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A study of biotechnology advances in the production of lactobionate by different processing methods

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Abstract
Lactobionic acid is a sugar acid. It is a disaccharide formed from gluconic acid and galactose. It can be formed by oxidation of lactose. The carboxylate anion of lactobionic acid is known as lactobionate. Lactobionate (LBA) is a bionic acid that occurs naturally in foods. As an antioxidant, chelator, and moisturiser, the compound has a long list of established benefits. As a result, this study discusses existing LBA production processes, general applications and regulations, potential prospects, and an overview of the difficulties the food industry faces in incorporating the acid into their products.

Keywords: Lactose, production method, lactobionate, application, acidulant

Introduction
Lactobionic acid (LBA) is an aldobionic acid with nine free hydroxyl groups that is made up of gluconic acid bonded to galactose. This configuration confers antioxidant, antimicrobial, moisturising, and chelating properties to the LBA (Alonso, Rendueles, & Daz, 2013; Illanes *et al*., 2016; Saha, Sasmal, Alam, & Das, 2014) [1, 2, 3]. Among these, the antioxidant and humectants potentials were tested in cosmetic studies (Tasic-Kostov *et al*., 2012) [4], however, no literature has been found on these properties in pure LBA.
The oxidation of lactose with specific enzymes or microorganisms as biocatalysts is used in the biocatalytic processing of LBA. The general reaction mechanism (Nakano, Kiryu, Kiso, & Murakami, 2010) [5] involves the formation of lactobionic-lactone as an intermediate product, which is then hydrolyzed to lactobionic acid.
Because of its antioxidant, chelating, and humectant properties, LBA (4-Ob-D-galactopyranosyl-D-gluconic acid; C;FW 358.30 Da; pKa3.8) has a lot of potential as a food and pharmaceutical ingredient (Playne & Crittenden, 2009) [6].
LBA has also been reported as an acidulant in dairy gels (Ribeiro *et al*., 2016) [34]; it can inhibit the growth of L. monocytogenes when combined with nisin and thymol (Chen & Zhong, 2017) [7]; and it can act as a cryoprotectant of proteins (Ribeiro *et al*., 2016) [34]. (Misugi *et al*., 2017). Furthermore, its chelating property was confirmed by titration with copper ions and UV–VIS changes in the LBA-iron (III) complex (Isaacson, Salem, Shepherd, & Van Thiel, 1989) [8].
In this context, the current review discusses recent advances in lactobionate bio-production through enzymatic or microbial biosynthesis, electrochemical oxidation, and current new trends in lactobionate application in the food industry.

Production method of Lactobionate
The oxidation of the free aldehyde group of glucose to the carboxylic group on the lactose molecule is needed for the preferential conversion of lactose to lactobionate. For the production of lactobionic acid, many processes have been studied, including biocatalytic, electrochemical, and heterogeneous catalytic oxidations.
Lactose is oxidised by particular enzymes or by using microorganisms as biocatalysts in the biocatalytic processing of lactobionic acid. The general reaction mechanism includes the formation of lactobionic-d-lactone, which is hydrolyzed to lactobionic acid as an intermediate product (Nakano *et al*., 2010) [5].
Lactobionic acid is produced by Pseudomonas species through the lactose oxidation pathway, in which a membrane bound dehydrogenase enzyme first catalyses the oxidation of lactose to a lactone intermediate (lactobionic-d-lactone), which is then hydrolyzed (its carbonyl group) by a lactonase to produce lactobionic acid (Alonso *et al* 2012; Nishizuka and Hayaishi, 1962) [11, 10].

Enzymatic catalysis produces more lactobionic acid, yields, and productivities than microbial fermentation, but enzymes are more susceptible to degradation in the enzymatic development method (Nordkvist *et al*., 2007) [12].

Lactose oxidising enzymes such as glucose fructose dehydrogenase, cellobiose dehydrogenase (Van Hecke *et al*., 2009) [13], and carbohydrate oxidase (Gutiérrez *et al*., 2012) [22] have been used to produce lactobionic acid, but technical challenges include coenzyme regeneration and enzyme inactivation, which is primarily caused by the formation of H2O, which must to be reduced, by the addition of catalase (Hua *et al.,* 2007) [15].

Other bacteria, such as Pseudomonas mucidolens, Pseudomonas myxogenes, and Pseudomonas fluorescens, were also capable of producing bionic acids from lactose, as well as maltose and isomaltose as carbon sources, indicating that LBA development has a bright future (Alonso, Rendueles, & Diaz, 2011; Goderska, Szwengiel, & Czarnecki, 2014; Sternberg & Lockwood, 1969) [11, 18, 17].

The importance of Pseudomonas species as the key bionic producer microorganisms was highlighted in research studies by Kluyver *et al.* (1951) [19] and Stodola and Lockwood (1947) [20]. P. mucidolens, P. myxogenes, and P. fluorescens strains have been found to be capable of directly oxidising lactose without the need for prior hydrolysis or phosphorolysis. Pseudomonas taetrolens (formerly known as P. graveolens) displayed the highest oxidative abilty, with a yield of 75% in shake-flask culture after 165 h (Stodola and Lockwood, 1947) [20].

In addition, a red algae has been discovered to be capable of oxidising a variety of carbohydrates at an optimum pH of 5.0 (Murakami *et al*., 2003; Alonso *et al*., 2011) [21, 18].

Electrolytic oxidation processes have also been used to make lactobionic acid. Gutiérrez *et al.* (2012) [50] found that electro-catalytic oxidation of lactose on noble metal electrodes (platinum, platinum-modified, and gold electrodes) in alkaline media would produce high yields (>90%) and selectivities (100%) against lactobionic acid.

Electrolytic oxidation methods have also been used to make LBA. Isbell (1934) [24] used graphite electrodes to electrochemically oxidise lactose in the presence of bromine and calcium carbonate to create calcium lactobionate. Magariello and Islip (1956) [23] improved this process by patenting a method for producing large amounts of LBA (yield w98%) by electrolytic oxidation of lactose with graphite electrodes, iodine or bromine as catalysts, and an alkaline solution to keep the pH above 5.2. Since then, there has been little research into the electrochemical processing of LBA, and only a few papers have been written (Aoun *et al*., 2003; Dutta & Basu, 1979; Kokoh & Alonso-Vante, 2006) [27, 26, 25].

Hendriks *et al.* (1990) [28] were the first to successfully produce lactobionic acid by heterogeneous catalytic oxidation of lactose on palladium and bismuth-palladium supported catalysts. Funded gold nanoparticles have shown exceptional activity and selectivity in the oxidation of carbohydrates (Belkacemi *et al*., 2007; Murzina *et al*., 2008; Gutiérrez *et al*., 2012) [29, 30, 50]. Gold catalysts have shown strong stability against over oxidation.

Lactobionate is a substance which is used in the food industry

The food industry has great interest or attention to the use of lactobionic acid as a food additive in the last years as calcium carrier, acidifier agent, antioxidant. The dairy field has been currently involved in the implementation and development of new production methods inclusive lactobionic acid as one of the main compounds in new dairy gaining technologies (Merrill & Singh, 2011).

As a natural source of LBA, we can mention the Caspian Sea Yogurt, which has similar characteristics to a Kefir and is highly consumed in Japan. The daily consumption of around 100 g of this yogurt by individuals would indicate a consumption of approximately 1g/person/year of LBA Kiryu *et al*., 2009 [32].

Lactobionic acid provides extra functional properties and sensory attributes through the reduction of undesirable Maillard browning in cooking products (Merrill and Singh, 2011), and also used as a flavor enhancer for foods or beverages (Walter and Begli, 2011).

Rheological properties, effects on the mobility of sodium, and odor characteristics of dairy gels acidified with LBA were attributes investigated by Ribeiro *et al.* (2016) [34]. LBA showed to be an efficient acidifier in dairy products that need a gelation step. The results were compared to those obtained using glucono delta-lactone (GDL), an acidulant regularly applied in dairy foods.

A study of the combined antimicrobial effect of LBA, nisin, and thymol in tryptic soy broth, 2% reduced-fat milk and whole milk (Chen & Zhong, 2017) [35] pointed out that the acid increases the synergistic effect between nisin and thymol against *L. monocytogenes* but cannot achieve the same result with *Escherichia coli* as antimicrobial (Chen & Zhong, 2017) [35].

In cheese and yogurt production LBA presents potential in the reduction of souring time and preservation of aroma, including the power to mask off-flavors (Kiryu *et al*., 2009; Ribeiro *et al*., 2016) [32, 34]. Kiryu *et al.* (2009) [36] fermented cow's milk to "Caspian Sea yogurt" with *A. orientalis* cells. These exhibited lactose-oxidizing activity, suggesting that this bacterium was primarily responsible for the LBA production in the yogurt.

Equally important in novel nondairy beverages, milk-based beverages and cheeses containing calcium lactobionate have been recently developed to provide a valuable approach for calcium supplementation (Nielsen, 2007; Nielsen and Hoeier, 2009) [38, 37].

Lactobionic acid containing functional milk, which may help to combat calcium deficiency, has been launched into the food market by 'Megmilk Snow', a well-known Japanese dairy company (Megmilk Snow, 2012) [39].

As a cosmetic ingredient, lactobionic acid offers multiple benefits for the therapeutic treatment of dermatological pathologies such as atopic dermatitis and rosacea (Briden and Green, 2006) [40] or can even be employed in antiacne treatments (Decker and Graber, 2012).

In addition to lactobionic acid antioxidant role, it also exhibits strong moisturizing, exfoliate and humectant, showing antiaging effects, including skin plumping and smoothing of surface topography with diminished appearance of fine lines and wrinkles (Green *et al.,* 2006; Tasic-Kostov *et al.,* 2010) [41, 42].

The use of lactobionic acid as a food additive has also received growing attention from the food industry in recent years. Lactobionic acid can serve as an antioxidant, stabilizer or gelling agent in dessert products (FDA, 2011) [43], an acidifier agent in fermented milk products (Faergemand *et al.,* 2012) [44], an aging inhibitor for bread

(Oe and Kimura, 2011). Additionally, lactobionic acid has been proposed as a technological feed additive for laying hens to improve egg shell qualities by boosting calcium absorption (Kimura, 2006) [45].

Baldwin *et al.*, (2004) [47] have also devised an antioxidant composition containing lactobionic acid and siderophores as key elements for retarding lipid oxidation in food products. Lactobionic acid act as a water holding capacity agent in meat products submitted to thawing and/or cooking processes has been recently reported for the first time, resulting in higher industrial product yields and water content after treating meat products with lactobionic acid (Nielsen, 2009) [37].

Lactobionic acid is used in the chemical industry as a sugar based surfactant in biodegradable detergents. Its iron chelating and emulsifying properties have suggested its potential use in many industrial operations, use as an important starting chemical for manufacturing detergents (Bize *et al.*, 2010) [48].

Numbers of lactobionic acid based surfactants has been currently developed as biodegradable surfactants with improved surface and performance properties (Oskarsson *et al.*, 2007) [49].

It does not have a specific colour, flavour or aroma, besides product has primarily antibacterial functions at small doses. Food and Drug Administration (FDA) has already approved the usage of calcium lactobionate as food additive, but the agreement by the European Food Safety Authority (EFSA) is still unsolved, because of the deficiency of the long term influence assessment of lactobionic acid on human health (Gutiérrez, Hamoudi, & Belkacemi, 2012) [50].

In addition, this compound as a feed additive has been suggested for laying hens, promoting the absorption of calcium and raising the quality of egg shell (Kimura, 2006) [45]. An antioxidant mixture containing lactobionic acid has been invented for reducing lipid oxidation in products (Baldwin *et al*., 2004) [47].

Conclusion

Lactobionate is a lactose oxidation compound with antioxidant, chelating, humectant, and emulsifying properties that could be useful in the food and chemical industries. Lactobionate can play an important role in functional and nutraceutical foods in the coming year. One of the most promising contributions to milk by-products was the invention of transformation processes to generate high-value lactose derivatives.

References

1. Alonso S, Rendueles M, Díaz M. Bio-production of lactobionic acid: Current status, applications and future prospects. Biotechnology Advances 2013;31(8):1275-1291. https://doi.org/10.1016/j.biotechadv.2013.04.010
2. Illanes A, Guerrero C, Vera C, Wilson L, Conejeros R, Scott F. Lactose-derived prebiotics: A process perspective. San Diego, US: Elsevier Science 2016. Retrieved from https://books.google.com.br/books?id=NwJKCgAAQBAJ
3. Saha T, Sasmal S, Alam S, Das N. Tamarind kernel powder: A novel agro-residue for the production of Cellobiose dehydrogenase under submerged fermentation by Termitomyces clypeatus. Journal of Agricultural and Food Chemistry 2014;62(15):3438-3445. https://doi.org/ 10.1021/jf405278y
4. Tasic-Kostov M, Pavlovic D, Lukic M, Jaksic I, Arsic I, Savic S. Lactobionic acid as antioxidant and moisturizing active in alkyl polyglucoside-based topical emulsions: The colloidal structure, stability and efficacy evaluation. International Journal of Cosmetic Science 2012;34(5):424-434. https://doi.org/10.1111/j.1468-2494.2012.00732.x
5. Nakano H, Kiryu T, Kiso T, Murakami H. In: Biocatalytic production of lactobionic acid (edited by Hou CT, Shaw JF). Biocatalysis and biomolecular engineering, New Jersey, John Wiley and Sons Inc, 2010, 391-404.
6. Playne MJ, Crittenden RG. Galacto-oligosaccharides and other products derived from lactose. In McSweeney PLH, Fox PF (Eds.), Lactose, waters alts and minor constituents (3rd ed.). Advanced dairy chemistry New York, NY, USA: Springer 2009;3:121e201.
7. Chen H, Zhong Q. Lactobionic acid enhances the synergistic effect of nisin and thymol against Listeria monocytogenes Scott A in tryptic soy broth and milk. International Journal of Food Microbiology 2017;260(1):36-41. https://doi.org/10.1016/j.ijfoodmicro.2017.08.013
8. Isaacson Y, Salem O, Shepherd RE, Van Thiel DH. Lactobionic acid as an iron chelator: A rationale for its effectiveness as an organ preservant. Life Sciences 1989;45(24):2373-2380. https://doi. org/10.1016/0024-3205(89)90120-
9. Nakano H, Kiryu T, Kiso T, Murakami H. In: Biocatalytic production of lactobionic acid (edited by Hou CT, Shaw JF). Biocatalysis and biomolecular engineering, New Jersey, John Wiley and Sons Inc, 2010, 391-404.
10. Nishizuka Y, Hayaishi O. Enzymic formation of lactobionic acid from lactose. J Biol. Chem 1962;237:2721-2728.
11. Alonso S, Rendueles M, Díaz M. Selection method of pH conditions to establish Pseudomonas taetrolens physiological states and lactobionic acid production. Appl. Microbiol. Biotechnol 2012;27:3-27.
12. Nordkvist M, Nielsen PM, Villadsen J. Oxidation of lactose to lactobionic acid by a Microdochium nivale carbohydrate oxidase: kinetics and operational stability. Biotechnology and Bioengineering 2007;97:694e707.
13. Van Hecke W, Bhagwat A, Ludwig R, Dewulf J, Haltrich D, Van Langenhove H. Kinetic modeling of a bi-enzymatic system for efficient conversion of lactose to lactobionic acid. Biotechnol. Bioeng 2009;102:1475-1482.
14. Gutiérrez LF, Hamoudi S, Belkacemi K. Lactobionic acid: A high value-added lactose derivative for food and pharmaceutical applications. International Dairy Journal 2012b;26(2):103-111. https://doi.org/10. 1016/j.idairyj.2012.05.003
15. Hua L, Nordkvist M, Nielsen PM, Villadsen J. Scale-up of enzymatic production of lactobionic acid using the rotary jet head system. Biotechnology and Bioengineering 2007;97:842-849.
16. Goderska K, Szwengiel A, Czarnecki Z. The utilization of Pseudomonas taetrolens to produce lactobionic acid. Applied Biochemistry and Biotechnology 2014;173(8):2189-2197. https://doi.org/10.1007/s12010-014-1024-x
17. Sternberg M, Lockwood LB. Oxidation of isomaltose by pseudomonas taetrolens. Journal of Bacteriology 1969;99(2):623-623. Retrieved from http://www.ncbi.nlm.nih. gov/pmc/articles/PMC250065/
18. Alonso S, Rendueles M, Díaz M. Efficient lactobionic

acid production from whey by Pseudomonas taetrolens under pH-shift conditions. Bioresour. Technol 2011;102:9730-9736.
19. Kluyver AJ, De Ley J, Rijven A. The formation and consumption of lacto-bionic and malto-bionic acids by Pseudomonas species. Antonie Van Leeuwenhoek J Microbiol 1951.
20. Stodola FHH, Lockwood LB. The oxidation of lactose and maltose to bionic acids by Pseudomonas. The Journal of Biological Chemistry 1947;171(1):213-221. Retrieved from http://www.jbc.org/content/171/1/213.short
21. Murakami H, Seko A, Azumi M, Ueshima N, Yoshizumi H, Nakano H *et al*. Fermentative production of lactobionic acid by *Burkholderia cepacia*. J Applied Glycoscience 2003;50:117-120.
22. Gutiérrez LF, Hamoudi S, Belkacemi K. Effective gold catalyst supported on mesoporous silica decorated by ceria for the synthesis of high value lactobionic acid. Applied Catalysis A: General 2012;4:425-426.
23. Magariello ER, Islip NY. Production of lactovionic acid and its d-lactone.US Patent 1956, 2.746.916.
24. Isbell HS. Process for the preparation of calcium lactobionate. US Patent 1934.
25. Kokoh KB, Alonso-Vante N. Electrocatalytic oxidation of lactose on gold nanoparticle modified carbon in carbonate buffer. Journal of Applied Electrochemistry 2006, 36, 147e151.
26. Dutta SK, Basu SK. Erythromycin aldobionates. US Patent 4.137.397. Elsevier Science 1979.
27. Aoun SB, Bang GS, Koga T, Nonaka Y, Sotomura T, Taniguchi I. Electrocatalytic oxidation of sugars on silver-UPD single crystal gold electrodes 2003.
28. Hendriks HEJ, Kuster BFM, Marin GB. The effect of bismuth on the selective oxidation of lactose on supported palladium catalysts. Carbohydrate Research 1990;204:121-129.
29. Belkacemi K, Vlad MC, Hamoudi S, Arul J. Value-added processing of lactose: preparation of bioactive lactobionic acid using a novel catalytic method. Int. J Chemical Reactor Engineering 2007;5:64.
30. Murzina EV, Tokarev AV, Kordás K, Karhu H, Mikkola JP, Murzin DY. D-lactose oxidation over gold catalysts. Catal Today 2008;131:385-392.
31. Merrill RK, Singh M. Food ingredients and food products treated with an oxidoreductase and methods for preparing such food ingredients and food products. Patent application EP 2009, 2 123 294 A1.
32. Kiryu T, Kiso T, Nakano H, Ooe K, Kimura T, Murakami H. Involvement of Acetobacter orientalis in the production of lactobionic acid in Caucasian yogurt (Caspian Sea yogurt) in Japan. Journal of Dairy Science 2009;92(1):25-34. https://doi.org/10.3168/jds.2008-1081
33. Walter T, Begli HA. U.S. Patent No. US20110244080. United States Patent. Südzucker Aktiengesell schaft Mannheim/Ochsenfurt 2011.
34. Ribeiro JCB, Granato D, Masson ML, Andriot I, Mosca AC, Salles C *et al*. Effect of lactobionic acid on the acidification, rheological properties and aroma release of dairy gels. Food Chemistry 2016;207(1):101-106. https://doi.org/10.1016/j.foodchem.2016.03.066
35. Chen H, Zhong Q. Lactobionic acid enhances the synergistic effect of nisin and thymolb against Listeria monocytogenes Scott A in tryptic soy broth and milk. International Journal of Food Microbiology 2017;260(1):36-41. https://doi.org/10.1016/j.ijfoodmicro.2017.08.013
36. Kiryu T, Kiso T, Nakano H, Ooe K, Kimura T, Murakami H. Involvement of Acetobacter orientalis in the production of lactobionic acid in Caucasian yogurt (Caspian Sea yogurt) in Japan. Journal of Dairy Science 2009;92(1):25-34. https://doi.org/10.3168/jds.2008-1081
37. Nielsen PM, Hoeier E. World Intellectual Property Organization. Patent No. WO2009007398A1. United States Patent. Chr. Hansen AS 2009.
38. Nielsen PM. Non-dairy beverage product comprising calcium lactobionate. United States Patent Application Pub 2007. No.: US 2007/0281066 A1.
39. Megmilk Snow. Press release. Available via: http://wwwmeg-snow.com/news/2012/ pdf/20120524-383.pdf 2012. [Accessed 30 January 2013 (in Japanese)]
40. Green B, Wildnauer R, Nguyen H, Edison B. Lactobionic acid: a bionic acid enhances skin clarity and provides skin plumping and firming effects. J the American Academy of Dermatology 2006;54:37.
41. Briden ME, Green BA. Topical exfoliation – clinical effects and formulating considerations. In: Cosmetic formulation of skin care products (edited by Draelos ZD, Thaman LA). New York: Taylor and Francis Group, 2006, 237-250.
42. Tasic-Kostov M, Savic S, Lukic M, Tamburic S, Pavlovic M, Vuleta G. Lactobionic acid in a natural alkylpolyglucoside-based vehicle: assessing safety and efficacy aspects in comparison to glycolic acid. J Cosmetic Dermatology 2010;9:3-10.
43. FDA. Code of Federal Regulations, Title 21, 21 CFR 172. 720. US Food and Drug Administration. 2011. [Availablevia:http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/ CFRSearch.cfm?fr=172.720. Accessed 30 November 2012].
44. Faergemand M, Gilleladen C, Qvist KB. Method for producing an acidified milk product. United States Patent Application Pub. No.: US 20120045546 A1 2012.
45. Kimura T. Feed additive for laying hens and feed containing the additive. European Patent Application Pub. No: EP 1731042 A1 2006.
46. Oe K, Kimura T. Mineral absorption promoter Japan Patent Application Pub. No.: JP2008303208 2008.
47. Baldwin C, Akashe A, Dinwoodie R, Koka R, West LG, Kortum O. US Patent No. 0170728. United States Patent. Kraft Foods Group Brands LLC 2004.
48. Bize C, Blanzat M, Rico-Lattes I. Self-assembled structures of catanionic associations: how to optimize vesicle formation. J Surfactant Deterg 2010;13:465-473.
49. Oskarsson H, Frankenberg M, Annerling A, Holmberg K. Adsorption of novel alkylaminoamide sugar urfactants at tailor-made surfaces. J Surfactant Deterg 2007, 1041-52.
50. Gutiérrez LF, Hamoudi S, Belkacemi K. Effective gold catalyst supported on mesoporous silica decorated by ceria for the synthesis of high value lactobionic acid. Applied Catalysis A: General 2012;4:425-426.