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Research review paper

Bio-production of lactobionic acid: Current status, applications and future prospects

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ABSTRACT

Lactobionic acid has appeared on the commercial scene as a versatile polyhydroxy acid with numerous promising applications in the food, medicine, pharmaceutical, cosmetics and chemical industries. This high value-added bio-product has recently received growing attention as a bioactive compound, providing an excellent chemical platform for the synthesis of novel potentially biocompatible and biodegradable drug delivery vehicles. Recent advances in tissue engineering and nanomedicine have also underlined the increased importance of this organic acid as a key biofunctionalization agent. The growing commercial relevance of lactobionic acid has therefore prompted the development of novel systems for its biotechnological production that are both sustainable and efficient. The present review explores recent advances and studies related to lactobionic acid bio-production, whether through microbial or enzymatic approaches, highlighting the key bioprocessing conditions for enhanced bio-production. Detailed overviews of the current microbial cell factories as well as downstream processing methodologies for lactobionic acid production are also presented. Furthermore, the potential prospects and current applications of this polyhydroxy acid are also discussed, with an emphasis on the role of lactobionic acid as a key platform in the development of novel drugs, biomaterials, nanoparticles and biopolymer systems.

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1. Introduction

The production of bulk organic acid chemicals by microbial fermentation has undoubtedly undergone continuing growth over the last decade, progressively expanding its market niche and portfolio (Jang et al., 2012; Sauer et al., 2008). In fact, bacteria as bio-production platforms have become a reliable, cost-competitive, feasible alternative for large-scale industrial production of many bulk and specialty organic acids (Demain, 2007). Organic acids represent a growing chemical segment in which bio-based compounds such as fumaric, propionic, itaconic or α-ketoglutaric acids have also emerged on the market as platform chemicals (Jang et al., 2012). This transition towards bio-based industrial production has concomitantly involved the development of novel sustainable bioprocesses focused on the use of cost-effective renewable resources, either already implemented at an industrial level or still in the development pipeline (Willke and Vorlop, 2004). Beyond traditional organic acids, the market has also shown substantial interest in novel carboxylic acids like lactobionic acid due to its unique physicochemical properties (Fig. 1). Lactobionic acid (LBA) is a high value-added lactose derivative which has recently emerged as a promising and versatile substance with countless applications in the cosmetics (Green et al., 2009; West, 2004a), pharmaceutical (Belzer et al., 1992) and food (Gerling, 1998; Gutiérrez et al., 2012) industries. The recent market glut suffered by traditional lactose-based products has additionally stimulated the dairy industry to seek new approaches for lactose utilization which could overcome the traditional view of lactose as a commodity (Affertsholt, 2007; Gänzle et al., 2008). As a result, novel lactose derivatives (such as lactitol, lactulose and LBA) have recently come onto the commercial market with considerable industrial applications (Playne and Crittenden, 2009; Seki and Saito, 2012).

In recent years, LBA has also received growing attention as a bioactive molecule since it provides an excellent platform for the synthesis of biocompatible and biodegradable drug delivery vehicles and biomaterials. In this respect, LBA will clearly play a major strategic role in the treatment of hepatic disorders through nanomedicine, with a potential near-term impact. Its prospect as a key biomolecule in the field of nanotechnology is thus of outstanding significance. In view of this commercial relevance, both the development and implementation of feasible LBA production systems emerge as crucial key challenges to meet market demands. To date, LBA is manufactured by chemical synthesis in an energy-intensive process which requires the use of costly metal catalysts (Kuusisto et al., 2007; Yang and Montgomery, 2005). However, this expensive methodology may also involve the generation of undesirable side-reaction products. Although this polyhydroxy acid has been available since the late 1940s (Stodola and Jackson, 1950; Stodola and Lockwood, 1947), its production by biotechnological means has not been developed so intensively up to now in comparison with other organic acids such as lactic, succinic or citric acid (Papagianni, 2011). Nevertheless, bio-production of LBA has emerged as both a promising and feasible approach to meet the growing demand for this bio-product. Furthermore, environmentally-friendly and cost-effective LBA bio-production can be accomplished by employing cheese whey as an inexpensive feedstock (Alonso et al., 2011, 2012a, 2013). Despite being a traditional natural source for whey protein isolate and lactose, cheese whey upgrading and treatment remain as two of the major challenges facing the dairy industry. Therefore, the search for innovative solutions in the disposal and management of this high-strength waste stream has become the driving force behind the development of novel sustainable biotechnological processes (Guimarães et al., 2010).

Within this context, the present review explores recent advances in LBA bio-production, either through enzymatic or microbial biosynthesis, as well as the current novel trends addressing the application of LBA in the marketplace, with particular emphasis on those emerging areas such as nanomedicine and tissue engineering. A detailed overview of current microbial cell factories, further downstream processing methodologies for LBA production and prospects are also provided.

2. Properties and current industrial status of lactobionic acid

The structure and physicochemical properties of LBA confer on it a plethora of current and potential commercial applications, as shown in Fig. 2. This organic acid exhibits a large number of newly discovered biological activities and great therapeutic potential due to its

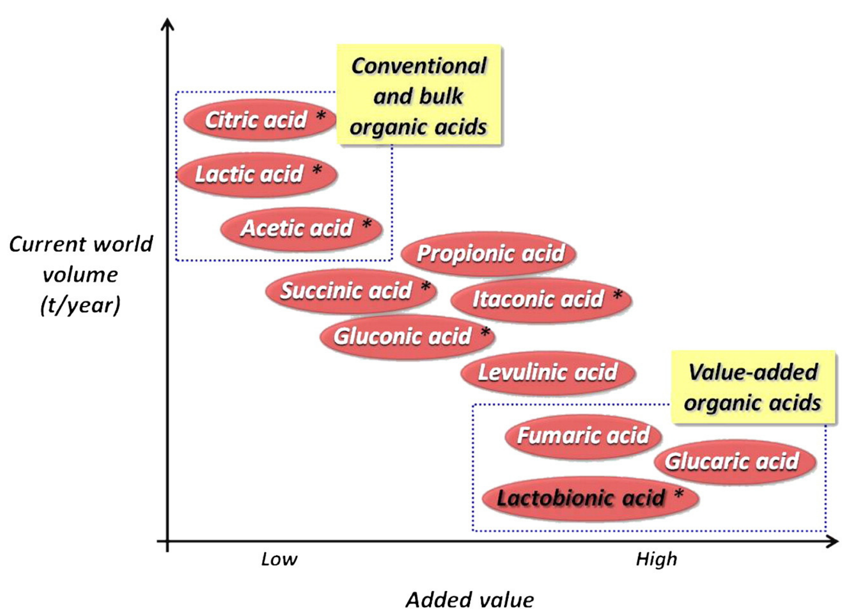

Fig. 1. Segmentation in the organic acids market. The biotech industry is currently moving from commodity bulk carboxylic acids towards value-added organic acids which display outstanding applications. LBA currently belongs to this latter segment. The symbol * denotes an implemented industrial production by microbial fermentation. Although microbial production of several organic acids such as succinic acid has been recently implemented on a commercial-scale, their successful commercial consolidation depends strongly on the reduction of production costs. Microbial production of organic acids can only compete on the basis of price with petroleum-based carboxylic acids if efficient fermentative processes based on low-cost substrates are developed.

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