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Succinic acid Production Strategy: Raw material, Organisms and Recent Applications in pharmaceutical and Food: Critical Review

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Abstract

Succinic acid is an essential base ingredient for manufacturing various industrial chemicals. Succinic acid has been acknowledged as one of the most significant bio based building block chemicals. Rapid demand for succinic acid has been noticed in the last 10 years. The production methods and mechanisms developed. Hence, these techniques and operations need to be revised. Recently, an omnibus rule for developing succinic acid is to find renewable carbohydrate Feedstocks. The sustainability of the resource is crucial to disintegrate the massive use of petroleum based-production. Accordingly, systematically reviewing the latest findings of bacterial production and related fermentation methods is critical. Therefore, this paper aims to study the latest research and assess the findings statistically comprehensively. The current review attempt is a step toward comprehending all the conditions surrounding succinic acid production from raw materials, microorganisms, and fermentation methods.

***Keywords**: Succinic acid, Food applications, pharmaceutical applications, fermentation process.*

1. Introduction

The dicarboxylic acid succinic acid ($C_4H_6O_4$) was initially isolated through microbial fermentation in 19th century [1]. Amber acid is the most common name for it, however it is also referred to as butanedioic acid. It is created by microbes, animals, and plants [2], although anaerobic fermentation by microbes produces the most of it. Succinic acid comes from the fermentation of carbohydrates and is widely employed in chemical markets and companies that produce food [3], biodegradable polymers [4], solvents [5], and pharmaceuticals [6]. Additionally, Succinic acid is employed as a raw material in the production of numerous industrial products, such as adipic acid [7], aliphatic esters [8], and 1,4-butanediol [9]. Table 1 lists the succinic acid's chemical and physical properties.

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Table 1,
Succinic acid properties [10].

(SA) names	Amber acid, Asuccin, Bernsteinsaure; Kyselina Jantarova, Dihydrofumaric Acid, Butanedioic acid
IUPAC name	Butanedioic Acid
Formula	$C_4H_6O_4(HOOCCH_2CH_2COOH)$
Physical state	Colorless, odorless white crystals
Melting point	185-187^oC
Boiling point	235 ^oC
Solubility in (solvents)	Not dissolved in benzene, carbon tetrachloride, carbon sulfide or oil ether; somewhat dissolved in ethanol, acetone and glycerin
Solubility in (water)	Soluble
Molar mass	118.09
Specific gravity	1.552
Flash point	206 ^oC
Density	1.56 g/cm^3
Vapor density	3.04
Acidity (pKa)	pKa1 = 4.2 pKa2 = 5.6
Stability	Stable in the ideal conditions
Occurrence	Occurs naturally in animal and plant tissues
Applications	Pharmaceuticals, Agriculture, Food and other many industrials

Succinic acid, an important organic acid found in humans [11], plants [12], and animals [13], plays a vital function in the biological metabolism. Four existing markets exist for succinic acid. The greatest of these sectors is the food business, where succinic acid is primarily employed as a flavoring agent [14] and an anti-microbial [15]. The second market is the pharmaceutical industry, where it is a production additive for antibiotics [16], amino acids [17], and vitamins [18]. Succinic acid, the third compound, is mostly utilized as a detergent [19], polymer additive [20], surfactant [21], and foaming agent [22]. Finally SA use in the paint industry as an ion chelator to prevent corrosion and [23]. (SA) is produced chemically from substrates derived from petroleum, such as butane or benzene, in the consolidated process. However, this approach has disadvantages for the environment and high raw material costs. Due to the prospect of employing affordable renewable resources as feedstocks and suggesting sustainable production methods, interest in the fermentative manufacture of (SA) has grown over the past ten years. Several bacteria, including *Actinobacillus succinogenes* [25], *Basfia succiniciproducens* [26], *Mannheimia succiniciproducens* [27], and numerous recombinant strains of *Escherichia coli* [28], are capable of producing succinic acid by microbial fermentations. For the industrial use, *Actinobacillus succinogenes* has proven to be a very promising biocatalyst. *A. succinogenes'* main benefits for producing succinic acid include its capacity to metabolize a wide range of carbon sources, including several mono- and disaccharides [29], adequate tolerance to inhibitors [30], pentose sugars, and hexose [31], and sufficient fermentation efficiency even when using renewable feedstock [32]. The primary fermentation byproduct produced by *A. succinogenes* is succinic acid, with acetic acid, formic acid, pyruvic acid, and ethanol serving as minor byproducts [33]. Several studies have concentrated on strain selection, fermentation medium optimization, and feeding management to increase (SA) production [34–36]. In fact, the inhibitory effect of the generated acid on cell development is what is most pressing the production of organic acids via fermentation at an industrial scale, including citric [37], lactic [38], glutamic [39], and gluconic acid [40]. As a result, designing and optimizing the fermenter to produce SA requires a detailed grasp of growth dynamics.

2. Raw Materials for Succinic Acid Production

Lignocellulosic biomass is pretreated to yield fermentable sugars, which are then converted into industrially significant chemicals [41]. Various bacteria and fungi are utilized to break down lignocellulosic biomass into glucose monomers. About 250 million tons of lignocellulosic Feedstocks are produced annually and come from industrial, agricultural, and forest sources. Wastes made of lignocellulosic materials are fairly common and come from both industrial and agricultural sources. Lignocellulosic biomass contains a high concentration of cellulose components, including oil palm [42], rice husk [43], wheat straw [44], cassava starch [45], and corn [46]. The following qualities of the raw material must exist for it to be deemed a good substrate for the manufacture of organic acids: ample availability throughout the year, renewable, affordable, high production rate, absence of competing food value, and low level of pollutants.

3. Succinic Acid Applications

One of the most well-known coformers is succinic acid, which crystallizes with a number of drugs but is best known for its connection to oxicams [47, 48, 49, 50, 51]. Figure 1 presents examples of succinic acid's potential uses. It was acknowledged that succinic acid is a pharmaceutically useful component. (SA) is an endogenous metabolite that is used in a variety of medicinal procedures. When it was revealed that (SA) could be utilized as an intermediary in the synthesis of various compounds with industrial applications because of its linear saturated structure, the succinic acid industry's potential was understood. Because it may be used to create a wide range of derivatives that have uses in numerous fields and are beneficial to all forms of life, (SA) is an interesting building block for the business. (SA) has a long history of use as a chemical intermediary in lacquer production, perfume ester production, and medicine. It has also frequently been employed in the food sector as a sequestrant, buffer, and neutralizing agent [52], as well as a known regulator of plant development [53]. After protracted illnesses and injuries, succinates—most frequently potassium succinate and calcium succinate are thought to be beneficial. These are typically used as, antispasmodics, sedatives, antirheoters and contraceptives in medicine. (SA) can also be employed as an antioxidant and a potassium ion inhibitor. (SA) is also a valuable substance for athletes, and as a result, it has the moniker "elixir of youth" [54].

The first and most harmful metabolite of alcohol is acetaldehyde, and these salts have a significant impact on the body's normal capacity to metabolize it [55]. As a result, the patient's resistance to disease, as well as their mental health and ability to concentrate, can be rebuilt. Also, Esterification is another method for producing a solvent called dimethyl succinate (SA).Using constant surface area tablets and powder, many researchers investigated the properties of how the griseofulvin-succinic acid eutectic mixture dissolved [56],[57]. The fusion technique was used to create the solid dispersions, which contained 2.5, 5, 10, 25, and 50% (eutectic composition) of the griseofulvin-(SA) mixture. Based on the results, it is hypothesized that the existence of extremely fine griseofulvin crystals is the main cause of the 10% griseofulvin dispersion's rising dissolving rate. A reversed phase ion-suppression high performance liquid chromatography was used in several studies in 1999 to develop an accurate approach for the simultaneous measurement of fumaric, oxalic, and (SA) in tartaric and malic acids for medicinal use High Performance Liquid Chromatography (HPLC)[58].The use of extremely diluted per chloric acid in water as the mobile phase reduces the overall time for analysis and lengthens the life of the column, according to the authors. The second feature was good separation of the trace and major constituents in real samples, which makes it easier to determine all the acids of interest simultaneously.

In 2016 Perform a qualitative analysis of the addition of succinic acid to the various medications to ascertain their pharmacological effects. The development of new medications based on succinic acid; ascorbic acid was researched by the authors [59]. They emphasize the anti-inflammatory, hepato-protective and renal protective effects. While in 2018 Ogienko and his group investigated the possibility of using freeze-drying to produce medicinal co-crystals when the solubility of the different components vary greatly. In a model system, meloxicam and (SA), Co-crystals could form from both pure crystalline phase and solid dispersion with a polymeric carrier [60]. The researchers show that the rate of meloxicam release from its fine solid dispersion in polyethylenglycol co-crystal with succinic acid obtained by freeze-drying was significantly higher than the rates of dissolution of I pure meloxicam co-crystals with succinic acid obtained by different variants of freeze-drying (thin film freezing, TFF, and spray freeze-drying, SFD), (ii) the powder of meloxicam. Figure :1 describe the most potential applications for succinic acid.

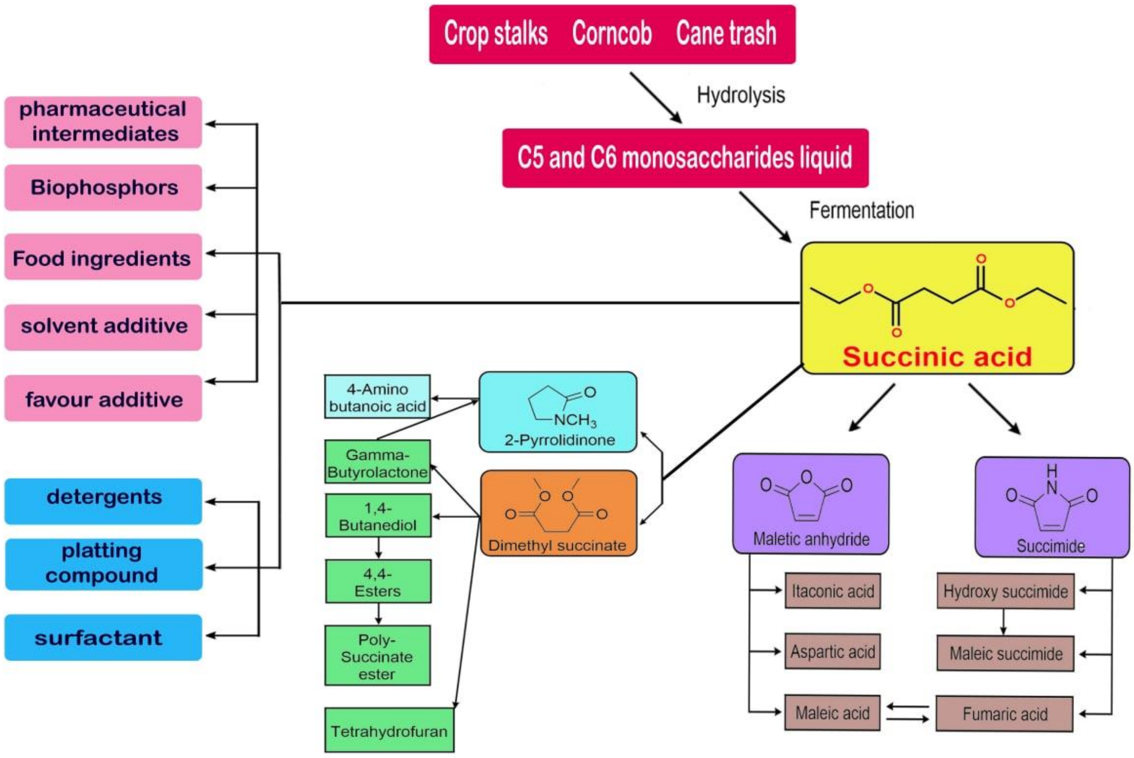

Fig. 1. Succinic acid applications [61].

4. Global Marketing of Succinic Acid

According to the succinic acid market annually survey [62], the succinic acid market is anticipated to grow from USD 131.7 million in 2018 to USD 182.8 million by 2023, at a predicted CAGR of 6.8%. Growing demand from the manufacturing, personal care, and food and beverage industries is driving the global market for succinic acid. Expanding APAC demand and rising use of succinic acid as an alternative to adipic acid in the manufacturing of polyurethane are two factors driving the global market for succinic acid. (SA) is a platform chemical used in the manufacture of several specialty chemicals and is a common chemical intermediate [63]. By 2025, it is expected that the succinic acid market would have grown by 30% annually. This is a result of both its expanding applications and the chemical industry's shift to environmentally friendly products sought through biological pathways. But the two biggest obstacles are the cost of processing and strong market competition [64]. Food, cosmetics, lubricants & solvents, medicines, are the key industries that use bio-based (SA) as opposed to petroleum-based (SA). Applications for plasticizers, polyester polyols, 1,4-butanediol, polybutyrate succinate, Due to the dire scenario surrounding the availability of fossil fuels, the risks related with the depletion of petroleum resources, and strict environmental regulations, investments in green chemicals are growing in popularity. These factors will surely hasten the growth of the future market [65]. However, the price of bio-succinic acid and the time-consuming and burdensome downstream processes are the key barriers to market growth. Studies show that the newest markets for pigments, resins, and coatings brought in the greatest money in 2013. The greatest application area for 1,4-butanediol, however, is predicted to surpass all others in ten years. This is primarily due to the increased use of bio-succinic acid in the manufacture of 1,4-butanediol [66], a maleic anhydride replacement. Instead of using 1 meter per ton of maleic anhydride, it is recommended to utilize 1.0_1.2 meters of bio succinic acid. In electroplating, SA is also employed as an ion chelator [67]. Succinic acid is typically employed as a flavoring ingredient in the food sector [68]. In several branches of the pharmaceutical sector, it is important as well [69].

Table 2,
Market size and market share for (SA) applications [70].

(SA) Applications	Market size (1000 MT)	Market Share (%)
BDO [1]	316	52.7
PBS, PBST[2]	82	13.7
Polyester polyols	51	8.5
Plasticizer	37	6.2
Food	26	4.3
Pharmaceutical	21	3.5
Alkyd resins	21	3.5
Resins, coatings	12	2
Cosmetics	12	2
Solvents and lubricants	6	1
De-icer solution	3	0.5
Others	13	2.2

Additionally, succinic acid's use in industrial applications fuels consumer demand for the substance. Because PBS/PBST are biodegradable and non-toxic, resistance to heat and more easily processed than other biopolymers, succinic acid is use in them for food packaging [71]. Increased disposable income, altering consumer preferences, rising plastics consumption, and expanding packaging sectors are the main factors driving the market for (SA) [72]. These factors have increased demand for non-toxic, biodegradable Polyethylene Terephthalate (PET) bottles, blood containers, disposable syringes, food containers, and other consumer goods in India, China, Japan, and Germany, which has fueled the (SA) market's expansion in the Polybutylene succinate/poly (butylenes succinate-co-terephthalate) segment. Finally, According to the growing demand for succinic acid in all areas of the industry, the demand is expected to reach $200 billion globally.

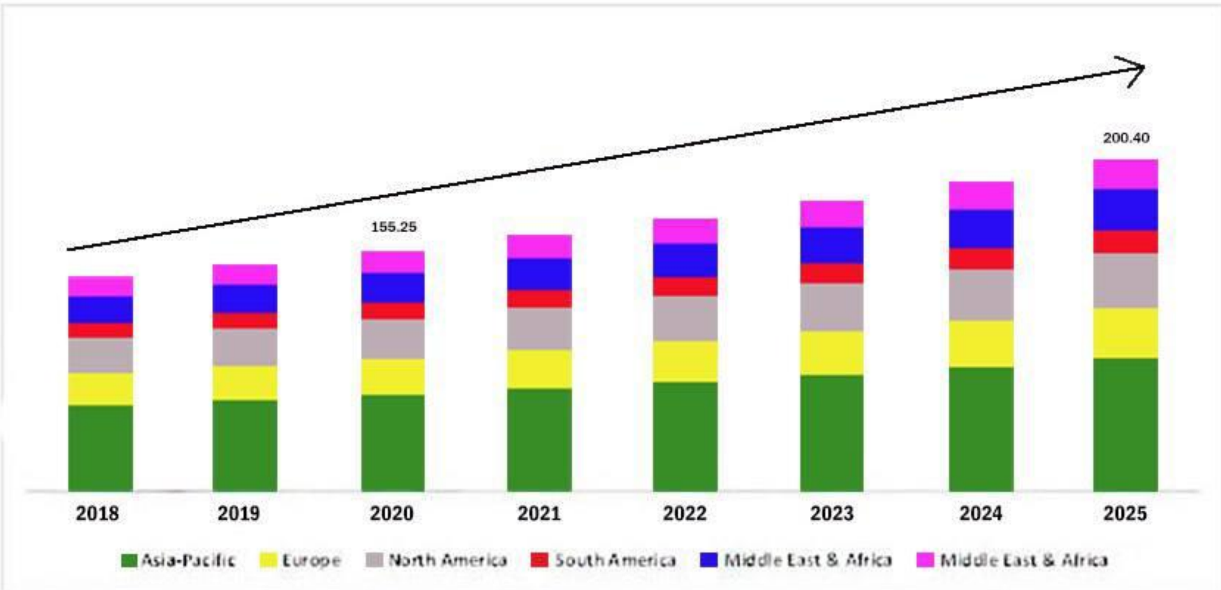

Fig. 2. Market for succinic acid anticipated to reach $200 billion globally.

5. Conclusion

This review paper reviewed 72 papers of succinic acid production. The paper thoroughly reviewed numerous substrates, raw materials for succinic acid synthesis. The review indicated 90% of the raw material were successful in a global production of 16,000–30,000 tons. This indicate the economic large-scale deployment of succinic acid is attainable. The optimization of production strategy is proved valid by modifying factors as fermentation process, operating conditions, types of raw material and technique of purification. The optimization contributes to the quality and cost reduction. Furthermore, it is necessary to promote more raw material and applied research for succinic acid production.

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استراتيجية إنتاج حمض السكسونيك: المواد الخام والكائنات الحية والتطبيقات الحديثة في الأدوية والغذاء: مراجعة نقدية

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الخلاصة

استعرضت ورقة المراجعة هذه 72 ورقة من إنتاج حمض السكسونيك. استعرض الورق بدقة العديد من الركائز والمواد الخام لتخليق حمض السكسونيك. أشارت المراجعة إلى أن 90٪ من المواد الخام كانت ناجحة في إنتاج عالمي يتراوح بين 16.000 و30.000 طن. هذا يشير إلى أن النشر الاقتصادي واسع النطاق لحمض السكسونيك يمكن تحقيقه. تم إثبات صحة تحسين استراتيجية الإنتاج من خلال تعديل العوامل مثل عملية التخمير وظروف التشغيل وأنواع المواد الخام وتقنية التنقية. يساهم التحسين في الجودة وخفض التكلفة. علاوة على ذلك، من الضروري تشجيع المزيد من المواد الخام والبحوث التطبيقية لإنتاج حمض السكسونيك.