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Research Article

ITACONIC ACID PRODUCTION A BIOTECHNOLOGICAL PERSPECTIVE

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A B S T R A C T

Itaconic acid (IA), also known as methylene butanedioic acid, methylene succinic acid, 3-carboxy-3-butanoic acid, propylene dicarboxylic acid is one of the promising substances within the group of organic acids. It is a white crystalline unsaturated dicarbonic acid with one carboxyl group conjugated to the methylene group. Itaconic acid is also an interesting starting material for biofuel production because it can easily be converted into 3-methyltetrahydrofuran (3-MTHF), a fuel with excellent physical and chemical combustion properties (Geilen *et al*., 2010).The present review focus on itaconic acid production and its biotechnological perspective.

INTRODUCTION

Itaconic Acid (IA) Production is progressively emerging as a new high-biotechnology industry across the globe. With rising concerns of diminishing fossil fuel resources, efforts are being made to produce chemicals from green feedstock rather than petrochemical raw materials. IA, although widely sourced from petrochemical feedstock, has the ability of being produced from renewable resources and is therefore being viewed as an ideal bio-based platform chemical for the chemicals industry. Currently, production of the organic compound is mainly restricted to a limited number of countries such as China, US, Japan and Russia, resulting in global production being much lower than the actual demand. The development of new fermentation technologies and more sophisticated bioprocess control has led to new interest in improving IA production, and novel fed-batch strategies and continuous processes using immobilized cells have now been developed and investigated. The attempts were also in progress to produce IA using cheap raw substrates like rice bran, corn cobs from Agro industry employing solid state fermentation (Yu Zhimin *et al*., 2006**).**

Itaconic acid was discovered by Baup (1837) as a thermal decomposition product of citric acid. Itaconic acid was originally known as a product of pyrolytic distillation of citric acid. Itaconic acid was first reported as a product of mold *Aspergillus itaconicus* metabolism which was isolated from the juice of salted plums (Kinoshita, 1932).

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This green species grows well only on media of high osmotic pressures such as concentrated sugar solutions and produces itaconic acid on media containing KNO_3 as nitrogen source and 25% sucrose. Calam, Oxford and Raistrick reported obtaining small quantities of itaconic acid from a strain of *Aspergillus terreus* and preliminary investigations conducted by Moyer and Coghill confirmed the suitability of *Aspergillus terreus* for bringing about this reaction. Over 300 strains of *A. terreus* were screened and found eleven as efficient producers of itaconic acid from glucose (Lockwood and Reeves,1945). Later, other fungal strains, mainly of the species *Aspergillus terreus,* were found to be more suitable. At the Northern Regional Research Laboratory (NRRL) of the U.S. Department of Agriculture in Peoria, Illinois, a screening programme of more than 300 strains identified the most published strain, *A. terreus* NRRL 1960 (Lockwood and Reeves 1945). A biotechnical process for IA production was developed at the same institute (Nelson *et al*. 1952; Pfeifer *et al*. 1952). Further, industrial processes which were optimized were established providing the limited market with IA. The main developments in IA production (batch fermentation, submerged fermentation) took place before and during 1966. The interest in IA production declined the next 15 years, as there were only few publications during this time. During the past two decades, circumstances in IA production has rapidly changed due to increasing concern regarding sustainability, environmental conservation, cheap raw substrates and rising energy costs.

Physicochemical Properties

Itaconic acid (IA), also known as methylene butanedioic acid, methylene succinic acid, 3-carboxy-3-butanoic acid, propylene dicarboxylic acid) is one of the promising substances within the group of organic acids. It is a white crystalline unsaturated

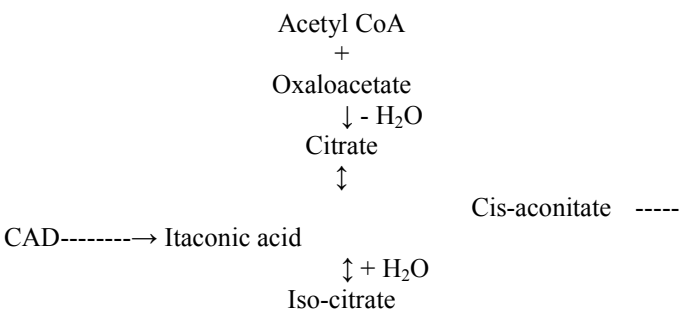
dicarbonic acid with one carboxyl group conjugated to the methylene group. The properties of IA are molecular weight 130.1, melting point 167-168^{0}C, Boiling point 268^{0}C, solubility in water 83.103 g/l, density 1.632 g/l at 20^{0}C, pH is 2 in aqueous solution of 80 mg/l and pka 3.84 and 5.55. IA can be regarded as an α-substituted acrylic or methacrylic acid and is isomeric with citraconic and mesaconic acid. It is stable at acidic, neutral and middle basic conditions at moderate temperatures (Tate, 1970; 1981). This α-substituted acrylic acid received this name by the rearrangement of aconitic acid, from which itaconic acid is formed by decarboxylation.

Chemical Synthesis

IA was chemically synthesized for the first time by pyrolytic hydrolysis of citric acid (Baup 1837). The decarboxylation of aconitic acid for production of IA was developed. Chemical synthesis is mainly performed by dry distillation of citric acid and subsequent treatment of the anhydride with water (Blatt 1943), or using the method of Montecatini (Italy), from propargyl chloride, carbon monoxide, nickel carbonyl and water (Chiusoli 1962). The other methods of IA synthesis are the oxidation of mesityl oxide and subsequent isomerisation of the formed citric acid (Berg and Hetzel, 1978), or the oxidation of isoprene (Pichler *et al*. 1967). A process model has been developed for itaconic acid production through catalytic condensation of dimethyl succinate and formaldehyde (Shekhawat *et al.* 2006). They also claimed that this catalytic conversion can be achieved at low cost than via the fungal fermentation route.

Biochemical Pathway

The biosynthesis of IA in fungi is via glycolysis and the tricarboxylic acid cycle (Kinoshita 1932; Eimhjellen and Larsen 1955; Shimi *et al*. 1962; Jakubowska 1977; Bently and Thiessen 1957; Winskill 1983; Bonnarme *et al*. 1995). Thus, citric acid and aconitic acid are intermediates, and IA is formed from the latter by enzymatic decarboxylation. Cis-aconitic acid, could be a substrate for an *A. terreus* crude enzyme preparation that contained cisaconiticacid decarboxylase (CAD; EC 4.1.1.6) and is converted to IA as reported by Bentley and Thiessen (1957a,b,c). The purification conditions for CAD enzyme were investigated and purified a 55-kDa protein with CAD activity from a high IA producing strain of *A. terreus* TN484-M1 (Dwiarti *et al*., 2002). The CAD1 gene was functionally expressed in yeast, and the results proved that the obtained CAD1 gene encoded the *A. terreus* CAD protein (Kanamasa *et al*. 2008). Fig1.Pathway



Fungal Production

Mostly frequently used microorganism for commercial production of IA is *A. terreus*. Few workers made attempts with other microorganisms which are not sensitive to some fermentation conditions such as substrate impurities or which have a more favorable product composition. Some filamentous fungi belonging to *Ustilaginales* also produce IA. Haskins *et al*. (1955) found IA in the fermentation broth of an *Ustilago zeae* strain while screening several *Ustilago* strains for the production of ustilagic acid and other metabolic products. One strain among these species, was found to produce about 15 g IA/l. The Iwata Corp. (Japan) tested different *Ustilago* species including *U. maydis,* which produced 53 g IA/l within 5 days from glucose (Tabuchi and Nakahara, 1980; Tabuchi 1991). Yeasts were also tested for IA production where screening and subsequent mutation yielded a strain, identified as *Candida* sp., which produced IA from glucose at about 35% yield (up to 35 g IA/l) in 5 days (Tabuchi 1981). A *Candida* mutant produced up to 42 g IA/l after 5 days (Hashimoto *et al*. 1989), whereas *Rhodotorula* species reached only 15 g IA/l from glucose after 7 days (Kawamura *et al*. 1981). Another way to find better IA producing strains is by mutagenesis. *Pseudozyma antarctica* was also reported to produce IA which yielded 37.5% and 30g/l IA from 80g/l glucose (Levinson *et al,* 2006). Meena *et al.* (2010) reported production of IA by *Aspergillus niger, A. nidulans, A. flavus* and *A. terreus.*

There are some reports on strain improvement for IA production. IA production was suppressed during cultivation of *A. terreus* because growth of this fungi was significantly inhibited by the IA produced (Kobayashi and Nakamura, 1964). The rate of production of IA drastically decreased in the presence of IA concentration higher than 20g/l by *A. terreus* IFO 6365. Yahiro *et al*., 1995, isolated a high IA yielding strain on an IA concentration gradient agar after N-methyl N′-nitro-N-nitrosoguanidine treatment. The mutant strain that produced more than 65 g/l of IA was selected as the most promising high IA-yielding producer, and it was designated TN-484. Industrially, more than 85 g/l of IA was produced by this strain in a 100-kl scale fermentor using a simple medium consisting of glucose, corn steep liquor, and small amounts of minerals (Role, 1997, personal communication). *A. terreus* SRK 10 was mutated using N-methyl N′-nitro-N-nitrosoguanidine, colchicine and sodium azide individually as well as mixed matagenic treatments. The mutant N 45 yielded 46 and 50 g/l IA with acid and amylase hydrolised corn starch respectively. The other mutant, UNCS1 was obtained as a result of treatment with NTG, colchicine and sodium azide at concentrations of 100, 0.02 and 2 µg/ml sequentially. With UNCS1 mutant, the yield of itaconic acid with acid and enzyme hydrolyzed corn starch (120 g l^{-1}) was 43.6 and 48.0 gl^{-1} of itaconic acid, respectively (Reddy and Singh, 2002).

Analysis

Quantitative analysis of fermentation broths is achieved by separation on an ion exclusion column in the hydrogen form (e.g. Aminex HPX87H, Biorad) and detection by UV spectroscopy at 385nm (Hartford, 1962) and at 210nm (Kautola *et al*. 1985; Welter 2000). Bromide absorption method (titration method) (Friedkin, 1945), HPLC (Riscaldati *et al.* 2000) and by chromatography (TLC) (Malony and Attwood 1976).

including Fe, Mn, Cu, Zn, P, and N. Hence to get high productivities, the substrate quality has to be controlled by

Table 1 Producers of Itaconic acid.

Strain No.	Type of fermentation	Substrate	Yield	Reference
Aspergillus terreus NRRL 1960	Submerged	Glucose	20.3g/l	H. Larsen and E. Eimhjellen, 1954
Aspergillus terreus NRRL 1960	Submerged	Glucose	52% w/w	E. Eimhjellen and H. Larsen, 1954
Penicillum charlesii	Submerged	--	--	A.P. Maloney and M.M. Attwood, 1976
Candida	Submerged	Glucose	42g/l 5d	Hashimoto *et al*., 1989
Rhodotorula	Submerged	Glucose	15g/l	Kawamura *et al*., 1989
Aspergillus terreus RC4	--	--	58.5g/l	P. Bonnarne *et al*., 1995.
Aspergillus terreus CM85J			16.7g/l	P. Bonnarne *et al*., 1995.
Aspergillus terreus TN-484	Submerged	Glucose	85g/l	Yahiro *et al*., 1995.
Aspergillus terreus TN-484	Submerged	Corn starch	19.8g/l	Petruccioli, *et al*, 1999
Aspergillus terreus NRRL 1960	Submerged	Corn starch	18.4g/l	Petruccioli, *et al*,1999
Aspergillus terreus	Submerged	Glucose	0.53g/g	Petruccioli, *et al*,1999
Aspergillus terreus	SSF	Sugar cane pressmud	55%	T.Sai *et al*., US Patent, US 6,171,831 B 1 Jan/9/2001
Aspergillus terreus SRK10	Submerged	Corn starch	48.0g/l	CSK Reddy and Singh, 2002
Pseudozyma antarctica	Shake flask	--	72.5g/l	Levinson *et al*., 2006
Aspergillus terreus	Submerged	Sago starch	48.0g/l (0.34g/g)	Dwiarti *et al*., 2007
Aspergillus terreus ATCC 20542	Submerged	--	491mg/l	Long Shan, *et al*., 2007.
Aspergillus terreus	Submerged	*Jatropha* seed cake	24.45g/l	D. M. Rao *et al*., 2007
Aspergillus terreus AS32811	SSF	Bran/corn cob	63.5% (w/w dried med)	Yu Zhimin *et al*., 2009
Ustilago mydis	Submerged	--	35g/l	Panacova *et al*., 2009
Aspergillus terreus	Submerged	Molasses	32g/l (0.4976g/g)	Meena *et al*., 2010
Aspergillus terreus MJL 05	Submerged	Glycerol	27.9g/l	M. Juy *et al*., 2010

Fermentation Conditions

The IA can be successfully produced under phosphate-limited growth conditions at sugar concentrations between 100 and 150 g l–1. For *A. terreus* NRRL1963, for instance, IA production started after phosphate depletion to a level less than 1 mg l^{-1} (Welter 2000). During fermentation, the pH decreases to about 2 and IA becomes the main product. The temperature normally is kept at around 37°C, but some investigators have tried to increase the optimum temperature. After mutagenesis, for example, at 40 °C, an *A. terreus* strain was able to produce five fold higher amounts of IA than the parent strain (Kariya and Fujiwara 1994). Dwiarti *et al*., (2007) also used *A. terreus* TN484-M maintained at 40 ^{o}C. An adequate oxygen supply is essential because anaerobic conditions will irreversibly damage the biomass. Studies have been conducted on the influence several medium components including Fe, Mn, Mg, Cu, Zn, P and N and regulation of these substances during the production process (Lockwood and Reeves 1945; Batti and Schweiger 1963). The most productive process which involves a submerged fermentation process using suspended *A. terreus* biomass, inoculated as spores on pretreated molasses was used by the Pfizer company. The initial pH of about 5 drops to less than about 3 during the initial growth phase. The second phase is characterized by phosphate-limited growth and increased production of IA, substantially free from other organic acids. In the batch process by Pfizer, after raising the pH to 3.8 with lime, about 150 g of sugar are converted to 71 g IA/l (Nubel and Ratajak 1964). A high product concentration of 75,87 and 70g/l of IA was reported by Batti and Schweiger (1963), von Fries (1966) and Jarry and Seraudie (1997) respectively.

The best yields of IA are achieved with glucose or sucrose as substrate, but other carbon sources like starch, molasses, hydrolysates of corn syrup (Grislis *et al*. 1976) or wood (Kobayashi 1978), *Jatropha* seed cake (Muralidhara Rao *et al.,* 2007) and many combinations thereof were also tested. IA production is very sensitive to several medium components, pretreatment of raw materials before or during fermentation, the choice of which depends on the location of plant, the market potentials, energy costs and other factors. The most frequently used substrates are beet or sugarcane molasses (Kane *et al*. 1945; Nubel and Ratajak 1964), hydrolysed starch (Cros and Schneider1993; Yahiro *et al*. 1997; Petruccioli *et al*. 1999); or simply sugars (sucrose, glucose). Glycerol, and mixtures of sucrose and glycerol, were also tested (Jarry and Seraudie 1997).

Solid State Fermentation

In addition to traditional fermentations, new versions of solid state fermentation (SSF) method have been invented which is effective for both small and large-scale fungal cultivation. For example, it is estimated that nearly a third of industrial SSF and koji processes in Japan has been modernized for large scale production of citric and itaconic acids. Furthermore, new applications of SSF have been suggested for the production of antibiotics (Barrios *et al*., 1988), secondary metabolites (Trejo-Hernandez *et al*., 1992, 1993) or enriched foodstuffs (Senez *et al*., 1980). Presently SSF has been applied to large-scale industrial processes mainly in Japan. New versions for SSF reactors have been developed in France (Durand *et al*., 1988; Roussos *et al*., 1993, Durand *et al*., 1997), Cuba (Cabello and Conde, 1985; Enríquez and Rodríguez, 1983 and Rodríguez *et al*., 1986), Chile (Fernández *et al*., 1996) and fundamental studies on process engineering are being conducted in Mexico (Saucedo-Castañeda, 1990).

Itaconic acid production was achieved by using a mutant strain of *Aspergillus terreus* where sugarcane pressmud or peeled sugarcane pressmud was used as support to adsorb liquid medium. This mutant strain was derived from *Aspergillus terreus* ATCC 10020 by successive mutation. Beside the remaining sucrose in the sugarcane pressmud, other carbon source, like glucose, fructose, sucrose, or starch hydrolysate can be added. Appropriate amounts of nitrogen source, mineral salts, such as potassium dihydrogen phosphate, magnesium

sulfate, calcium sulfate, ferric chloride, zinc sulfate, and copper sulfate can be added to the medium. The suitable amount of liquid medium that can be added to the support was 4 to 6 times its dry weight for the sugarcane pressmud and 8 to 14 times its dry weight for the peeled sugarcane pressmud. The optimal pH of the medium is between 2.0-3.0. The fermentation temperature is between 30-40 degrees centigrade (Min-Chang Huang *et al*., 2001 Tsai *et al*., 2001 Yu Zhimin, *et al*., 2009).

Production of IA from cheap carbon substrates: The higher yields of IA was achieved with glucose as the substrate, but for commercial production the use of glucose is not economical. Hence, attempts were made with the raw materials cheaper than glucose, like starch, molasses, corn syrup hydrolysates or wood. The most frequently used substrates are beet or sugarcane molasses (Nubel and Ratajak 1964). Among the various carbohydrates available, corn starch is one of the best carbon sources, since it is very pure, inexpensive (Reddy and Singh 2002). But it is very difficult to sterilize corn starch due to gelatinization upon heating, this problem was solved by hydrolyzing the starch using acid or enzymes. Hydrolysis using glucoamylase resulted in IA yields of up to 0.36 g/g starch, whereas hydrolysis with nitric acid at pH 2.0 yielded 0.35 g/g starch. More than 60 g/l of IA was produced by *A. terreus* TN-484 in a 2.5-l air-lift bioreactor from a medium consisting of 140 g/l of cornstarch with no nitrogen source or other ingredients (Yahiro *et al*. 1997b). The IA yield based on the amount of cornstarch consumed was more than 50% and was similar to that from crystalline glucose. In the case of sago starch, the medium containing nitric acid for both hydrolysis and IA production from sago starch was optimized, and 48.2 g/l of IA was produced with a yield of 0.34 g/g sago starch (Dwiarti *et al*. 2007). Market refuse, apple, and banana were also used as substrates for IA production, and IA yields of 28.5 and 31.0 g/l were obtained using acid- and α-amylase-hydrolyzed corn starch. (Reddy and Singh 2002).

Downstream of Itaconic acid

Biomass and solids are removed by filtration. Industrial grade IA was obtained After evaporation under acidic conditions with cooling and crystallization. ForAnalytical grade IA, the evaporate is treated with activated carbon and filtered. Mother liquor from crystallisation may then be solvent-extracted or treated by anion exchange.(Milsom and Meers 1985). Precipitation of insoluble IA salts is also possible. (Kobayashi 1971). To lower the costs, new technologies such as ultrafiltration, reverse osmosis (Kobayashi *et al*. 1973), ion exchange (Kobayashi *et al*. 1980), or electrodialysis have been evaluated. In the case of purified substrates, like sugars, electrodialysis can be used which reduces the plant investment costs by about 40% (Kobayashi *et al*. 1972, Willke and Vorlop, 2001). To reduce the manufacturing costs, waste starch may be used in IA production. When sago starch was used as the carbon source, the IA recovery yield was almost the same as that obtained when glucose was used; however, the purity was slightly lower than that obtained when glucose was used as the carbon source (Dwiarti 2006; Dwiarti *et al*. 2007).

Applications

IA has been used as industrial adhesives and poly IA is used as a detergent and in shampoos and sequestrants (Carter and Irani 1968,Lancashire1969).The polymerized methyl, ethyl, or vinyl esters of IA are used as plastics, adhesives, elastomers, and coatings. (Smith *et al*. 1974, Pitzl 1951). In the textile industry, IA was employed in non-woven fabric binders. Polyacrylo nitrile copolymers incorporating low levels of IA exhibit improved dye receptivity, which results in more efficient dying and deeper shades (Tate 1981), a process which is used in the textile industry. Pigmented dispersion resins containing 0.1–1.5% IA possess improved wet abrasion resistance (Zhao *et al*. 1999). Later the use of IA has been extended to biomedical fields, such as the dental, ophthalmic, and drug delivery fields. (De *et al*. 2004; Stanojević *et al*. 2006; Tasdelen *et al*. 2004 Sen and Yakar, 2001,Blanco *et al*. 2003). Another potential application of IA is in the preparation of glass ionomer cement (GIC). (Nagaraja and Kishore 2005). This copolymer was the first commercial marketable cement, latter an N-vinyl caprolactam-containing copolymer of acrylic-IA (Moshaverinia *et al*. 2009) and poly (acrylic acid-co-IA) (Culbertson 2006) was developed for use in functional and mechanical GICs, which are finding increasing applications in clinical dentistry.

IA may also be used as an hardening agent in organosiloxanes for use in contact lenses (Novicky 1981; Ellis *et al*.1994). New fields of research include artificial gems and synthetic glasses with special nonlinear characteristics (Kin *et al*. 1998).Detergents, cleaners and other products Copolymers of acrylic acid and IA (5–95%) applied at concentrations up to 100 ppm may be used as a scale inhibitor in boilers (Walinsky 1984). An important reaction of IA with amines results in N substituted pyrrolidones, which can be used as thickeners in lubricating grease (Gordon and Coupland 1980). An imidazoline derivative has also been claimed as anactive component in shampoos (Christiansen 1980). In the detergent industry, IA competes with fumaric or malic acid (Smith *et al*. 1974). It may remove unsaturated polyester resins, cleans gel coat lines, paint-guns and lines, chopper guns, uncured polyurethane foam, most paints, graffiti and inks (InTech 1996). IA monoester compounds with excellent hardness, compression strength and durability are useful for dental adhesives or dental fillers (Saitoh *et al*. 1993).

Bioactive components Several mono- and diesters of partly substituted IA possess significant anti-inflammatory or analgesic activities and nootropic agents (Bagavant *et al*. 1994 Valenta *et al*. 1994). Some monoesters of IA have several plant-growth related properties. In the 1980s, much work was done, especially in Eastern Europe and Japan, on the influences of IA-methylester and hexylester of IA on plant physiology (Karanov *et al*. 1989; Isogai *et al*. 1987; Suzuki *et al*.1986). A special new market has opened for the use of IA in artificial glass (Kin *et al*. 1998) and in bioactive compounds in agriculture, pharmacy and medicine (Bagavant *et al*. 1993). Additionally, as a multipurpose starting material, IA is used in many selective enzymatic transformations to form useful polyfunctional building-blocks (Ferraboschi *et al*. 1994).

Future Prospects*:* IA is considered as one of the top building block molecule obtained from sugars in biorefineries (Kurian, 2005). Day to day demand for IA is escalating in the market. Research is going on to elucidate new properties of this compound which opened the possibilities for its application in the fields of pharmacy, medicine, polymer science and in agriculture. The downstream process should be simplified. There is every need to reduce the production cost of this value added compound by replacing the expensive sugars with cheap

cellulosic and ligocellulosic raw materials derived as agriculture or industrial wastes. Improvement of strains by biotechnological and metabolic engineering is also essential. Moreover, it is recommended that the usual fermentation methods are to be substituted with solid state fermentation, which are to be optimized for higher yields of IA.

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