Intl. J. Food. Ferment. 6(1): 25-33, June 2017

DOI: 10.5958/2321-712X.2017.00003.5

Lactobionic Acid: Significance and Application in Food and Pharmaceutical

Minal, N., Bharwade, Smitha Balakrishnan*, Nisha N. Chaudhary and A.K. Jain

SMC College of Dairy Science, AAU, Anand, India

*Corresponding author: smithabalu2001@yahoo.co.in

Abstract

Lactose has long been used as a precursor for the manufacture of high-value derivatives with emerging applications in the food and pharmaceutical industries. This review focuses on the main characteristics, manufacturing methods, physiological effects and applications of lactobionic acid. Lactobionic acid is a product obtained from lactose oxidation, with high potential applications as a bioactive compound. Recent advances in tissue engineering and application of nanotechnology in medical fields have also underlined the increased importance of this organic acid as an important biofunctional agent.

Keywords: Lactobionic acid, oxidation, physiological effects, applications

Carbohydrates have been used in the manufacture of bulk and fine chemicals, and are viewed as a renewable feedstock for the 'green chemistry of the future. Lactose, a unique disaccharide, occurring extensively in the mammalian milk plays an important role in nutrition. Most of the lactose that is manufactured on an industrial scale is produced from the whey derived from the production of cheese, casein or paneer by using drying, crystallization and purification technologies.

However the use of lactose is limited in many applications, because of its low sweetness and solubility, as well as due to the intolerance of some population segments (Gutierrez *et al.*, 2011). Lactose can be converted to various derivatives like lactobionic acid, lactulose, lactitol, galacto-oligosaccharides, epilactose etc., using laboratory or industrial processes. Lactobionic acid is produced by oxidation of lactose. It is widely used in food and in pharmaceutical field due to its excellent biocompatibility, biodegradability, nontoxicity, chelating, amphiphilic and antioxidant properties (Alonso *et al.*, 2013).

CHEMISTRY

Lactobionic acid (4-0-β-D-galactopyranosyl-D-gluconic acid) belongs to the aldobionic family of acids (Pezzotti and Therisod, 2006). Chemically lactobionic acid comprises a galactose moiety linked with a gluconic acid molecule via an ether-like linkageand featured by the presence of multifunctional groups. Thus it acts as a metal ion chelator and can sequester calcium (Alonso *et al.*, 2013). It has a molecular weight of 358.3 Da with pKa 3.6 (Armarego and Chai, 2009). From a nutritional point of view, this substance may be considered a low calorie sweetener which provides only 2 kcal/g (Schaafsma, 2008). Lactobionic acid appears as a white solid powder which is freely soluble in water and slightly soluble in anhydrous ethanol and methanol. It has a melting point in the range of 128-130ºC (Alonso *et al.,* 2013). Lactobionic acid can be dehydrated to a lactone. It is hygroscopic in nature. Its superior water-retention ability is valuable for cosmetic applications (Playne and Crittenden, 2009). Lactobionic acid and its mineral salts (mainly Na, Ca and K lactobionate) are commercially produced for industrial and medical applications, as well as for research purpose (Nakano *et al.*, 2010).

PRODUCTION

The selective conversion of lactose to lactobionic acid consists of the oxidation of the free aldehyde group of glucose on the lactose molecule to the carboxylic group. Several processes including biocatalytic, electrochemical and heterogeneous catalytic oxidations have been investigated for the production of lactobionic acid.

Biocatalytic oxidation

The biocatalytic production of lactobionic acid comprises the oxidation of lactose by means of specific enzymes or by using microorganisms as biocatalysts. The general reaction mechanism, involves the formation of lactobiono-δ-lactone as an intermediate product, which is hydrolyzed to lactobionic acid (Nakano *et al.,* 2010). The process is generally carried out at mild temperature conditions 25-50°C, and the pH must be kept constant during reaction by adequate addition of a Na, Ca or K base, the product can be lactobionic acid or its salts. When lactobionate salts are produced, the solution can be passed through cation exchange resins to obtain a lactobionic acid solution, which can be further concentrated and crystallized to produce pure lactobionic acid.

Microbial production

Pseudomonas species are the main bionic producer microorganisms, lactobionic acid is formed via the lactose oxidation pathway, in which a membrane bound dehydrogenase enzyme initially catalyzes the oxidation of the lactose to a lactone intermediate (lactobiono-δ-lactone) which is subsequently hydrolyzed (its carbonyl group) by a lactonase into lactobionic acid (Alonso *et al.,* 2012; Nishizuka and Hayaishi, 1962).

While the production of lactobionic acid from lactose by using filamentous fungi, gives only 50% yield after 120 h, which suggests the presence of residual lactose oxidase activity in this fungus (Pedruzzi *et al.,* 2011; Malvessi *et al.,* 2013). In addition, the lactose-oxidizing ability has been also found in a red algae, which are capable of oxidizing diverse carbohydrates at an optimum pH of 5.0 (Murakami *et al.*, 2003; Alonso *et al.,* 2011). Oxidation of lactose by using *Acetobacter orientalis* gives 97 to 99% yield under resting cell conditions in nutrient rich media at the shake flask scale (Kiryu *et al.,* 2012).

The oxidation of lactose to lactobionic acid by acetic acid bacteria, such as *Gluconobacter cerinus* UTBC-427 showed the highest lactose oxidizing activity of the screened microorganisms (Oe *et al.,* 2008). This latter GRAS microorganism has been recently selected by Unitika Company in Japan as microbial platform for lactobionic acid industrial bio-production under resting cell conditions (Kimura, 2012).

Enzymatic synthesis

Enzymatic catalysis produces higher lactobionic acid, yields, and productivities than microbial fermentation, but enzymes are rather unstable under enzymatic production process conditions (Nordkvist *et al.,* 2007). Lactose oxidizing enzymes are glucose-fructose dehydrogenase, cellobiose dehydrogenase (Van Hecke *et al.,* 2009), and carbohydrate oxidase (Gutiérrez *et al.*, 2012), have been used for lactobionic acid production, but technological challenges are many that require coenzyme regeneration and enzyme inactivation mostly by the formation of H_2O_2, which has to be reduced, by the addition of catalase (Hua *et al.,* 2007) in addition, redox mediators required they may be incompatible with the intended use of the product (Ludwig *et al.,* 2004).

Cellobiose dehydrogenase has been the mostly used enzyme for the synthesis lactobionic acid, it is an extracellular enzyme produced by several fungi, like *Sclerotiumrolfsii*, *Phanerochaete chrysosporium*, and *Trametes versicolor* (Zamocky *et al.*, 2006; Kiryu *et al.*, 2008). The enzyme requires a redox mediator like 2, 2-azinobis 3-ethylbenzothiazoline-6-sulphonic acid and 2, 6-dichloroindophenol as efficient electron acceptors that can be regenerated by an additional enzyme, like laccase. Even though the system produces lactobionic acid from lactose at a high volumetricproductivity, the system is complex involving two enzymes and a redox mediator (Murakami *et al.*, 2008; Van Hecke *et al.*, 2009).

In an industrial context, an enzymatic mixture called 'LactoYIELD' was launched onto the market in 2009 as a result of the joint venture in between the Danish companies and Novozymes A/S in 2002 (Novozymes, 2009). This standardized enzymatic mixture allows cheese manufacturers to convert lactose from cheese whey into lactobionic acid.

Electrochemical oxidation

Lactobionic acid has been also prepared by electrolytic oxidation processes. The studies carried out by Gutiérrez *et al.*, (2012) reported that high yields (>90%) and selectivities (~100%) toward lactobionic acid can be obtained by means of the electro-catalytic oxidation of lactose on noble metal electrodes (platinum, platinum-modified and gold electrodes) in alkaline media. Gold electrodes are the best catalyst for the oxidation of sugars, and that lactone is the primary product of the electrochemical oxidation of lactose, which is hydrolyzed to lactobionic acid.

Heterogeneous catalytic oxidation

During this reaction, the desired lactobionic acid is normally obtained as the main product. In order to selectively produce lactobionic acid, the reaction should be carried out at atmospheric pressure in alkaline media at pH between 8.0 and 9.0, in the temperature range of 50-70°C, using air or oxygen as eco-friendly oxidizing agents (Gutiérrez *et al.*, 2011).

Lactobionic acid production by means of heterogeneous catalytic oxidation of lactose on palladium and bismuth-palladium supported catalysts was first successfully performed by Hendriks *et al.*, (1990). To strip off the dissolved oxygen, and to maintain the overall reaction kinetics, Periodic bubbling of air and nitrogen has been successfully used (Belkacemi and Hamoudi, 2010). Gold catalysts have shown high stability against over oxidation and supported gold nanoparticles have shown an exceptional activity and selectivity in the oxidation of carbohydrates (Belkacemi *et al.*, 2007; Murzina *et al.*, 2008; Gutiérrez *et al.*, 2012).

EXTRACTION AND PURIFICATION

In order to achieve a higher productivity of lactobionic acid, the enzymatic reaction can be interrupted after few hours of operation and unreacted substrates can be recycled after the separation of substrates from products (Silveira, 2003). Liquid chromatography is a high efficiency separation technique that could be useful in the current process since species can be recovered with high-purity (Pedruzzi *et al.*, 2008).

By passing the solution of lactobionate ions through a series of ion-exchange resins, a batch of pure lactobionic acid solution with negligible amounts of calcium ions can be produced. Other techniques like ethanol precipitation (Armarego and Chai, 2009), evaporation and crystallization(Jones *et al.*, 2002) and electrodialysis are also employed for the recovery of lactobionic acid (Peretti *et al.*, 2009).

PHYSIOLOGICAL EFFECT

Anticoagulant and Antithrombotic activity

The most important physiological effect of lactobionic acid is the anticoagulant and antithrombotic activity of its sulfated derivative bislactobionic acid amides, which have been studied as potential anticoagulant and antithrombotic agents, without a risk of bleeding (Raake *et al.*, 1989).

This compound, also known as Aprosulate sodium, stimulated HCII activity in *vitro* (Klauser, 1991) and has been found to delay the activation of factor X and prothrombin in plasma (Ofosu *et al.*, 1992).

Antioxidant

Lactobionic acid has also revealed antioxidant properties in tissues, by inhibiting the production of hydroxyl radicals as a result of its iron chelating properties (Charloux *et al.,* 1995). It also prevent the oxidation of other substances such as anthralin, hydroquinone and banana peel (Van *et al.,* 2004).

Wound healing

Lactobionic acid also promotes wound healing, and it is useful for general care of skin, hair, nail, oral and vaginal mucosa, and oral and gum diseases (Yu and Van Scott, 2010). Lactobionic acid has been recently used in the fabrication of lactobionic modified materials for carrying drugs for the treatment of liver and breast cancer (Lu *et al.,* 2010; Zhang *et al.,* 2011).

Prebiotic action

Lactobionic acid also exerts potential prebiotic effects as a bioactive ingredient in functional foods, as this organic acid is resistant to digestive enzymes. It is poorly absorbed in the small intestine and can be eventually fermented by the gastrointestinal microflora (Saarela *et al.,* 2003; Schaafsma, 2008). Lactobionic acid has also been described as an active bifidus promoter molecule for diverse functional foods and beverages (Kontula *et al.,* 2000).

Enhancement of mineral absorption

Lactobionic acid is valuable for its chelating properties due to its capability to form complex structures with Mn, Cu, Fe and Ca (Shepherd *et al.,* 1993; Oe *et al.,* 2008)**.** The incorporation of lactobionic acid into foods may stimulate intestinal Ca^{2+} or mineral absorption, therefore exerting a health-promoting influence (Baldwin *et al.,* 2007).

COMMERCIAL APPLICATION

Food and dairy applications

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), an acidifier agent in fermented milk products (Faergemand *et al.,* 2012), 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). Equally important in novel non-dairy 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). 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).

The dairy industry has been particularly involved currently in the development and implementation of innovative manufacturing processes including lactobionic acid as a key ingredient in novel dairy making technologies (Novozymes, 2009; Merrill and Singh, 2011). In fact, adding lactobionic acid either directly (10% of the mix) or indirectly (an added lactose oxidase) enhanced production yields, lower processing times and cost savings in manufacturing of processed cheese (Bradburry *et al.,* 2002).

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).

Baldwin *et al.,* (2004) 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).

Cosmetics field

The cosmetics industry is currently employing lactobionic acid as the key active component of novel antiaging and regenerative skin-care products due to its therapeutic efficacy. The use of lactobionic acidin cosmetics has grown three to five-folds since it was launched commercially. Lactobionic acid represents a major market niche as a novel and essential protective component of skin care formulations. The cosmetics company NeoStrata (USA) has invent a broad portfolio of skin care products based on the unique properties offered by lactobionic acid (West, 2004). 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) or can even be employed in antiacne treatments (Decker and Graber, 2012). Due to metal chelation property of lactobionic acid, act as an inhibitor of the breakdown of matrix metalloproteinase enzymes, thus reducing the appearance of photoageing and wrinkles (Grimes *et al.,* 2004; Tasic-Kostov *et al.,* 2010). In addition to lactobionic acid antioxidant role, it also exhibits strong moisturizing, exfoliative 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). Which expand its commercial relevance within the cosmetics field. Some of the cosmetic products containing lactobionic acid are available in market such as Bionic eye cream, Bionic face cream, Intimate creamy wash, Lactobionic acid peel, Lactobionic acid Miceller Gel etc. (Yu and Van Scott, 2010; Hachem *et al.,* 2010).

Chemical industry

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

Lactobionic acid has been proposed as a building block for the biocatalytic synthesis of novel polymers with possible industrial applications (Araki *et al.,* 2006). Aside from the aforementioned applications, lactobionic acid can be used for the synthesis of innovative industrial systems such as functionalized carbon nanotubes with lactobionic acid amide amphiphile molecules which are capable of adsorbing proteins (Feng *et al.,* 2011).

Drug delivery systems

Lactobionic acid offers unique properties such as biocompatibility, biodegradability, ion chelating ability and self assembly, in addition to their synergistic combination(Ortial *et al.,* 2006). Owing to these unique properties, lactobionic acid provides an excellent platform for the synthesis of potentially biocompatible and targetable drug delivery vehicles, from DNA to bioactive molecules (Duan *et al.*, 2011; Chen *et al.,* 2012). In fact, lactobionic acid based drug delivery systems can successfully target hepatocytes due to the presence of asialoglycoprotein receptors (ASGPR) located on their surface, since lactobionic acid works as a ligand of these receptors (Lin *et al.,* 2011).

Nanoparticle diagnosis

Bio-functionalized nanoparticles are used for biomedical applications such as biodetection, cancer therapies, magnetic resonance imaging or bio-labeling. Lactobionic acid has attracted increasing attention in recent years as a surface coating materials due to their enhanced properties (Peng *et al.,* 2007; Knopp *et al.,* 2009).

Tissue engineering

Although lactobionic acid does not contribute directly to the growth ofany tissue or biomaterial, this organic acid may ease the attachmentand entrapment of hepatocytes, as well as the establishmentand construction of biocompatible scaffolds for liver tissue engineeringpurposes (Kim *et al.,* 2008).

Galactosylated matrices through lactobionic acid have been proved to be effective in hepatocyte entrapment and attachment, which offer an efficient extracellular matrix for hepatocyte aggregation during liver tissue engineering approaches (Mi *et al.*, 2006). Specifically, the incorporation of lactobionic acid in a synthetic polymer may provide a better microenvironment for cell aggregation along with nutrition and metabolite transfer (Wang *et al.*, 2010).

SAFETY AND REGULATIORY STATUS

The role of lactobionic acid as a food preservative is anticipated, its use as calcium lactobionate has already been approved in the USA by the FDA (FDA, 2011).

SUMMARY

Lactobionic acid, an oxidation product of lactose, is a relatively new lactose derivative with potential applications in the food, pharmaceutical and chemical industries, owing to its antioxidant, chelating, humectant and emulsifying properties. Lactobionic acid and its salts are attractive as new and value added food materials because of the good taste, the health-promoting functions, as well as the excellent solubility. Moreover, due to the remarkable growth of nanotechnology, the applications of lactobionic acid can be expanded as a functional molecule for carrying drugs. Lactobionic acid may undoubtedly play a fundamental role in functional and nutraceutical foods over the coming year. Efficient and safer processes for the production are therefore increasingly desired. More over long-term safety and clinical studies are required before recommendations can be made for clinical application.

REFERENCES

Alonso, S., Rendueles, M. and Díaz, M. 2011. Efficient lactobionic acid production from whey by Pseudomonas taetrolens under pH-shift conditions. *Bioresour. Technol.*, **102**: 9730–9736.

Alonso, S., Rendueles, M. and Díaz, M. 2012. Selection method of pH conditions to establish Pseudomonas taetrolens physiological states and lactobionic acid production. *Appl. Microbiol. Biotechnol.*, **27**: 3-27.

Alonso, S., Rendueles, M. and Díaz, M. 2013. Bio-production of lactobionic acid: Current status, applications and future prospects. *Biotechnol. Advances*, **31**: 1275–1291.

Araki, K., Fujii, K., Ueno, H., Fujii, N. and Takahane, M. 2006. New antibacterial agent composition. Japan Patent Application Pub. No.: JP2006104164.

Armarego, W.L. and Chai, C.L. 2009. Purification of biochemicals and related products. In: Purification of laboratory chemicals (edited by Armarego, W.L. and Chai, C.L.). Sixth edn. Oxford: Elsevier Inc, pp. 577–708.

Baldwin, C., Akashe, A., Dinwoodie, R., Koka, R., West, L.G. and Kortum, O. 2004. Use of siderophores and organic acid to retard lipid oxidation. United States Patent Application Pub. No.: US /0170728 A1

Baldwin, C., Akashe, A., Zeller, A.L. and Marquez-Sanchez, M. 2007. Mineral complexes of lactobionic acid and method of using for mineral fortification of food products. United States Patent Application Pub. No.: US 2007/0026110 A1.

Belkacemi, K. and Hamoudi, S. 2010. Chemocatalytic oxidation of lactose to lactobionic acid over PdeBi/SBA-15: reaction kinetics and modeling. *Industrial and Engineering Chemistry Research*, **49**: 6878-6889.

Belkacemi, K., Vlad, M.C., Hamoudi, S. and Arul, J. 2007. Value-added processing of lactose: preparation of bioactive lactobionic acid using a novel catalytic method. *Int. J. Chemical Reactor Engineering*, **5**: 64.

Bize, C., Blanzat, M. and Rico-Lattes, I. 2010. Self-assembled structures of catanionic associations: how to optimize vesicle formation. *J. Surfactant Deterg.*, **13**: 465–473.

Bradbury, A.G.W., Fritsch, R., Habermeier, P., Koka, R., Mehnert, D.W., Rose, M., Steffan, W. and Wolfschoon-Pombo, A. 2002. Process for manufacturing cheeses and other dairy products and products thereof. Google Patents.

Briden, M.E. and Green, B.A. 2006. Topical exfoliation - clinical effects and formulating considerations. In: Cosmetic formulation of skin care products (edited by Draelos, Z.D. and Thaman, L.A.). New York: Taylor and Francis Group, pp. 237–250.

Bucek, W., Connors, W.M., Cort, W.M. and Roberts, H.R. 1956. Evidence for the formation and utilization of lactobionic acid by *Penicillium chrysogenum*. *Arch. Biochem. Biophys.*, **63**: 477–478.

Charloux, C., Paul, M., Loisance, D. and Astier, A. 1995. Inhibition of hydroxyl radical production by lactobionate, adenine, and tempol. *Free Radical Biology and Medicine*, **19**: 699-704.

Chen, Z., Xiao, L., Liu, W., Liu, D., Xiao, Y.Y. and Chen, J. 2012. Novel materials which possess the ability to target liver cells. *Expert Opin Drug Deliv.*, **9**: 649–656.

Decker, A. and Graber, E. 2012. Over-the-counter acne treatments. *J. Clin. Aesthet Dermatol.*, **5**: 32–40.

Duan, C., Gao, J., Zhang, D., Jia, L., Liu, Y. and Zheng, D. 2011. Galactose-decorated pH-responsive nanogels for hepatoma-targeted delivery of oridonin. Biomacromolecules, **12**: 4335–4343.

Faergemand, M., Gilleladen, C. and Qvist, K.B. 2012. Method for producing an acidified milk product. United States Patent Application Pub. No.: US 20120045546 A1.

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].

Feng, W., Xiao, J., Li, L. and Ji, P. 2011. Protein adsorption on functionalized carbon nanotubes with a lactobionic amide amphiphile. *Ind. Eng. Chem. Res.,* **50**: 11608–1613.

Fisher, E. and Meyer, J. 1889. Oxydation des milchzuckers. *Ber Dtsch Chem Ges*., **22**: 361–364.

Green, B., Wildnauer, R., Nguyen, H. and Edison, B. 2006. Lactobionic acid: a bionic acid enhances skin clarity and provides skin plumping and firming effects. *J. the American Academy of Dermatology*, **54**: 37.

Grimes, P.E., Green, B.A., Wildnauer, R.H. and Edison, B.L. 2004. The use of polyhydroxy acids (PHAs) in photoaged skin. *Cutis,* **73**: 3-13.

Gutiérrez, L.F., Hamoudi, S. and Belkacemi, K. 2011. Selective production of lactobionic acid by aerobic oxidation of lactose over gold crystallites supported on mesoporous silica. *Applied Catalysis A: General,* **402**: 94-103.

Gutiérrez, L.F., Hamoudi, S. and Belkacemi, K. 2012. Effective gold catalyst supported on mesoporous silica decorated by ceria for the synthesis of high value lactobionic acid. *Applied Catalysis A: General,* **4**: 425-426.

Hachem, J.P., Roelandt, T., Schürer, N., Pu, X., Fluhr, J. and Giddelo, C. 2010. Acute acidification of stratum corneum membrane domains using polyhydroxyl acids improves lipid processing and inhibits degradation of corneodesmosomes. *J. Invest. Dermatol.,* **130**: 500–510.

Hendriks, H.E.J., Kuster, B.F.M. and Marin, G.B. 1990. The effect of bismuth on the selective oxidation of lactose on supported palladium catalysts. *Carbohydrate Research,* **204**: 121-129.

Hua, L., Nordkvist, M., Nielsen, P.M. and Villadsen, J. 2007. Scale-up of enzymatic production of lactobionic acid using the rotary jet head system. *Biotechnology and Bioengineering.,* **97**: 842–849.

Jones, W.E., Vestal, N.Y. and Chi, Y.H. 2002. Novel techniques for the Preparation and crystallization of 4-o-beta-d-galactopyranosyl-d-gluconic acid. Pub. No.: US 2002/0006884 A1.

Kim, I.Y., Seo, S.J., Moon, H.S., Yoo, M.K., Park, I.Y. and Kim, B.C. 2008. Chitosan and its derivatives for tissue engineering applications. *Biotechnol., Adv.*, **26**: 1-21.

Kimura, T. 2006. Feed additive for laying hens and feed containing the additive. European Patent Application Pub. No: EP 1731042 A1.

Kimura, T. 2012. Development of new functional oligosaccharides from lactose lactobionic acid. *Seibutsu-kogaku Kaishi,* **90**: 595–597.

Kiryu, T., Kiso, T., Nakano, H., Ooe, K., Kimura, T. and Murakami, H. 2009. Involvement of *Acetobacter orientalis* in the production of lactobionic acid in Caucasian yogurt “Caspian Sea yogurt” in Japan. *J. Dairy Science,* **92**: 25-34.

Kiryu, T., Nakano, H., Kiso, T. and Murakami, H. 2008. Purification and characterization of a carbohydrate: acceptor oxidoreductase from Paraconiothyrium sp that produces lactobionic acid efficiently. *Bioscience Biotechnology and Biochemistry,* **72**: 833-841.

Kiryu, T., Yamauchi, K., Masuyama, A., Ooe, K., Kimura, T. and Kiso, T. 2012. Optimization of lactobionic acid production by *Acetobacter orientalis* isolated from Caucasian fermented milk, “Caspian Sea yogurt”. *Biosci. Biotechnol. Biochem.,* **76**: 361–363.

Klauser, R.J. 1991. Interaction of the sulfated lactobionic acid amide Lw-10082 with thrombin and its endogenous inhibitors. *Thrombosis Research,* **62**: 557-565.

Knopp, D., Tang, D. and Niessner, R. 2009. Review: bioanalytical of biomolecule-functionalized nanometer-sized doped silica particles. *Anal Chim. Acta,* **647**: 14–30.

Lin, W.J., Chen, T.D., Liu, C.W., Chen, J.L. and Chang, F.H. 2011. Synthesis of lactobionic acid graftedpegylated- chitosan with enhanced HepG2 cells transfection. *Carbohydr. Polym.,* **83**: 898–904.

Lu, B., Wu, D.Q., Zheng, H., Quan, C.Y., Zhang, X.Z. and Zhuo, R.X. 2010. Galactosyl conjugated N-succinyl-chitosan-graft-polyethylenimine for targeting gene transfer. *Molecular Biosystems* **6**: 2529-2538.

Ludwig, R., Ozga, M., Zámocky, M., Peterbauer, C., Kulbe, K. and Haltrich, D. 2004. Continuous enzymatic regeneration of electron acceptors used by flavoenzymes: cellobiose dehydrogenase catalyzed production of lactobionic acid as an example. *Biocatal Biotransform,* **22**: 97-104.

Malvessi, E., Carra, S., Pasquali, F.C., Kern, D.B., da Silveira, M.M. and Ayub, M.A.Z.2013. Production of organic acids by periplasmic enzymes present in free and immobilized cells of *Zymomonas mobilis. J. Ind. Microbiol. Biotechnol.,* **40**: 1-10.

Megmilk Snow. Press release. Available via:http://www.meg-snow.com/news/2012/ pdf/20120524-383.pdf2012. [Accessed 30 January 2013 (in Japanese)].

Merrill, R.K. and Singh, M. 2011. Food ingredients and food products treated with an oxidoreductase and methods for preparing such food ingredients and food products. United States Patent Application Pub. No.: US 8021704.

Mi, F.L., Yu, S.H., Peng, C.K., Sung, H.W., Shyu, S.S. and Liang, H.F. 2006. Synthesis and characterization of a novel glycoconjugated macromolecule. *Polymer,* **47**: 4348–4358.

Murakami, H., Kiryu, T., Kiso, T. and Nakano, H. 2008. Production of calcium lactobionate by a lactose-oxidizing enzyme from Paraconiothyrium sp. KD-3. *J. Applied Glycoscience,* **55**: 127-132.

Murakami, H., Seko, A., Azumi, M., Ueshima, N., Yoshizumi, H., Nakano, H. and Kitahata, S. 2003. Fermentative production of lactobionic acid by *Burkholderia cepacia*. *J. Applied Glycoscience,* **50**: 117–120.

Murzina, E.V., Tokarev, A.V., Kordás, K., Karhu, H., Mikkola, J.P. and Murzin, D.Y. 2008. D-lactose oxidation over gold catalysts. *Catal Today,* **131**: 385–392.

Nakano, H., Kiryu, T., Kiso, T. and Murakami, H. 2010. In: Biocatalytic production of lactobionic acid (edited by Hou, C.T. and Shaw, J.F.). Biocatalysis and biomolecular engineering, New Jersey, John Wiley and Sons Inc, pp 391–404.

Nielsen, P.M. 2007. Non-dairy beverage product comprising calcium lactobionate. United States Patent Application Pub. No.: US 2007/0281066 A1.

Nielsen, P.M. 2009. Meat based food product comprising lactobionic acid. United States Patent Application Pub. No.: US 2009/0214752 A1.

Nishizuka, Y. and Hayaishi, O. 1962. Enzymic formation of lactobionic acid from lactose. *J. Biol. Chem.,* **237**: 2721–2728.

Nordkvist, M., Nielsen, P.M. and Villadsen, J. 2007. Oxidation of lactose to lactobionic acid by a *Microdochium nivale* carbohydrate oxidase: kinetics and operational stability. Biotechnol. Bioeng., 97: 694-707.

Novozymes. Pressrelease. Available via: http://www.novozymes.com/en/news/newsarchive/Pages/45275.aspx 2009. [Accessed 30 November 2012].

Oe, K. and Kimura, T. 2008. Mineral absorption promoter. Japan Patent Application Pub. No.: JP2008303208.

Oe, K. and Kimura, T. 2011. Aging inhibitor for bread. Japan Patent Application Pub. No.: JP2011177121.

Ofosu, F.A., Fareed, J., Smith, L.M., Anvari, N., Hoppensteadt, D. and Blajchman, M.A. 1992. Inhibition of factor-X, factor-V and prothrombin activation by the bis lactobionic acid amide LW10082. *European J. Biochemistry,* **203**: 121-125.

Ortial, S., Durand, G., Poeggeler, B., Polidori, A., Pappolla, M.A. and Böker, J. 2006. Fluorinated amphiphilic acid derivatives as antioxidant carriers: a new class of protective agents. *J. Med. Chem.,* **49**: 2812–2820.

Oskarsson, H., Frankenberg, M., Annerling, A. and Holmberg, K. 2007. Adsorption of novel alkylaminoamide sugar surfactants at tailor-made surfaces. *J. Surfactant Deterg.,* **10**: 41–52.

Papoulias, U.E., Wyld, P.J., Haas, S., Stemberger, A., Jeske, W. and Hoppensteadt, D.A. 1993. Phase-1 study with aprosulate, a new synthetic anticoagulant. *Thromb. Res.,* 72: 99-108.

Pedruzzi, I., Borges da Silva, E.A. and Rodrigues, A.E. 2008. Selection of resins, equilibrium and sorption kinetics of lactobionic acid, fructose, lactose and sorbitol. *Separation and Purification Technology,* **63**: 600–611.

Pedruzzi, I., da Silva, E.A.B. and Rodrigues, A.E. 2011. Production of lactobionic acid from lactose/fructose substrate using GFOR/GL enzymes from *Zymomonas mobilis* cells: a kinetic study. *Enzyme Microb. Technol.,* **49**: 183–191.

Perettia, F.A., Silveiraa, M.M. and Zeni, M. 2009. Use of electrodialysis technique for the separation of lactobionic acid produced by *Zymomonas mobilis. Desalination*, **245**: 626–630.

Pezzotti, F. and Therisod, M. 2006. Enzymatic synthesis of aldonic acids. *Carbohydr. Res.,* **341**: 2290–2292.

Playne, M.J. and Crittenden, R.G. 2009. Galacto-oligosaccharides and Other Products Derived from Lactose. In: Advanced Dairy Chemistry Volume 3: Lactose, Water, Salts and Minor Constituents. (edited by McSweeney P.L.H. Fox, P.F.) Springer, pp 121-188.

Raake, W., Klauser, R.J., Elling, H. and Meinetsberger, E. 1989. Anticoagulant and antithrombotic properties of synthetic sulfated bis-lactobionic acid-amides. *Thrombosis Research,* **56**: 719-730.

Saarela, M., Hallamaa, K., Mattila-Sandholm, T. and Mättö, J. 2003. The effect of lactose derivatives lactulose, lactitol and lactobionic acid on the functional and technological properties of potentially probiotic Lactobacillus strains. *Int. Dairy J.,* **13**: 291–302.

Schaafsma, G. 2008. Lactose and lactose derivatives as bioactive ingredients in human nutrition. *Int. Dairy J.,* **18**: 458–465.

Shepherd, R.E., Isaacson, Y., Chensny, L., Zhang, S.S., Kortes, R. and John, K. 1993. Lactobionic and gluconic acid complexes of FeII and FeIII control of oxidation pathways by an organ-transplantation preservant. *J. Inorganic Biochemistry,* **49**: 23-48.

Silveira, M.M. 2003. Technical design project: Produc¸ ão de sorbitol e ácidos orgânicos por *Zymomonas mobilis*, University of Caxias do Sul, Caxias do Sul, RS.

Stodola, F.H. and Lockwood, B.L. 1947. The oxidation of lactose and maltose to bionic acids by Pseudomonas. *J. Biol. Chem.,* 213–221.

Sugidachi, A., Asai, F. and Koike, H. 1993. *In vivo* pharmacology of aprosulate, a new synthetic polyanion with anticoagulant activity. *Thromb. Res.,* **69**: 71-80.

Sugidachi, A., Breiter, N., Ogawa, T., Asai, F. and Koike, H. 1996. *In vitro* effects of aprosulate sodium, a novel anticoagulant, on plateletactivation: Possible mechanism for antiplatelet action. *Thromb. Haemost.,* **76**: 786-790.

Tasic-Kostov, M., Savic, S., Lukic, M., Tamburic, S., Pavlovic, M. and Vuleta, G. 2010. Lactobionic acid in a natural alkylpolyglucoside-based vehicle: assessing safety and efficacy aspects in comparison to glycolic acid. *J. Cosmetic Dermatology,* **9**: 3-10.

Tournier, C., Sulmont-Rossé, C., Sémon, E., Vignon, A., Issanchou, S. and Guichard, E. 2009. A study on texture–taste–aroma interactions: Physico-chemical and cognitive mechanisms. *Int. Dairy J.,* **19**: 450–458.

Van Hecke, W., Bhagwat, A., Ludwig, R., Dewulf, J., Haltrich, D. and Van Langenhove, H. 2009. Kinetic modeling of a bi-enzymatic system for efficient conversion of lactose to lactobionic acid. *Biotechnol. Bioeng.,* **102**: 1475–1482.

Van Scott, E.J. and Yu, R.J. 2004. Hydroxyacids and their topical use in the elderly. In: Skin diseases in the elderly (edited by L. Nall, G. Cauwenbergh, P. Jacobs). New York, NY, USA: Marcel Dekker. 27: 3-5.

Walter, T. and Begli, H.A. 2011. Flavour enhancer. United States Patent Application Pub. No.: US 2011/0244080 A1.

Wang, J., Xiao, F., Zhao, Y., Chen, L., Zhang, R. and Guo, G. 2010. Cell proliferation and thermally induced cell detachment of galactosylated thermo-responsive hydrogels. *Carbohydr. Polymer,* **82**: 578–584.

West, D. 2004. AHA wrinkle creams come of age. *Chem. Week,* **166**: 20.

Yu, R.J. and Van Scott, E.J. 2010. Oligosaccharide aldonic acids and their topical use. Patent application number 20100099632.

Zamocky, M., Ludwig, R., Peterbauer, C., Hallberg, B.M., Divne, C., Nicholls, P. and Haltrich, D. 2006. Cellobiose dehydrogenase – a flavocytochrome from wood-degrading, phytopathogenic and saprotrophic fungi. *Current Protein and Peptide Science,* **7**: 255–280.

Zhang, J., Li, C., Xue, Z.Y., Cheng, H.W., Huang, F.W. and Zhuo, R.X. 2011. Fabrication of lactobionic-loaded chitosan microcapsules as potential drug carriers targeting the liver. *Acta Biomaterialia,* **7**: 1665-1673.