological ways starting from renewable resources, imprinting at the same time the concept of a circular economy. In this context, the target of the present review paper is to bring an overview of SA market demands, production, biotechnological approaches, new strategies of production, and last but not least, the possible limitations and the latest perspectives in terms of natural biosynthesis of SA.

1. Background

Worldwide, there is a constantly growing concern about climate change, the greenhouse effect, fossil carbon dependency, and more rigorous environmental legislation, which has turned the focus of researchers on developing innovative methods for producing industrially important chemicals from renewable resources [1,2]. In this context, extensive research on the fermentative production of organic products such as succinic acid (SA) has been conducted since the US Department of Energy (DOE) published its reports on bio-based chemicals [3,4]. Conventionally, SA was obtained by catalytic hydrogenation of malic anhydride, a fossil-based chemical [5,6], but nowadays SA is one of the most produced organic acids through biotechnological routes with a wide prevalence as bulk material in various industries, such as bioplastics, cosmetics, pharmaceuticals, and food industries [7,8]. According to the recent review paper of Narisetty et al. (2022), the petrochemical SA's production costs were evaluated at €2554/MT, which is more expensive than bio-based SA synthesis (€1045/MT) [9]. Furthermore, SA obtained through the biotechnological process may reduce greenhouse gas (GHG) emissions by more than 60 % when correlated with carbon footprints from petrochemical-based SA production [9].

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SA can be produced by various microbial strains as a secondary metabolite through several metabolic pathways [10]. In fact, commonly-known yeast strains such as *Saccharomyces cerevisiae* and *Yarrowia lipolytica* produce SA as a metabolic co-product through ethanolic fermentation alongside other compounds like glycerol, lactic acid, and acetic acid [5,10,11]. Bacterial species like *Escherichia coli* and *Actinobacillus succinogenes* are also capable of producing substantial quantities of SA (up to 2.5–3.22 g_{SA}/L/h), making them viable at industrial scale production [12–14]. Although, the production of bio-SA at a commercial scale and the potential for a bulk chemical market represent a challenge and require the development of microorganisms that could deliver the product in high concentrations to justify economically feasible recovery. The importance of SA is highlighted by its global production, which is expected to be over 115.000 tons in 2025 (annual market size), Europe being the market leader with a revenue share of more than 30 % in 2021 [1].

Bio-SA applications in the above-mentioned industries are also linked to food additives (E363 -used is beverages, sausages, etc.), surfactants and detergents, flavours and fragrances, and biodegradable polymers (clothing fibers) [2,15]. As in the pharmaceutical industry, SA is used as feedstock for several chemicals, including adipic acid, 2-pyrrolidinone, succinate salts, 1,4-butanediol, maleic anhydride, etc. [8,16,17]. Moreover, one of the most recent applications of SA is related to the production of biodegradable plastic, polybutylene succinate, having properties comparable to polypropylene [7]. Nonetheless, its versatility is closely linked to its water-soluble characteristics, as it is slightly soluble in ethanol, acetone, ether, and glycerine, and not at all soluble in benzene, carbon sulfide, and oil ether [2].

The global bio-SA market was estimated at $117.2 million in 2021 and is expected to grow with a compound annual growth rate (CAGR) of 10.6 % between 2022 and 2030, reaching $272.4 million. Anyhow, out of the three trillion chemicals needed worldwide, it is predicted that by 2025, more than 15 % will come from bio-based source [9]. The rising demand for resins, coatings, dyes, and ink maintain the growth of the global bio-SA market, as bio-SA is a key component in manufacturing these products. In addition, there is a globally increasing request for bio-based products as they are harmless to humans and are environmental friendly alike. The bio-SA market is highly competitive due to several multinational corporations constantly engaged in various production, research, and development activities [6,18].

With all the above in mind, and moreover, the reduction of environmental pollution and the circular economy regulations, the present narrative review paper shows perspectives on the chemical synthesis of the SA produced from fossil fuels, in parallel with the biotechnological approaches of bio-SA production. Last but not least, within this review work was aimed to highlight the most promising renewable sources used for the biosynthesis of SA, considering both hydrophobic and hydrophilic substrates, and at the same time, to point out the possible limitations and the latest trends in terms of natural production of SA.

2. The synthesis of succinic acid

2.1. Chemical synthesis of succinic acid

SA, also called amber acid, is a dicarboxylic acid (1,4-butanedioic acid) with the chemical formula $C_4H_6O_4$ and several particular properties.

At the industrial scale, most of the SA is produced from fossil fuels through petrochemical processes. Until recently, the only available commercial route for SA synthesis was via catalytic hydrogenation [19], electrolytic reduction, or paraffin oxidation of maleic acid or maleic anhydride (MA) derived from fossil resources. For instance, butane or benzene was oxidized to MA (step I), followed by hydrogenation of MA to succinic anhydride and hydration to SA (step II). This technology was well-established, allows SA production at high yields, and fulfil the annual worldwide demand of over 30.000 tons [2,20]. Both production steps of MA from fossil fuels and hydrogenation of MA to SA present several drawbacks, such as environmental and economic-related issues.

Firstly, the unstable oil prices and the limited fossil fuels, as well as worldwide environmental concerns are the main reasons to replace petroleum-based chemicals with bio-based chemicals produced from renewable resources [20,21]. The fossil route can become fully renewable if MA is derived from biomass feedstock [9]. In this sense, oxidation of furfural has shown promising results for producing MA and maleic acid at the laboratory scale. Furfural (2-furaldehyde) is produced from lignocellulosic biomass and is currently a commercially bio-based chemical [22]. SA was successfully produced, almost with complete conversion of furfural from inedible biomass using heterogeneous acid catalysts. SA was selectively formed by oxidation of furfural in the presence of Amberlyst-15 (353 K) as a solid acid catalyst and H_2O_2 (4 mmol) as a green oxidant in aqueous media. Furfural was also oxidized with Na_2MoO_4, $Pd(NO_3)_2$, H_2SO_4, $Hg(NO_3)_2$ with formation of SA [23,24]. Secondly, MA is hydrogenated by Pd/C, Zn/Hg, H_3PO_4 for obtaining SA. The use of homogeneous metals is highly undesirable because of the depleting mineral resources and metal toxicity concerns [24,25]. SA can also be produced via the electrolytic reduction of MA in acidic medium with a better reaction rate under mild conditions. However, this method is expensive because of involving large quantities of electricity [26]. Additionally, new strategies to avoid the safety issues associated with the handling and storage of H_2 gas at high pressure in conventional hydrogenation process are required. The aqueous phase hydrogenation of MA to SA has been proved in the absence of any organic solvent and using stoichiometric amount of formic acid (FA) as source of green H_2 and using Pd/C as the best catalyst [27]. FA is liquid at room temperature and can also be obtained from biomass. Recently, Orozco-Saumell and colleagues (2022) explored the robustness limits of Pd/C catalysts and their deactivation under highly demanding operating conditions using high Weight Hourly Space Velocity (WHSV). The catalyst was very stable and deactivation could only be detected when the WHSV was higher than 13 $g_{MA}\ g_{catalyst}^{-1}\ h^{-1}$. The catalyst's deactivation can be compensated by increasing the temperature and/or the contact time (decreasing the flow rate) and still achieving very high SA productivity. As future perspective, more research must be directed at how to prevent/minimize the leaching of Pd, revealing the nature and location of the organic deposits and preventing the formation of deposits and the CO chemisorption [19]. Fig. 1 shows a

conventional route for producing SA from fossil fuels and a bio-based chemical route of SA production from biomass-derived sources.

2.2. Biochemical synthesis of succinic acid

The biosynthesis of the targeted dicarboxylic acid, namely SA, can be generated through the cellular tricarboxylic acid cycle (TCA-cycle or Krebs cycle) [8]. There are several studies that analyse the best method of succinate production from facultative-anaerobic to anaerobic fermentation technologies, with the first best known microorganisms including *Actinobacillus succinogenes*, *Anaerobiospirillum succiniciproducens*, *Mannheimia succiniciproducens*, *Basfia succiniciproducens Yarrowia lipolytica*, *Pichia kudriavzevii*, *Clostridium* spp., *S. cerevisiae*, and the versatile strain of *Escherichia coli* [28–32].

The effectiveness of fermentations using *A. succinogenes* as a host strain for SA production exhibits variability influenced by various factors. These factors encompass the choice of substrate, environmental conditions such as pH, viscosity, temperature, and substrate concentration [33]. In addition to natural SA producers, significant efforts have been directed toward metabolic engineering of various strains to facilitate the production of targeted C4-dicarboxylic acids. For instance, the microorganism *Corynebacterium glutamicum* S071 serves as an illustrative example, achieving an impressive SA concentration of 152.2 g L^{-1} under specific anaerobic fermentation conditions [29,34]. Some other microorganisms that have been metabolically engineered for the production of succinate, or increase the original SA pproduction rate, are *E. coli* strains (e.g., W1485, DY329, SD121, AFP111, MG1655, NZN111), *C. glutamicum* (ATCC 13032, BOL), *Y. lipolytica* (Y-3314, PGC01003), *S. cerevisiae* (CEN, PK2–1C, PMCFfg), *Lactobacillus plantarum* (NCIMB 8826), and several other less known strains [35–37]. In these microbial species, SA biosynthesis is regulated over gene expression encoding key enzymes that are engaged in these pathways [37]. The production of SA across various microorganisms is characterized by notable functional differences. Comparative assessments have underscored several advantages associated with SA production in yeasts when compared to bacteria. Notably, yeast organisms exhibit a compartmentalized approach to SA biosynthesis, partitioning pathways between the cytoplasmic and mitochondrial environments. This differentiation is particularly advantageous when considering the reverse TCA pathway [10]. Furthermore, yeasts demonstrate enhanced resilience to low pH conditions, facilitating the production of succinate via the fumarate reductase enzyme. They also possess the capability to utilize transporters for succinate extrusion from the cell, generate fewer undesirable by-products, and offer simplified processes for the isolation and purification of the final SA product [38–40]. This juxtaposition highlights the critical perspective that must be considered when evaluating SA production in distinct microorganism hosts, emphasizing the nuances that impact their performance and efficiency.

The biochemical succinate production can be categorized as metabolic or non-metabolic, taking place also in mitochondria (anabolic and catabolic courses), but if it accumulates, it is carried to the cytosol. Being the nucleus of the Krebs cycle and being performed by succinyl coenzyme A synthetase out of succinyl coenzime A (Fig. 2), in a commutative reaction, it can maintain multiple roles [41]. The metabolic production of SA involves several pathways, each with its unique characteristics and potential drawbacks. These pathways include the reductive routes, such as the phosphoenolpyruvate carboxylase (PPC) pathway, phosphoenolpyruvate carboxykinase (PCK) pathway, and malic enzyme (MAE) pathway, as well as the glyoxylate shunt pathway, the oxidative branch of the TCA cycle, and a by-product pathway known as the 3-hydroxypropionate cycle (3HP), which can yield succinate as a secondary product [39,42]. While these pathways offer flexibility and diverse options, it's essential to critically evaluate their efficiency, resource requirements, and environmental impact. Each pathway involves specific enzymes, such as PPC, PCK, pyruvate carboxylase (PYC), MAE, propionyl-CoA carboxylase (PCC), and acetyl-CoA carboxylase (ACC), which contribute to their functionality. The selection of a particular pathway should consider factors like energy efficiency, carbon source availability, and the potential for by-product formation, as these aspects can significantly influence the overall yield and sustainability of succinic acid production.

The reductive branch (reverse TCA cycle) is the main pathway used by the anaerobic microorganisms (predominantly used by fungi and bacteria) that involves two NADH units. Still, through this way, from 1 mol of glucose (after the conversion to phosphoenolpyruvate (PEP), oxaloacetate, and malate), only 1 mol of SA can be obtained (1:1). Accordingly, the highest efficiency is restrained by

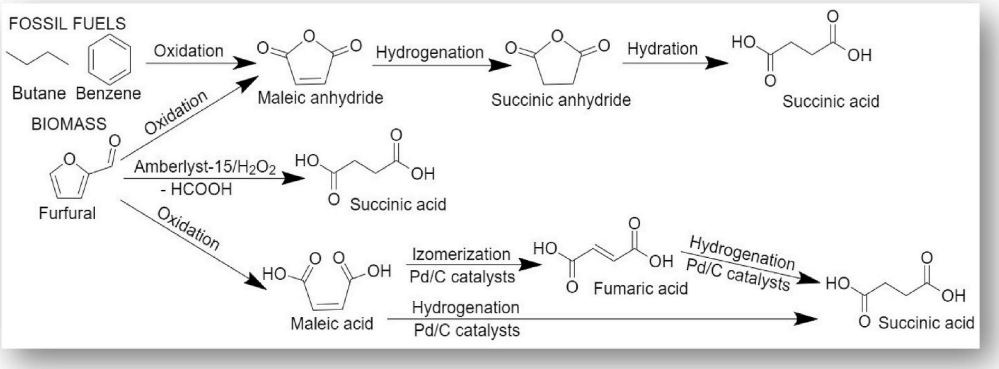

Fig. 1. Examples of chemical reactions for producing SA from fossil fuels and biomass-derived sources. Adapted after [16,20,21].

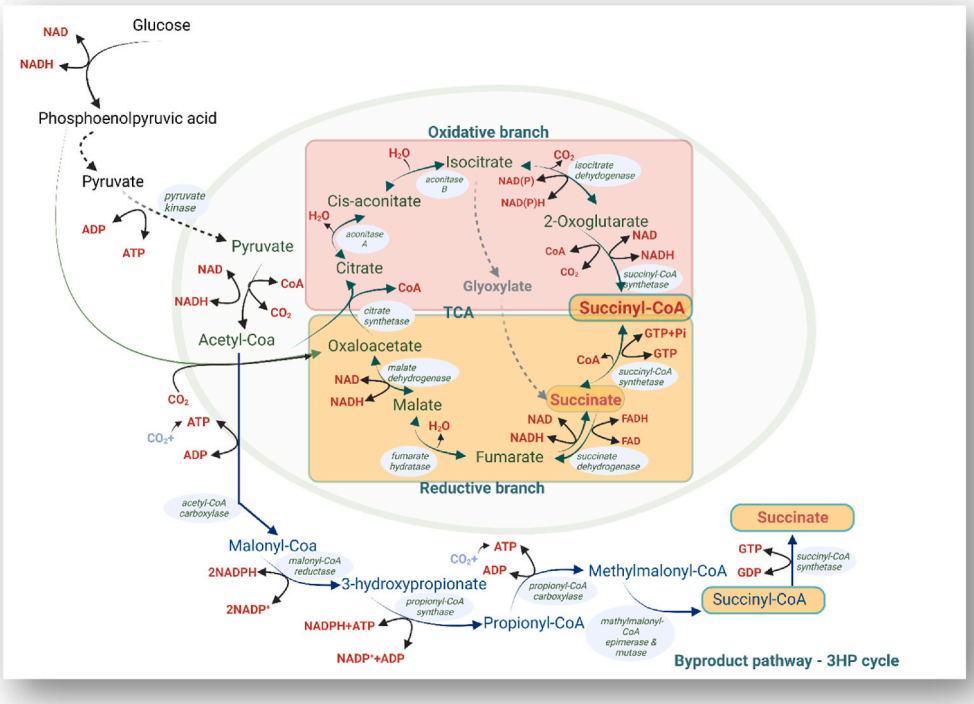

Fig. 2. Biosynthetic pathways to succinic acid generation. Adapted after [41,104].

NADH deficiency. Within this method takes place the fixation of CO_2, an essential function of the PEP carboxylase pathway, mainly with the help of the PCK enzyme (but also MAE, PPC, and PYC) [35,43]. This enzyme is able to facilitate the decarboxylation of PEP, along with ADP and bicarbonate, to create ATP and oxaloacetate [42]. With the help of malate dehydrogenase from oxaloacetate through mitigation, malate is produced employing NADH as a cofactor. Malate is then converted from here with fumarate hydratase which generates fumarate and also, through succinate dehydrogenase SA is produced [40].

The other TCA pathway, specifically the oxidative pathway, requires the addition of oxygen (excessive NADH and other cofactors are generated) and implies the glycolysis of glucose to pyruvate, its transformation through pyruvate dehydrogenase to acetyl-CoA and CO_2. Acetyl-CoA reacts with oxaloacetate for citrate formation. Finally, it is transformed to SA over double decarboxylation stages producing two extra CO_2 molecules along with one NADH and one SA molecule [38]. Through oxidative phosphorylation, ATP is generated effortlessly. Nevertheless, NADH is extracted from the reductive cycle [44,45]. The glyoxylate path is triggered if no oxygen is present in this pathway. Besides, through the activation of the glyoxylate shunt and by combining both pathways (reductive and oxidative), succinate production can be increased. This method implies first the condensation of oxaloacetate together with acetyl-CoA which constructs citrate, followed by isocitrate isomerization and finally through the activity of isocitrate lyase takes place the conversion to glyoxylate and SA. Additionally, the cycle is finalized by condensing glyoxylate and the alternative acetyl-CoA molecule to create MA and ultimately oxidising to oxaloacetate [42,44].

The byproduct, 3-hydroxypropionate cycle (3HP), is performed under aerobic environmental conditions and is a natural CO_2-fixing pathway, mostly present in photosynthetic green non-sulphurous bacteria. The 3HP process is intricate and comprises 16 enzymatic stages catalysed by 13 types of enzymes. From acetyl-CoA through acetyl-CoA carboxylase enzyme malonyl-CoA is generated, afterwards reduced to malonyl-CoA. This malonyl-Coa is transformed to 3-hydroxypropionate, from where with the propionyl-CoA synthase (Propionyl-CoA), and with propionyl-CoA carboxylase (Methylmalonyl-CoA), and finally methylmalonyl-CoA epimerase and mutase convert this methylmalonyl-CoA towards its isomer succicnyl-CoA. Following de-esterification, SA is produced with the use of succinyl-CoA synthetase. Through this pathway also from 1 mol of acetyl-CoA 1 mol of SA can be obtained, with an additionally attached 2 mol of CO_2 [31,46,47]. This pathway is better in fixating CO_2, correlated with pyruvate or PEP carboxylation, because of the two essential enzymes acetyl-CoA carboxylase and propionyl-CoA carboxylase. While there are multiple pathways available for SA production, it's evident that significant challenges persist in enhancing the final SA yield. Addressing these challenges is crucial for optimizing production efficiency. One approach involves modifying the substrate by utilizing waste materials, which can be advantageous due to their minimal or low costs. Additionally, employing metabolically engineered microorganisms with adaptability and efficient key enzymes offers another avenue for improving biosynthesis pathways. However, it's essential to critically assess the feasibility and scalability of these strategies. Factors such as substrate availability, process scalability, and the actual impact on SA yield need to be thoroughly evaluated to determine their practicality in achieving higher SA production.

3. Renewable sources for the bioproduction of succinic acid

Organic products such as the SA represent high-value compounds that can be produced from renewable sources of both lipophilic and hydrophilic origin. The elevated amount of SA that is required by different industries such as bio-based plasticizers, polyester polyols, lubricants and biopolymers, food products, cosmetics, or pharmaceuticals, is constantly increasing (27.4 % annual growth rate), therefore new methods of cost and environmental-efficient production must be pointed out [48–51]. As is shown by the scientific literature, SA is most often produced by applying biotechnological routes, such as fungal-derived microbial cells (e.g., *Aspergillus awamori*), bacterial cells (e.g., *A. succinogenes*) or yeast cells type (e.g., *Y. lipolytica*) that are able to assimilate and convert different renewable substrates and excrete the targeted product outside the cell [8,48,52]. In addition, to raise the efficiency of the bio-based SA production with minimal costs, the integration of SA production with other biorefinery processes (such as the lignocellulosic biomass conversion), is more in the eyes of biotechnologists in order to maximize the biomass resources and to enhance the overall sustainability of the process [53,54]. As was shown that SA has quite a high production cost (up to $3 per kg) and a negative impact concerning the environment when it comes to the commercial sources of carbon (especially in petrochemical process), the interest to substitute these with renewable substrates represents a hot research topic for the biosynthesis of SA [48,55]. The focus on utilizing non-food biomass aligns with the pursuit of sustainable and environmentally friendly bioprocesses. Integrating SA production with lignocellulosic biomass conversion pathways presents an appropriate opportunity to create synergies between various bio-based production routes. This integration can potentially allow for the co-utilization of biomass feedstocks, leading to increased efficiency and reduced waste [56].

The intensification of the bio-based SA production process through bioreactor design and process optimization to meet the sustainability criterion for this operation, is another crucial aspect. The bioreactor configuration (free-cell, immobilized cell, packed bed bioreactor, fluidized bed reactor, etc.) and operation mode (batch, fed-batch, repeated, continuous) impact the final bio-SA concentration and productivity [57]. For instance, in a study conducted by Uysal and Hamamci regarding the SA production from cheese whey by employing alginate-immobilized *A. succinogenes* cells in batch cultivation, led to an elevated SA yield of 74.9 % and 1.09 g L^{-1} h^{-1} productivity, towards the free cells batch cultivation that led to the highest yield of 2.49 % [58]. In another study performed by Ercole and his team, alginate-immobilized cells of *A. succinogenes* proved efficacy in the substrate conversion to SA up to 76.4 % (productivity of 35.6 g $L^{-1}h^{-1}$ and concentration of 31 g L^{-1}), when fluidized bed reactor was used [59]. Poly-vinyl-alcohol beds entrapping *A. succinogenes* cells are also efficient in the conversion of substrate into bio-SA during batch fermentations yielding up to 0.621 g g^{-1}, and up to 0.699 g g^{-1} during fed-batch trials [60].

Last but not least, a generous range of renewable biomass that can be successfully converted into SA by means of microbial entities is both of lipophilic and hydrophilic nature, as it is described in the following sub-sections.

3.1. Lipophilic substrates for bio-SA production

Among the crude renewable resources of carbon necessary for the growth of oleaginous strains for the production of bio-SA are included the hydrophobic substrates such as fats, greases, waste cooking oil, and crude glycerol derived from biodiesel [10,61,62]. The largest quantities of used cooking oils and fats result from households, hotels, restaurants, and the catering sector. According to estimates, used cooking oil accounts for 20 %–30 % of the world's annual consumption of vegetable oil (41–67 MT/year) [8]. As the majority of wasted cooking oils are either eliminated as solid residues and end up in landfills or are discharged through sinks and end up in wastewater collecting and purification facilities, represent an additional reason to use these lipid residual fractions as nutrient source for the biotechnological production of SA [28,63–65]. From another perspective, according to the current circular economy trend, used cooking oil is considered a proper renewable source of energy that can be used as biomass for the production of value-added green chemicals such as biofuels, plasticizers, binders, epoxides, surfactants, lubricants, polymers, and biomaterials, [30,66,67].

Biomass is the primary source of production for biofuels including bioethanol and biodiesel. The biodiesel production process is based on triglycerides derived from vegetable oils or animal fats, but the major disadvantage of the biodiesel manufacturing process is its insufficient financial sustainability [40,68]. Therefore, this disadvantage can be minimized by valorising the by-products of the biodiesel process, such as crude glycerol, by integrating them into biotechnological conversions for the manufacturing of value-added products [69,70]. Biodiesel-derived glycerol consists of elevated amounts of lipophilic compounds with nutritional properties (e.g., oleic acid, linoleic acid) for the oleophilic microorganisms like yeasts, which are able to produce organic compounds like SA [10,71,72]. For example, in our previous studies have observed that yeast species of *Yarrowia* and *Candida* genus adapt easily to lipophilic substrates and excrete outside the cell organic acids like SA and citric acid [8,61]. Moreover, in another recent study performed by Efthymiou and colleagues (2021) was pointed out that not only yeasts, but bacterial strains too adhere efficiently to the lipophilic substrates. These authors created a bio-economy business model that uses by-products from the sunflower biodiesel industry to produce SA by fed-batch fermentation using *A. succinogenes* and *Y. lipolytica* [48]. The integration of *A. succinogenes* in the fed-batch cultures using sunflower meal fractions as substrate resulted in a concentration of 34 g L^{-1} SA, with a process yield of 0.6 g g^{-1}. On the other hand, through the integration of the oleophilic yeast strain of *Y. lipolytica*, the addition of crude glycerol to the sunflower meal substrate boosted the concentration of SA to 69.1 g L^{-1} (yielding 0.39 g g^{-1}). As a consequence, the sunflower meal fractions containing crude glycerol provided a nutritious substrate for proper SA synthesis [48]. In another research study conducted by Vlysidis and colleagues (2011) was explored and estimated the co-production of biodiesel and SA using the idea of integrated biorefineries from four distinct biorefinery schemes. The simulated process included the waste disposal of crude glycerine, the purification of crude glycerine, and the fermentation of glycerine to produce SA. The synthesis of SA was based on the conversion of glycerol to succinate,

followed by a downstream separation process that purifies and crystallizes the product to obtain SA crystals [68]. The analysis revealed that integrated SA production preceded by biodiesel can enhance the financial sustainability of biorefineries by 60 % over a 20-year timeframe [68]. As a result, renewable biomass has been validated as a significant resource in the production of biofuels and high-value chemicals in key industries such as organic acids, biopolymers, food products, medicines, and cosmetics.

3.2. Hydrophilic substrates for bio-SA prodution

As mentioned previously, SA is a valuable compound that can be obtained from various sources, but mostly from oily substrates [16,73]. In addition to hydrophobic sources, a significant place in the biogenic SA production is occupied by agro-industrial residues, from the perspective of increasing the waste quantities worldwide [74,75]. This sustainable alternative, as a solution to waste valorisation, to reuse the sub-products from agro-industrial sources can raise questions regarding storage and processing time. As an optimistic possibility to preserve and reuse on long term, from an economical point of view, Hillion and colleagues (2018) have identified a solution to co-ensiling two different wastes (sugar beet leaves and wheat straw), which had better stability over 180 days, for further use in anaerobic digestion, and which could be considered as a feasible solution for SA production from agro-industrial-derived biomass [76].

As has been previously reported in the literature, all the agro-industrial-based by-products are nutrient-rich substrates that significantly contribute to the obtaining of bio-based products [77,78]. The composition of all these wastes is represented by more than 60 % carbohydrates. This substrate can be used in the production of SA, and the most common sources are represented by vegetables, fruits, and cereals [79–81]. As highlighted by Zhang et al. (2013), products rich in carbohydrates, in this case, bakery wastes, were used as efficient carbon sources in the form of hydrolysates for the SA production [82]. All these results have been concluded in a big project called “Starbucks Biorefinery”, by bringing into the light how valuable can be the waste fractions coming from the food industry [82]. In this context, Filippi and the group (2022) also developed an integrated biorefinery by using winery wastes like grape pomace, stalks, and wine lees as a feedstock for SA production by *A. succinogenes*. In this particular example, winery wastes were enzymatically hydrolysated and converted into 37.2 g L^{-1} SA. The same biorefinery produced 42.65 g bacterial cellulose, 24.3 g oil, 40.3 g phenolic-rich extract, 80.2 g ethanol, 624.8 g crude tannin extract, 20.03 g tartaric acid and 157.8 g SA from 1 kg of each waste stream [83].

There have been numerous studies that investigate the sources from which SA can be produced [84]. In this regard, there exists a considerable body of literature on using *A. succinogenes* as bacterial strain in the fermentative processes of different types of biomass. In the case of sorghum bagasse as primary hydrophilic source, *A. succinogenes* 130Z was used by Lo and collaborators (2020), and the results pointed out a conversion rate from 29.2 g L^{-1} of cellulosic glucose to 17.8 g L^{-1} of SA. As intermediate steps used in this research, mild phosphoric acid pre-treatment and subsequent enzymatic hydrolysis were applied [73]. In addition, in line with the same *A. succinogenes* strain (130Z), it was observed that CO_2 pressure in the cultivation broth impact the final metabolites formation. In this regards, a final titer for SA of 25.5 ± 2.4 g L^{-1} was detected at a gas pressure of 1.4 atm, while the yield raised from 0.48 g g^{-1} to 0.64 and 0.65 g g^{-1} when 1.4 and 1.6 atm pressure was applied, respectively [85]. From hydrolysate of Napier grass used by Lee and colleagues (2022) for SA production through *A. succinogenes* was achieved 312 17.54 ± 3.80 g L^{-1} with a productivity of 0.79 ± 0.07 during batch cultivations [86].

Another renewable source that can be more rentable for the price of SA production and commercialization is the organic fraction of municipal solid waste (OFMSW) from MSW treatment plants. In the study performed by Stylianou et al. (2020) the SA obtaining yield was 29.4 g L^{-1}, using the same bacterial strain as the previously mentioned study, namely *A. succinogenes* 130Z (DSM-22257). The explanation for the increased SA yield was associated with the supplementation with 5 g L^{-1} yeast extract and 5 g L^{-1} $MgCO_3$ [52]. OFMSW was also used by Ladakis and collaborators (2022) for SA biosynthesis. This group hydrolysated OFMSW with crude enzymes derived from *Aspergillus awamori* via SSF to make the sugars more available to *A. succinogenes*, which finally delivered 31.7 g_{SA}/L with 0.68 g g^{-1} yield and 0.67 g L^{-1} h^{-1} productivity [87]. Nonetheless, *Y. lipolytica* strain PSA02004 proved to be efficient in converting hydrolysate OFMSW into SA under fed-batch fermentation inside of an electrochemical membrane bioreactor. By optimizing pH control, membrane surface area, and other factors like electrolysis cell operation, the process achieved high SA yield (66.7 g_{SA}/L, 0.51 g g^{-1} yield, 0.78 g/(L·h) productivity, high coulombic efficiency (66.2 %) and relatively low electricity consumption for SA separation (2.6 kWh/kg_{SA})), and purity without the need for conventional purification methods, making the SA suitable for various applications [88].

Hemicellulosic fractions of two important lignocellulosic feedstock such as olive pits and sugarcane bagasse also represent a valuable carbon source for SA production by *A. succinogenes*. For instance, Jokodola and colleagues (2022) used this feedstock as a xylose-rich nutrient source for SA biosynthesis and achieved 36.7 g L^{-1} and 0.27 g g^{-1} [89]. Other agro-industrial by-products that were used for the production of SA are corn stalks and cotton stalks. By employing the same strain of *A. succinogenes* as in previous studies, the achieved SA yield was 17.8 ± 0.2 g L^{-1} in the case of corn stalks and 15.8 ± 0.1 g L^{-1} for cotton stalks. Anyhow, to obtain high concentrations of carbohydrates and an increase content of available glucose (65–80 %), an enzymatic treatment was applied to the solid residual fractions beforehand [90]. In the same line, corn stalks hydrolysates as such and in combination with other lignocellulosic fractions derived from tomato, grapes, and papaya processing are valuable nutrient substrates for the growth of *E. coli* strains and production of bio-SA [91,92]. Another extremely valuable carbon source is represented by the organic waste fractions obtained from restaurants. In this case, a recombinant strain of *E coli* was proved to be an efficient SA producer from food waste hydrolysate by reaching a yield of 29.9 g L^{-1} SA and an overall yield of 0.2 g g^{-1} substrate [37]. According to these studies, household kitchen waste can also be used in the production of biogenic SA [37,93]. Referring also to the pathogenic *E. coli* species, it was observed that the engineered strains with plasmids isolated from *Bacillus subtilis* and *Rhizobium etli,* and grown on diverse sugar mixtures (glucose,

xylose) can be exploited for better SA productivity results. These combinations allow individual bacterial strains to be modified without antagonistic effects and can be applied to different substrates [94]. *Citrobacter amalonaticus* is another bacterial strain that proved to be efficient in producing SA from renewable feedstock. Amulya and Mohan (2022) tested *C. amalonaticus* in acidogenic conditions under continuously supply of CO_2, and observed that up to 14.7 g L^{-1} SA is produced from alternative resources [95].

Molasses represent another low-cost hydrophilic substrate of easy-accessible glucose needed for the production of bio-SA. For instance, in a study conducted by Liu et al. (2008), the concentration of SA was 55.2 g L^{-1}, using *A. succinogenes* CGMCC1593 and molasses as the main carbon source [96]. Similar results were obtained by Shen et al. (2014), where the concentration of SA was 57.43 g L^{-1} from the fermentation of molasses [97]. The outcomes of the microbial conversions depend a lot on implemented biotechnology. For example, cane molasses fermented by *A. succinogenes* through a fed-batch fermentation with the utilization of an electric MEC bioreactor was proved to be more efficient in terms of SA yield than those fermented through a simple fed-batch process [98]. Another way to improve the efficiency of bio-fermentation with *A. succinogenes* consists in the adoption of the cell-recycled continuous fermentation (CRCF) process, which increases the SA production yield by 5.1 fold approximately [99]. Two other different sources deriving from the food sector from which SA can be generated are whey and lactose. As has been previously reported by Louaste et al. (2020), whey and lactose can be valuable substrates for SA biotechnological production, as being recorded a higher yield in the case of lactose (65 %) as in the case of whey (62.1 %) [36]. Last but not least, besides the organic residues derived from the food sector, biodegradable fractions contained by some textile materials can be used as feedstock for the natural production of SA, as has been reported by the latest literature [100]. In an experimental research designed by Li et al. (2019), was shown a two-step bioconversion process of biodegradable textile into SA. The authors applied an enzymatic hydrolysis followed by a bio-char treatment in order to eliminate the azo dyes, and the resulting glucose-rich hydrolysate was used as nutrient source for *Y. lipolytica* PGC202, that gave further a bio-SA titer and yield of 22.1 g L^{-1} and 0.53 g g^{-1}, respectively, by using an optimized fermentation medium [101]. Anyhow, impressive quantities of SA can be achieved biotechnologically from a variety of renewable biomass resources, as it can be observed from Table 1.

Anaerobic fermentation is a green technology alternative through which bio-SA can be produced from different valuable and little-exploited resources. All the by-products resulting from the food industry, or even from the household level, can be reused to extract

Table 1
Examples of microbial entities that efficiently convert biomass into SA.

Microorganism	Substrate	Fermentation type	SA titer (g L^{-1})	SA yield (g g^{-1}) or (mol mol $^{-1}$)	SA productivity (gL^{-1} h^{-1})	Ref.
E. coli C (TXXP + TXG0)	Glucose Xylose	Dual phase fermentation	–	0.97	1.7–2.0; 0.3–0.4	[94]
E. coli BA002	Sorbitol Glucose Glutamate	Anaerobic fermentation	13.1 ± 0.4 9.8 ± 0.2 7.2 ± 0.3	–	–	[102]
E. coli KLPPP	*Palmaria palmata* hydrolysate	Dual-phase fermentation	22.4 ± 0.12	1.13 ± 0.02	–	[103]
E. coli K12	Glucose Glycerol	Anaerobic fermentation	–	0.9 0.6	–	[104]
E. coli SD121	Corn stalk hydrolysate	Anaerobic fermentation	36.55	0.77	-	[92]
E. coli BS002	*Laminaria japonica* hydrolysate	Dual-phase fermentation	17.44 ± 0.54	1.01 ± 0.05	–	[105]
E. coli KMG111	lignocellulosic hydrolyzates	Fed-batch	32.16	0.86	2.15	[12]
E. coli M6PM	*Cocos nucifera* water	Dual-phase fermentation	11.78 ± 0.02	1.23 ± 0.01	–	[106]
A. succinogenes ATCC 55618	Cheese whey	Repeated-batch fermentation	–	0.18	0.72	[57]
A. succinogenes ATCC 55618	Sugars from *Chlorella vulgaris* ESP-31	Continuous fermentation	–	0.62	3.53	[60]
A. succinogenes NJ113	Glucose, corn-liquor	Batch-fermentation	20.77	0.63	–	[107]
A. succinogenes GXAS137	Duckweed *Landoltia punctata*	SSSF	75.46	0.83	–	[108]
A. succinogenes Z130	Citrus peel waste hydrolyzate	Batch-fermentation	8.3	0.7	–	[109]
A. succinogenes Z130	Sweet sorghum bagasse	Batch-fermentation	17.8	0.61	–	[73]
A. succinogenes Z130	Cane molasses	Batch, Fed-batch, repeated batch	45.6	0.76	1.27	[110]
A. succinogenes Z130	corn stover hydrolysate	Batch-fermentation	39.6	0.78	1.77	[111]
S. cerevisiae Z56	sucrose	Batch-fermentation	1.13	–	–	[112]
S. cerevisiae (2nd-generation)	glycerol	Batch-fermentation	–	0.6	0.25	[113]
Y. lipolytica PSA02004	Sugarcane bagasse	Free-cell batch	33.2 ± 0.3	0.58 ± 0.01	0.33 ± 0.01	[72]
Y. lipolytica PSA02004	Organic biowaste	Batch Fed batch	54.4	0.44	0.82	[114]
Y. lipolytica PSA02004	Acetate	Batch Fed-batch	20.1	–	–	[115]
Y. lipolytica PGC01003	Crude glycerol	Fed-batch	160.2	0.4	0.4	[116]

valuable compounds with applicability to a wide spectrum of uses, such as SA. While using this green technology, several factors must be considered to optimize the fermentation process. Among these factors are the carbon source used (in this case the agro-industrial by-products), the nitrogen source, pH, and also the fermentation parameters [117,118]. Corroborating all these factors (e.g., green technologies, waste recycle, environmental impact, circular economy), with the aim of providing alternative sources to obtain broad-spectrum beneficial compounds, represent key points started and continued successfully by researchers and industry alike, so as highlighted in the present review.

4. Limitations in succinic acid manufacturing and production

The increasing interest in succinic acid (SA) derived from biomass can be attributed to growing environmental concerns and the depletion of fossil resources [9]. However, several significant challenges hinder the widespread adoption of bio-SA in the market. These challenges primarily revolve around the substantial costs associated with both raw materials and the complex recovery and purification processes involved. Moreover, the overall manufacturing cost can be influenced by factors such as low productivity and suboptimal yield of the desired product [119]. Addressing these issues is imperative for bio-SA to become a more cost-effective and sustainable alternative. A critical examination of the various cost components and process efficiencies is essential to develop strategies that can mitigate these challenges and promote the broader utilization of bio-SA.

One of the most common challenges of the SA bioprocess is its mode of operation at neutral pH. It leads to the generation of SA salts, and thus greatly complicates the downstream process [9,120]. Also, limiting factors for SA production include the processing, purification, separation, and recovery phase [43]. The separation method needs to be time and cost-efficient and increase SA productivity and yield. Current downstream procedures have inherent limitations, thus advancements are needed, particularly in terms of purity, yield, and energy usage. In a fermentation-based process, the cost of downstream purification often makes up more than 60 % of the overall production cost [71,121]. For SA purification, the separation of by-products, involving acetic, lactic, formic, citric, and pyruvic acids, is mainly important. Therefore, to extract and recover SA from fermentation broths, a cost-effective downstream technique is required [55]. Pre-treatment, which may also account for up to 30 % of the whole cost, is regarded as one of the most expensive processes stage [9]. To optimize the potential of biomass to replace non-sustainable resources and satisfy global demand for SA production, the implementation of the circular economy system toward actualizing sustainable waste management is of urgent need [122,123]. Research studies showed that reducing equivalents (NADH) plays an important role in the production of bio-SA and may also be considered a limitation in biogenic SA production [18,43]. Anyhow, the competitive strategies that stands at the basis of industrial production of bio-based SA definitely involve the metabolic manipulation and stimulation of particular microbial entities that naturally biosynthesize SA, including techniques of genetic engineering.

Last but not least, the entire production chain of SA faces several critical limitations and challenges that can be summarized, as follows.

- SA production heavily relies on feedstock availability and cost-effectiveness, with bio-based alternatives introducing issues related to feedstock competition and land use;
- Yield and productivity issues persist, resulting in high production costs;
- Downstream processing for SA purification remains energy-intensive and generates waste by-products;
- Strain stability is a concern for genetically modified microorganisms used in production;
- Precise control of fermentation conditions is necessary but adds complexity and cost;
- SA faces competition from other chemicals in the market, demanding improved cost-efficiency and product quality;
- Environmental impacts, such as land-use changes and resource consumption, must be managed;
- Regulatory hurdles and market demand fluctuations add complexity, while maintaining accurate sustainability claims is essential;

Addressing these limitations requires ongoing research, innovation, and industry-wide collaboration [37].

5. Perspectives and future trends in SA production

The most critical challenges in SA production are secondary by-products inhibition, the build-up of specific by-products, auxotrophy, pH sensitivity, lack of equipment, and NADH restriction. These factors can affect SA performance, purification process, along with the medium cost [1].

In recent years, the major issue with producing bio-based SA was the by-products accumulation. To overcome the build-up of the residues (presence of proteins, microbial cells, carbohydrates, and cell debris), membrane-based separation approaches have been suggested as the most promising among the traditional technologies (reactive extraction, electrodialysis, Ca-precipitation, and crystallization) [18]. Anyhow, membrane fouling restricts its application in bio-refineries. Thus, nanoparticles encapsulated in the composite membrane need to be evaluated due to their low fouling capability and resistance to high pressure and complex feed [11].

Another restriction in the increased SA yield is the NADH restriction. As discussed above, for NADH units, the majority of the researchers have focused on TCA cycle oxidation or glyoxylate shunt. Its application is complex because bacteria must perform oxidative and fermentative metabolism simultaneously. For example, synthesizing 1 mol of SA by glucose in *E. coli* requires 2 mol of NADH [18]. In this context, removing competing processes (metabolic gene knockouts) that consume NADH would improve precursor availability for target SA synthesis.

Furthermore, other requests of bacterial strains in SA production consist of preferring neutral pH conditions. But, the production of

SA results in an acidic environment. In this context, yeasts are a popular alternative approach because of their genetic editing tools, effective intracellular pH regulation, and strong endurance to harsh fermentation conditions [11]. However, yeast producers' SA yield is still low compared to bacterial hosts. It is essential to enable the bio-based synthesis of SA by developing a competitive acid-tolerant strain to reach the maximum concentration of SA.

In particular, high-throughput gene target identification techniques such as sRNA technology, genome-scale computational tools, and the high-throughput robotics system are being explored to accelerate strain generation and screening. However, there are still certain obstacles to overcome in designing the adaptability of microbial hosts. As reported by several researchers, most bacteria are auxotrophic for amino acids and vitamins [124,125]. Therefore, supplementing minimum media or using a nutrient-rich complex medium must be supplemented at an additional cost. Regarding the production cost (comparative with the petrochemical approach) and environmental advantages, SA represents a much more affordable option than other bio-based chemicals (additional CO_2 fixing and using renewable non-food biomass as a substrate).

Besides the metabolic engineering challenges, it is also acknowledged the importance of a detailed techno-economic analysis in understanding the cost drivers, market dynamics, and commercialization prospects associated with SA production. Moving forward, it is highly important to delve deeper into these aspects to provide a more comprehensive understanding of the economic landscape, including factors influencing production costs, market demands, scalability, investment attractiveness. Furthermore, the significance of environmental sustainability and life cycle assessments (LCAs) in evaluating the overall impact of bio-based SA production compared with petrochemical-based SA production on the environment, is also elevated [53]. Comparing the LCAs for SA production from biomass and petrochemicals involves evaluating the environmental impacts of each production pathway across their respective life cycles [126].

Hence, the imperative task at hand involves the creation of a truly competitive bio-based SA manufacturing method that can effectively tackle these multifaceted challenges. This endeavour fundamentally hinges on the enhancement of strains through metabolomics. Looking ahead, it becomes increasingly apparent that we must pivot towards a more comprehensive approach, where strain engineering and optimization, intimately entwined with sophisticated modelling, play a pivotal role in driving the cost-efficiency of bio-based SA production to the forefront.

6. Conclusions

SA represent an extremely valuable platform compound with a wide range of applications, whose market demand is continuously increasing. Chemical synthesis of SA from fossil fuels represents the main route for fulfilling the worldwide demand for SA. An increased interest in transforming the fossil route of producing SA via MA hydrogenation into a fully renewable route has been observed in the past few years. However, future research must be directed at how this innovative strategy in producing bio-based SA could become technically and cost-effective feasible. Even though there are several studies that tackle SA production through pathway regulation, the utilization of low-cost substrates, or through metabolic engineering, SA production is not yet economically feasible through biochemical synthesis. To resolve these issues, and to be more competitive compared to fossil based chemicals, further studies regarding the engineered microbial factories along with their key plasmids, genes, and enzymes that have an important role in SA production should be also considered.

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Data availability statement

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

CRediT authorship contribution statement

Laura Mitrea: Writing – original draft, Conceptualization. **Bernadette-Emőke Teleky:** Writing – original draft, Funding acquisition. **Silvia-Amalia Nemes:** Writing – original draft. **Diana Plamada:** Writing – original draft, Conceptualization. **Rodica-Anita Varvara:** Writing – original draft, Visualization. **Mihaela-Stefana Pascuta:** Writing – original draft, Validation. **Calina Ciont:** Writing – original draft. **Ana-Maria Cocean:** Writing – original draft. **Madalina Medeleanu:** Writing – original draft, Conceptualization. **Alina Nistor:** Writing – review & editing. **Ancuta-Mihaela Rotar:** Validation, Supervision. **Carmen-Rodica Pop:** Writing – original draft,

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] O.V. Okoro, A. Shavandi, An assessment of the utilization of waste apple slurry in bio-succinic acid and bioenergy production, Int. J. Environ. Sci. Technol. 19 (3) (2022) 1323–1334.
[2] R.K. Saxena, et al., 27 - production and applications of succinic acid, in: A. Pandey, S. Negi, C.R. Soccol (Eds.), Current Developments in Biotechnology and Bioengineering: Production, Isolation and Purification of Industrial Products, Elsevier, 2017, pp. 601–630.
[3] M. Ferone, et al., Bioreactors for succinic acid production processes, Crit. Rev. Biotechnol. 39 (4) (2019) 571–586.
[4] M. Ferone, et al., Continuous succinic acid fermentation by Actinobacillus succinogenes: assessment of growth and succinic acid production kinetics, Appl. Biochem. Biotechnol. 187 (3) (2019) 782–799.
[5] M.L.A. Jansen, W.M. van Gulik, Towards large scale fermentative production of succinic acid, Curr. Opin. Biotechnol. 30 (2014) 190–197.
[6] A.I. Magalhães Júnior, et al., Challenges in the production of second-generation organic acids (potential monomers for application in biopolymers), Biomass Bioenergy 149 (2021) 106092.
[7] J. Lu, et al., Recent progress on bio-succinic acid production from lignocellulosic biomass, World J. Microbiol. Biotechnol. 37 (1) (2021) 16.
[8] L. Mitrea, et al., Waste cooking oil and crude glycerol as efficient renewable biomass for the production of platform organic chemicals through oleophilic yeast strain of Yarrowia lipolytica, Environ. Technol. Innovat. 28 (2022) 102943.
[9] V. Narisetty, et al., Technological advancements in valorization of second generation (2G) feedstocks for bio-based succinic acid production, Bioresour. Technol. 360 (2022) 127513.
[10] H. Liu, et al., Yarrowia lipolytica as an oleaginous platform for the production of value-added fatty acid-based bioproducts, Front. Microbiol. 11 (3249) (2021).
[11] C. Li, et al., Promising advancement in fermentative succinic acid production by yeast hosts, J. Hazard Mater. 401 (2021) 123414.
[12] J. Wang, et al., Enhanced succinic acid production and magnesium utilization by overexpression of magnesium transporter mgtA in Escherichia coli mutant, Bioresour. Technol. 170 (2014) 125–131.
[13] M. Alexandri, et al., Succinic acid production by immobilized cultures using spent sulphite liquor as fermentation medium, Bioresour. Technol. 238 (2017) 214–222.
[14] N.T.H. Thuy, et al., Fermentation and crystallization of succinic acid from Actinobacillus succinogenes ATCC55618 using fresh cassava root as the main substrate, Bioresour. Technol. 233 (2017) 342–352.
[15] N. Nghiem, S. Kleff, S. Schwegmann, Succinic acid: technology development and commercialization, Fermentation-Basel 3 (2) (2017) 26.
[16] L. Mitrea, et al., Isolated microorganisms for bioconversion of biodiesel-derived glycerol into 1,3-propanediol, Bull. Univ. Agric. Sci. Vet. Med. Cluj-Napoca. Food Sci. Technol. 74 (2) (2017) 43–49.
[17] J.P. Tan, et al., Overview of the potential of bio-succinic acid production from oil palm fronds, J. Phys. Sci. 28 (2017).
[18] F. Guo, et al., Improved succinic acid production through the reconstruction of methanol dissimilation in Escherichia coli, Bioresources and Bioprocessing 9 (1) (2022) 62.
[19] A. Orozco-Saumell, et al., Aqueous phase hydrogenation of maleic acid to succinic acid mediated by formic acid: the robustness of the Pd/C catalytic system, Sustain. Energy Fuels 6 (22) (2022) 5160–5176.
[20] J.W. Lee, et al., 3.15 - organic acids: succinic and malic acids, in: M. Moo-Young (Ed.), Comprehensive Biotechnology, second ed., Academic Press, Burlington, 2011, pp. 149–161.
[21] M.S. Pascuta, et al., Polysaccharide-based edible gels as functional ingredients: characterization, applicability, and human health benefits, Gels 8 (2022), https://doi.org/10.3390/gels8080524.
[22] C. Xu, et al., Identification of lignocellulosic derivatives inhibiting succinic acid fermentation and molecular mechanism investigation, Ind. Crop. Prod. 187 (2022) 115466.
[23] D.Y. Murzin, et al., Kinetic modelling of heterogeneous catalytic oxidation of furfural with hydrogen peroxide to succinic acid, Chem. Eng. J. 382 (2020) 122811.
[24] H. Choudhary, S. Nishimura, K. Ebitani, Metal-free oxidative synthesis of succinic acid from biomass-derived furan compounds using a solid acid catalyst with hydrogen peroxide, Appl. Catal. Gen. 458 (2013) 55–62.
[25] Y.N. Palai, A. Shrotri, A. Fukuoka, Selective oxidation of furfural to succinic acid over lewis acidic Sn-beta, ACS Catal. 12 (6) (2022) 3534–3542.
[26] R. Kumar, B. Basak, B.-H. Jeon, Sustainable production and purification of succinic acid: a review of membrane-integrated green approach, J. Clean. Prod. 277 (2020) 123954.
[27] M. López Granados, et al., Catalytic transfer hydrogenation of maleic acid with stoichiometric amounts of formic acid in aqueous phase: paving the way for more sustainable succinic acid production, Green Chem. 22 (6) (2020) 1859–1872.
[28] D.T.H. Do, C.W. Theron, P. Fickers, Organic wastes as feedstocks for non-conventional, Yeast-Based Bioprocesses Microorganisms 7 (8) (2019) 229.
[29] S.-C. Chung, et al., Improvement of succinate production by release of end-product inhibition in Corynebacterium glutamicum, Metab. Eng. 40 (2017) 157–164.
[30] A. Patel, L. Matsakas, A comparative study on de novo and ex novo lipid fermentation by oleaginous yeast using glucose and sonicated waste cooking oil, Ultrason. Sonochem. 52 (2019) 364–374.
[31] X. Liu, et al., Biosynthetic pathway and metabolic engineering of succinic acid, Front. Bioeng. Biotechnol. 10 (2022).
[32] J. Wang, A.-p. Zeng, W. Yuan, Succinic acid fermentation from agricultural wastes: the producing microorganisms and their engineering strategies, Current Opinion in Environmental Science & Health 25 (2022) 100313.
[33] T.A. Gonzales, et al., Optimization of anaerobic fermentation of Actinobacillus succinogenes for increase the succinic acid production, Biocatal. Agric. Biotechnol. 27 (2020) 101718.
[34] C.M. Matei, et al., Evaluation of endotoxemia, soluble Cd14 and il-1β in dogs with intestinal dysbiosis that were treated with probiotics: a prospective study, FARMACIA 69 (6) (2021).
[35] A. Tsuji, et al., Metabolic engineering of Lactobacillus plantarum for succinic acid production through activation of the reductive branch of the tricarboxylic acid cycle, Enzym. Microb. Technol. 53 (2) (2013) 97–103.
[36] B. Louasté, N. Eloutassi, Succinic acid production from whey and lactose by Actinobacillus succinogenes 130Z in batch fermentation, Biotechnology Reports 27 (2020) e00481.
[37] Z. Sun, et al., Mixed food waste as renewable feedstock in succinic acid fermentation, Appl. Biochem. Biotechnol. 174 (5) (2014) 1822–1833.
[38] A. Carlson, et al., Industrial production of succinic acid, in: Chemicals and Fuels from Bio-Based Building Blocks, 2016, pp. 173–190.
[39] S.A. Wahl, et al., Intracellular product recycling in high succinic acid producing yeast at low pH, Microb. Cell Factories 16 (1) (2017) 90.
[40] L. Mitrea, et al., Utilization of biodiesel derived-glycerol for 1,3-PD and citric acid production, Microb. Cell Factories 16 (1) (2017) 190.
[41] F. Grimolizzi, L. Arranz, Multiple faces of succinate beyond metabolism in blood, Haematologica 103 (10) (2018) 1586–1592.
[42] L.-W. Zhu, Y.-J. Tang, Current advances of succinate biosynthesis in metabolically engineered Escherichia coli, Biotechnol. Adv. 35 (8) (2017) 1040–1048.

[43] W. Dessie, et al., Opportunities, challenges, and future perspectives of succinic acid production by Actinobacillus succinogenes, Appl. Microbiol. Biotechnol. 102 (23) (2018) 9893–9910.
[44] J.J. Beauprez, M. De Mey, W.K. Soetaert, Microbial succinic acid production: natural versus metabolic engineered producers, Process Biochem. 45 (7) (2010) 1103–1114.
[45] C.M. Matei, et al., Hematological aspects on dogs with apparent dysbiosis after Bacillus subtilis, Bacillus licheniformis and pediococcus acidilactici probiotic administration- pilot study, Bulletin UASVM Veterinary Medicine 77 (2) (2020).
[46] X. Liu, et al., Characterization and directed evolution of propionyl-CoA carboxylase and its application in succinate biosynthetic pathway with two CO2 fixation reactions, Metab. Eng. 62 (2020) 42–50.
[47] D.C. Vodnar, et al., 11 - removal of bacteria, viruses, andother microbial entities by means of nanoparticles, in: B. Lucian, et al. (Eds.), Advanced Nanostructures for Environmental Health, Elsevier, 2020, pp. 465–491.
[48] M.-N. Efthymiou, et al., Restructuring the sunflower-based biodiesel industry into a circular bio-economy business model converting sunflower meal and crude glycerol into succinic acid and value-added co-products, Biomass Bioenergy 155 (2021) 106265.
[49] E. Stylianou, et al., Optimization of fermentation medium for succinic acid production using Basfia succiniciproducens, Environ. Technol. Innovat. 24 (2021) 101914.
[50] L. Mitrea, et al., Separation and purification of biogenic 1, 3-propanediol from fermented glycerol through flocculation and strong acidic ion-exchange resin, Biomolecules 10 (12) (2020) 1601.
[51] L. Mitrea, D.C. Vodnar, Klebsiella pneumoniae—a useful pathogenic strain for biotechnological purposes: diols biosynthesis under controlled and uncontrolled pH levels pathogens, Basel, Switzerland) 8 (4) (2019) 293.
[52] E. Stylianou, et al., Evaluation of organic fractions of municipal solid waste as renewable feedstock for succinic acid production, Biotechnol. Biofuels 13 (1) (2020) 72.
[53] A. Geraili, et al., A simulation and techno-economic optimization-based methodology to design multi-product lignocellulosic biorefineries, Chemical Engineering Transactions 32 (2013) 1183–1188.
[54] W. Dessie, et al., Towards the development of efficient, economic and environmentally friendly downstream processing for bio-based succinic acid, Environ. Technol. Innovat. 32 (2023) 103243.
[55] N. Jusoh, et al., Development of vegetable oil-based emulsion liquid membrane for downstream processing of bio-succinic acid, Food Bioprod. Process. 119 (2020) 161–169.
[56] R. Sikkema, et al., The international logistics of wood pellets for heating and power production in Europe: costs, energy-input and greenhouse gas balances of pellet consumption in Italy, Sweden and The Netherlands, Biofuels, Bioproducts and Biorefining 4 (2) (2010) 132–153.
[57] L. Longanesi, et al., Succinic acid production from cheese whey by biofilms of Actinobacillus succinogenes: packed bed bioreactor tests, Journal of Chemical Technology & Biotechnology 93 (1) (2018) 246–256.
[58] U. Uysal, H. Hamamcı, Succinic acid production from cheese whey via fermentation by using alginate immobilized Actinobacillus succinogenes, Bioresour. Technol. Rep. 16 (2021) 100829.
[59] A. Ercole, et al., Continuous succinic acid production by immobilized cells of Actinobacillus succinogenes in a fluidized bed reactor: entrapment in alginate beads, Biochem. Eng. J. 169 (2021) 107968.
[60] Y.-Y. Chiang, et al., Succinic acid fermentation with immobilized Actinobacillus succinogenes using hydrolysate of carbohydrate-rich microalgal biomass, Bioresour. Technol. 342 (2021) 126014.
[61] L. Mitrea, et al., Biodiesel-derived glycerol obtained from renewable biomass—a suitable substrate for the growth of Candida zeylanoides yeast strain ATCC 20367, Microorganisms 7 (2019) 265.
[62] L. Mitrea, M. Trif, D.C. Vodnar, The effect of crude glycerol impurities on 1,3-propanediol biosynthesis by Klebsiella pneumoniae DSMZ 2026, Renew. Energy 153 (2020) 1418–1427.
[63] W.T. Tsai, Mandatory recycling of waste cooking oil from residential and commercial sectors in taiwan, Resources (2019) 38.
[64] L. Mitrea, et al., The physicochemical properties of five vegetable oils exposed at high temperature for a short-time-interval, J. Food Compos. Anal. 106 (2022) 104305.
[65] A. Orjuela, J. Clark, Green chemicals from used cooking oils: trends, challenges, and opportunities, Curr. Opin. Green Sustainable Chem. 26 (2020) 100369.
[66] A. Patel, et al., Chapter 3 - in-depth analysis of waste cooking oil as renewable and ecofriendly biofuel candidate, in: C.M. Hussain, S. Singh, L. Goswami (Eds.), Waste-to-Energy Approaches towards Zero Waste, Elsevier, 2022, pp. 87–103.
[67] C.R. Chilakamarry, et al., Technological Perspectives for Utilisation of Waste Glycerol for the Production of Biofuels: A Review, vol. 24, Environmental Technology & Innovation, 2021 101902.
[68] A. Vlysidis, et al., A techno-economic analysis of biodiesel biorefineries: assessment of integrated designs for the co-production of fuels and chemicals, Energy 36 (8) (2011) 4671–4683.
[69] Y. Pang, et al., Engineering the oleaginous yeast Yarrowia lipolytica to produce limonene from waste cooking oil, Biotechnol. Biofuels 12 (1) (2019) 241.
[70] E.G.d. Morais, et al., Glycerol increases growth, protein production and alters the fatty acids profile of Spirulina (Arthrospira) sp LEB 18, Process Biochem. 76 (2019) 40–45.
[71] E. Cavallo, et al., Yarrowia lipolytica: a model yeast for citric acid production, FEMS Yeast Res. 17 (8) (2017).
[72] K.L. Ong, et al., Co-fermentation of glucose and xylose from sugarcane bagasse into succinic acid by Yarrowia lipolytica, Biochem. Eng. J. 148 (2019) 108–115.
[73] E. Lo, et al., Biochemical conversion of sweet sorghum bagasse to succinic acid, J. Biosci. Bioeng. 129 (1) (2020) 104–109.
[74] A. Foulet, et al., Life cycle assessment of a bioelectrochemical system as a new technological platform for biosuccinic acid production from waste, Environ. Sci. Pollut. Control Ser. 25 (36) (2018) 36485–36502.
[75] S.A. Nemes, et al., Integrated technology for cereal bran valorization: perspectives for a sustainable industrial approach, Antioxidants 11 (11) (2022) 2159.
[76] M.-L. Hillion, et al., Co-ensiling as a new technique for long-term storage of agro-industrial waste with low sugar content prior to anaerobic digestion, Waste Manag. 71 (2018) 147–155.
[77] J. Son, et al., Microbial cell factories for the production of three-carbon backbone organic acids from agro-industrial wastes, Bioresour. Technol. 349 (2022) 126797.
[78] L.F. Cälinoiu, et al., Sustainable use of agro-industrial wastes for feeding 10 billion people by 2050, in: Professionals in Food Chains: Ethics, Roles and Responsibilities, Wageningen Academic Publishers, Viena, Austria, 2018.
[79] J. Merrylin, et al., Chapter 6 - production of organic acids and enzymes/biocatalysts from food waste, in: J.R. Banu, et al. (Eds.), Food Waste to Valuable Resources, Academic Press, 2020, pp. 119–141.
[80] K. Ong, et al., Fermentation of fruit and vegetable wastes for biobased products, in: Food Industry Wastes, Academic Press, 2020, pp. 255–273.
[81] V. Coman, et al., Bioactive potential of fruit and vegetable wastes, in: Advances in Food and Nutrition Research, Academic Press, 2019.
[82] A.Y.-z. Zhang, et al., Valorisation of bakery waste for succinic acid production, Green Chem. 15 (3) (2013) 690–695.
[83] K. Filippi, et al., Integrated biorefinery development using winery waste streams for the production of bacterial cellulose, succinic acid and value-added fractions, Bioresour. Technol. 343 (2022) 125989.
[84] N.A. Bukhari, et al., Prospects and state-of-the-art in production of bio-based succinic acid from oil palm trunk, Journal of Oil Palm Research 35 (4) (2023) 555–581.
[85] F. Vigato, et al., Dissolved CO2 profile in bio-succinic acid production from sugars-rich industrial waste, Biochem. Eng. J. 187 (2022) 108602.
[86] J.-S. Lee, et al., Production of succinic acid through the fermentation of Actinobacillus succinogenes on the hydrolysate of Napier grass, Biotechnology for Biofuels and Bioproducts 15 (1) (2022) 9.
[87] D. Ladakis, et al., Biorefinery development, techno-economic evaluation and environmental impact analysis for the conversion of the organic fraction of municipal solid waste into succinic acid and value-added fractions, Bioresour. Technol. 354 (2022) 127172.

[88] E. Stylianou, et al., Development of an electrochemical membrane bioreactor for succinic acid production and in situ separation with engineered Yarrowia lipolytica cultivated on municipal biowaste hydrolysate, Chem. Eng. J. 466 (2023) 142877.
[89] E.O. Jokodola, et al., Process optimisation for production and recovery of succinic acid using xylose-rich hydrolysates by Actinobacillus succinogenes, Bioresour. Technol. 344 (2022) 126224.
[90] Q. Li, et al., Efficient conversion of crop stalk wastes into succinic acid production by Actinobacillus succinogenes, Bioresour. Technol. 101 (9) (2010) 3292–3294.
[91] R. Kaur, et al., Microbial production of dicarboxylic acids from edible plants and milk using GC-MS, Journal of Analytical Science and Technology 9 (1) (2018) 21.
[92] D. Wang, et al., Efficient production of succinic acid from corn stalk hydrolysates by a recombinant Escherichia coli with ptsG mutation, Process Biochem. 46 (1) (2011) 365–371.
[93] M. Babaei, et al., Valorization of organic waste with simultaneous biogas upgrading for the production of succinic acid, J Biochemical engineering journal 147 (2019) 136–145.
[94] T. Xia, E. Altman, M.A. Eiteman, Succinate production from xylose-glucose mixtures using a consortium of engineered Escherichia coli, Eng. Life Sci. 15 (2015).
[95] K. Amulya, S. Venkata Mohan, Green hydrogen based succinic acid and biopolymer production in a biorefinery: adding value to CO2 from acidogenic fermentation, Chem. Eng. J. 429 (2022) 132163.
[96] Y.-P. Liu, et al., Economical succinic acid production from cane molasses by Actinobacillus succinogenes, Bioresour. Technol. 99 (6) (2008) 1736–1742.
[97] N. Shen, et al., Optimization of succinic acid production from cane molasses by Actinobacillus succinogenes GXAS137 using response surface methodology (RSM), Food Sci. Biotechnol. 23 (6) (2014) 1911–1919.
[98] Z. Wang, et al., Enhanced succinic acid production from polyacrylamide-pretreated cane molasses in microbial electrolysis cells, J. Chem. Technol. Biotechnol. 93 (3) (2018) 855–860.
[99] S.Y. Kim, et al., Development of a cell-recycled continuous fermentation process for enhanced production of succinic acid by high-yielding mutants of Actinobacillus succinogenes, Biotechnol. Bioproc. Eng. 26 (1) (2021) 125–136.
[100] A.M. Mazotto, et al., How can microbiology help to improve sustainability in the fashion industry? Environ. Technol. Innovat. 23 (2021) 101760.
[101] X. Li, et al., Efficient succinic acid production using a biochar-treated textile waste hydrolysate in an in situ fibrous bed bioreactor, Biochem. Eng. J. 149 (2019) 107249.
[102] L. Liang, et al., Effects of overexpression of NAPRTase, NAMNAT, and NAD synthetase in the NAD(H) biosynthetic pathways on the NAD(H) pool, NADH/NAD + ratio, and succinic acid production with different carbon sources by metabolically engineered Escherichia coli, Biochem. Eng. J. 81 (2013) 90–96.
[103] A.M. Olajuyin, et al., Efficient production of succinic acid from Palmaria palmata hydrolysate by metabolically engineered Escherichia coli, Bioresour. Technol. 214 (2016) 653–659.
[104] Z. Bodor, et al., Using genome-scale model to predict the metabolic engineering impact on Escherichia coli metabolism during succinic acid production optimization, Romanian Biotechnological Letters 25 (3) (2020) 1666–1676.
[105] B. Bai, et al., Efficient production of succinic acid from macroalgae hydrolysate by metabolically engineered Escherichia coli, Bioresour. Technol. 185 (2015) 56–61.
[106] A.M. Olajuyin, et al., Effective production of succinic acid from coconut water (Cocos nucifera) by metabolically engineered Escherichia coli with overexpression of Bacillus subtilis pyruvate carboxylase, Biotechnology Reports 24 (2019) e00378.
[107] W. Zhang, et al., Adaptive evolution improves acid tolerance and succinic acid production in Actinobacillus succinogenes, Process Biochem. 98 (2020) 76–82.
[108] N. Shen, et al., Efficient production of succinic acid from duckweed (Landoltia punctata) hydrolysate by Actinobacillus succinogenes GXAS137, Bioresour. Technol. 250 (2018) 35–42.
[109] M. Patsalou, et al., Development of a citrus peel-based biorefinery strategy for the production of succinic acid, J. Clean. Prod. 166 (2017) 706–716.
[110] W. Cao, et al., Succinic acid biosynthesis from cane molasses under low pH by Actinobacillus succinogenes immobilized in luffa sponge matrices, Bioresour. Technol. 268 (2018) 45–51.
[111] M.F. Bradfield, et al., Continuous succinic acid production by Actinobacillus succinogenes on xylose-enriched hydrolysate, Biotechnol. Biofuels 8 (1) (2015) 1–17.
[112] R. Franco-Duarte, et al., Genomic and transcriptomic analysis of Saccharomyces cerevisiae isolates with focus in succinic acid production, FEMS Yeast Res. 17 (6) (2017).
[113] Z. Malubhoy, et al., Carbon dioxide fixation via production of succinic acid from glycerol in engineered Saccharomyces cerevisiae, Microb. Cell Factories 21 (1) (2022) 1–15.
[114] E. Stylianou, et al., Bioprocess development using organic biowaste and sustainability assessment of succinic acid production with engineered Yarrowia lipolytica strain, Biochem. Eng. J. 174 (2021) 108099.
[115] V. Narisetty, et al., Development of hypertolerant strain of Yarrowia lipolytica accumulating succinic acid using high levels of acetate, ACS Sustain. Chem. Eng. 10 (33) (2022) 10858–10869.
[116] C. Gao, et al., Robust succinic acid production from crude glycerol using engineered Yarrowia lipolytica, Biotechnol. Biofuels 9 (1) (2016) 179.
[117] D.N. Putri, et al., Progress of fermentation methods for bio-succinic acid production using agro-industrial waste by Actinobacillus succinogenes, Energy Rep. 6 (2020) 234–239.
[118] M. Boro, et al., Strategies involved in biofuel production from agro-based lignocellulose biomass, Environ. Technol. Innovat. 28 (2022) 102679.
[119] A. Rigaki, C. Webb, C. Theodoropoulos, Double substrate limitation model for the bio-based production of succinic acid from glycerol, Biochem. Eng. J. 153 (2020) 107391.
[120] M. Jiang, et al., Progress of succinic acid production from renewable resources: metabolic and fermentative strategies, Bioresour. Technol. 245 (2017) 1710–1717.
[121] H. Song, S.Y. Lee, Production of succinic acid by bacterial fermentation, Enzym. Microb. Technol. 39 (3) (2006) 352–361.
[122] O.O. Sadare, et al., Membrane purification techniques for recovery of succinic acid obtained from fermentation broth during bioconversion of lignocellulosic biomass: current advances and future perspectives, Sustainability 13 (2021), https://doi.org/10.3390/su13126794.
[123] E. Mancini, et al., Economic and environmental analysis of bio-succinic acid production: from established processes to a new continuous fermentation approach with in-situ electrolytic extraction, Chem. Eng. Res. Des. 179 (2022) 401–414.
[124] H.-Y. Zhou, et al., Re-designing Escherichia coli for high-yield production of β-alanine by metabolic engineering, Biochem. Eng. J. 189 (2022) 108714.
[125] B. Ryback, M. Bortfeld-Miller, J.A. Vorholt, Metabolic adaptation to vitamin auxotrophy by leaf-associated bacteria, ISME J. 16 (12) (2022) 2712–2724.
[126] S. Gadkari, et al., Life cycle analysis of fermentative production of succinic acid from bread waste, Waste Manag. 126 (2021) 861–871.