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Research review paper

Amino acids production focusing on fermentation technologies – A review

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ABSTRACT

Amino acids are attractive and promising biochemicals with market capacity requirements constantly increasing. Their applicability ranges from animal feed additives, flavour enhancers and ingredients in cosmetic to specialty nutrients in pharmaceutical and medical fields.

This review gives an overview of the processes applied for amino acids production and points out the main advantages and disadvantages of each.

Due to the advances made in the genetic engineering techniques, the biotechnological processes, and in particular the fermentation with the aid of strains such as *Corynebacterium glutamicum* or *Escherichia coli*, play a significant role in the industrial production of amino acids. Despite the numerous advantages of the fermentative amino acids production, the process still needs significant improvements leading to increased productivity and reduction of the production costs.

Although the production processes of amino acids have been extensively investigated in previous studies, a comprehensive overview of the developments in bioprocess technology has not been reported yet. This review states the importance of the fermentation process for industrial amino acids production, underlining the strengths and the weaknesses of the process. Moreover, the potential of innovative approaches utilizing macro and microalgae or bacteria are presented.

1. Introduction

Amino acids market demand is increasing since the production of monosodium glutamate (MSG) started in 1907 (Sano, 2009). Amino acids are used in many industrial applications as bulk biochemical to produce a wide range of products such as animal feed additives, flavour enhancers in human nutrition or as ingredients in cosmetic and medical products.

Besides the amino acids important role as intermediates as building blocks of proteins, they are involved in the regulation of key metabolic pathways and processes that are crucial for the growth and the maintenance of organisms (Cesari et al., 2005; Wu, 2009). In particular, they promote health by several actions, including maximizing the efficiency of food utilization, reducing the adiposity, regulating the muscle protein metabolism and controlling the growth and immunity of the organism (Yamane et al., 2007; Wu et al., 2004b; Weinert, 2009). Indeed, it is well documented that an amino acids deficiency causes serious diseases both in humans and animals (Paul et al., 2014; Wu et al., 2004a). Therefore, the interest in investigating and developing new routes to produce them in a more cost-effective and sustainable way has significantly increased in the last years.

Amino acids can be produced by different processes such as

extraction from protein hydrolysates, chemical synthesis or enzymatic and fermentation pathways with the aid of microorganisms. In particular, the fermentation process is becoming one of the most promising processes for amino acids commercial production because of the new genetic engineering tools applied to maximize yield, specificity and productivity of the target compounds (Ikeda, 2003).

This paper provides an overview of the different processes used for amino acid production and underlines the main advantages and disadvantages of each method. Moreover, the most common industrially used amino acid producing bacteria *Corynebacterium glutamicum* and *Escherichia coli*, are presented. Furthermore, process parameters, technological issues associated to an industrial amino acid plant and possible improvements are also discussed.

2. Amino acid production

2.1. Amino acid production: a short history

The interest in the production of amino acids has increased over the years resulting in the development of a variety of technologies. In the 1907, Kikunae Ikeda, at the Tokyo Imperial University, started his experiments with the aim of identifying and purifying the flavour

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Table 1

Comparison among different amino acid production methods. Advantages and disadvantages of the different methods are presented.

Process	Principle	Advantages	Disadvantages
Extraction from protein hydrolysates	An amino acid can be separated from the others present in the protein-hydrolysates if its properties are different from the others	<ul style="list-style-type: none"> ● Large scale industrial production (Ikeda, 2003) ● Can use industrial by-products or waste (Hauer et al., 2004) ● Common reagents such as hydrochloric acid and sodium hydroxide (Lütke-Eversloh et al., 2007) 	<ul style="list-style-type: none"> ● Few kinds of amino acids (Ikeda, 2003) ● Depend on the availability of natural protein rich resources (Hauer et al., 2004) ● Possible protein degradation (Ikeda, 2003) ● By-products (Hauer et al., 2004) ● Wastewater generation (Lütke-Eversloh et al., 2007; Sereewatthanawut et al., 2008)
Chemical synthesis	Amino acids obtained through a chemical reaction	Produce achiral-amino acids (Ivanov et al., 2014)	<ul style="list-style-type: none"> ● Production of racemic mixtures additional optical resolution step is necessary to obtain only the L-forms (Ikeda, 2003) ● Price of the catalyst (Hauer et al., 2004) ● Hazardous sources (Zuend et al., 2009) ● Price and instability of the enzyme (Ikeda, 2003) ● Not favorable for production of L-amino acids at industrial scale (Ikeda, 2003)
Enzymatic synthesis	Application of proteases to peptide hydrolysis	<ul style="list-style-type: none"> ● Produce optically pure D and L- amino acids (Ikeda, 2003) ● Very few amount of by-product (Ivanov et al., 2014) ● Simple process downstream (Ivanov et al., 2014) 	
Fermentation	Microorganisms convert the sugars present in a substrate into amino acids	<ul style="list-style-type: none"> ● Large scale industrial production of most of L- amino acids (Ivanov et al., 2014) ● Economic method (Ikeda, 2003) ● Production of L- amino acids form (Hauer et al., 2004) ● Mild conditions (Ugimoto, 2010) ● Low plant maintenance costs (Ugimoto, 2010) 	<ul style="list-style-type: none"> ● Sterility has to be ensured (Ugimoto, 2010) ● Energy required for oxygen transfer and mixing (Ugimoto, 2010) ● High operational costs (Ivanov et al., 2014)

enhancing principle from the seaweed konbu (*Laminaria japonica*). After a year of research he discovered that the extract consisted of MSG (Kurihara, 2009).

Soon after his discovery Ajinomoto Co. began extracting MSG from acid-hydrolyzed wheat gluten or defatted soybean and selling it as a flavour enhancer (Sano, 2009). Kikunae Ikeda is considered the father of MSG as he provided the bases for the amino acid production industry.

The development of new applications for amino acids, such as pharmaceutical, food additives, feed supplements, cosmetics, polymer materials and agricultural chemicals, led to a fast increase in the amino acid production. Indeed, in 2008 the total amino acids market was estimated around USD 5.4 billion (März, 2009) and it is expected to be worth over USD 9.4 billion by 2018 (Transparency Market Research, 2013). However, the industrial processes to produce amino acids still need to be optimized. For this reason, many companies (Kim, 2010) and academic institutions (Kumagai, 2013; Hauer et al., 2004) started research in this field with the aim of finding more cost-effective and sustainable routes to produce amino acids.

2.2. Amino acid production processes

Amino acids are at the present produced through three different routes, namely, extraction from protein-hydrolysates, chemical synthesis and microbial processes (enzymatic synthesis and fermentation). In Table 1, the different amino acids production methods are compared and in Table 2 and Table 3 an overview of the yield obtained with the different methods is presented.

2.2.1. Extraction from protein-hydrolysates

Extraction from protein-hydrolysates is suitable for large scale industrial production of only a few kinds of amino acids such as L-cysteine, L-leucine and L-tyrosine (Ikeda, 2003). This method exploits the differences in physicochemical properties (such as chemical affinity and pH) of the amino acids to separate them (Zhang et al., 2016).

According to the amino acid of interest different extraction processes can be developed. For instance, L-cysteine, traditionally produced from keratin contained in animal and human material such as feathers, hair, bristles and hooves, is extracted using activated charcoal and

Table 2

Overview of yield obtained with different amino acids production methods.

Method	Source	Reaction ^a or enzyme ^b	Amino acid	Yield (% w w ⁻¹)	Reference
Extraction	Hair	–	L-cysteine	10	Renneberg, 2008 Sereewatthanawut et al., 2008 Cheng et al., 2008
	Deoiled rice bran	–	Mixture	0.8	
	Feather	–	L-leucine	0.7	
			L-alanine	0.1	
			L-serine	0.2	
Chemical synthesis	Trichloroethylene	Ammonolysis ^a	L-glycine	40–70	Inoue and Enomoto, 1982 Ogata and Inaishi, 1981 Ramakrishnan et al., 2013
	(±)-2-chloropropionic acid	Ammonolysis ^a	D,L-alanine	78.0	
Enzymatically catalyzed synthesis	Fish waste	Alcalase and Neutrase ^b	L-alanine	7.6	
			L-glycine	5.8	Hsiao et al., 1988
			L-phenylalanine	4.2	
			L-leucine	9	
			L-serine	4.3	
			L-phenylalanine	63	
	Phenylpyruvate	Polyazetidine immobilized <i>E. coli</i> ^b	L-phenylalanine	63	

^a Indicates the reaction involved in the process.

^b Indicates the enzyme involved in the process.

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