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Lactose Derivatives: Properties, Preparation and Their Applications in Food and Pharmaceutical Industries

Laila K. Hassan[a], Khaled G. Abd-Wahhab[b] and Mahmoud Abd El-Aziz[a]*

[a]Dairy Dept., Food Industries and Nutrition Research Institute, National Research Centre, Cairo12622, Egypt
[b]Medical Physiology Dept., National Research Centre, Dokki, Cairo 12622, Egypt

Abstract

Lactose is a unique disaccharide that exists in mammal's milk, being synthesized from galactose and glucose in the mammary gland. It presents in three anomeric forms: monohydrate α-lactose, anhydrous β-lactose, and amorphous lactose. Lactoseis used as a source for many lactose derivatives like lactulose, lactitol, galacto-oligosacchrides and lactobionic acid. Lactose derivatives can be obtained through different processes including isomerization, oxidation,electrochemical and biotechnological (biocatalytic–microbial and enzymatic) processes. Lactose derivatives can be applied in a wide range of dairy, non-dairy as a stabilizer, gelling agent, antioxidant, aging inhibitor and emulsifier. Pharmaceuticals applications for many health disorders such as hepatic encephalopathy, constipation, diabetes, hepatic malignancy and obesity have been reported. In this review, we will focus on lactose derivatives, their properties, method of preparation and applications in the food and pharmaceutical industries.

Keywords: Lactose derivatives; Properties; Preparation; Applications

1. Introduction

Before the 17th century, milk was stated to be composed of three components, curd, fat and whey. In 1633, lactose was discovered in milk, and isolated as "essential salt without nitrogen" from whey. In 1688, it was isolated from evaporated whey and purified by recrystallization [1]. During the 18th century, lactose became a commercial commodity. However, during early 20th century, the basis for current information about lactose was laid, particularly concerning the chemistry and molecular structure for understanding of the properties and utility of this unique sugar [2]. Lactose can be found in dairy products in two crystalline forms, α-hydrate and β-anhydride, and non-crystalline "glass" mixture of α- and β-forms in the same ratio. Lactose solutions can be highly supersaturated before spontaneous crystallization develops. Finally, Lactose can simply be extracted from milk or whey in pure form, and utilized as an ingredient in nutrition, food and pharmaceutical applications [3].

Lactose can have an important effect on a variety of dairy products; for example, it is important in fermentation by lactic acid bacteria in the preparation of yoghurt and many other dairy products coagulated with acid, as well as in many types of cheese [4]. Also, it can be applied in a wide range of dairy and non-dairy foods, as well as non-food products. Lactose is also used as a source for many lactose derivatives, including lactulose, lactitol, galacto-oligosacchrides, and lactobionic acid [2]. Moreover, as lactose is a reducing carbohydrate, it can take part in the Maillard reaction (hot dairy products) especially when heated under aseptic conditions [5]. In this review, we will focus on the properties of lactose and its derivatives, the properties and methods of preparing these derivatives and their applications in the food and pharmaceutical industries.

*Corresponding author e-mail: mabdelaziz69@yahoo.com; mabdelaziz1969@gmail.com
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2. Characteristics of lactose

2.1 Occurrence and properties

Lactose is a unique disaccharide exists in mammal's milk; its concentration varies from 0.0 to 10.0%, as shown in Table 1. The lactose level in fermented cows' milk is lower than that in milk with one-third, due to its transformation by lactic acid bacteria [6]. Through the manufacture of cheese, whole lactose in milk is expelled with whey; therefore hard cheese doesn'tcontain lactose [3]. Lactose is composed of D-galactose and D-glucose subunits; it has a molecular formula $C_{12}H_{22}O_{11}$ and chemical formula 4-O-β-D-galactopyranosyl-α-D-glucopyranose (Fig. 1). It presents in two anomeric types: α- and β-lactose, which are different only in the relative location of the $H_2$and the OH group at the C1 atom of the pyranosidic glucose-part. In general, α- and β-form are stable solids, but in solution, they rapidly equilibrate [7]. Lactose always crystallizes in monohydrate α-lactose form (with melting point 201.6ºC) at a moderate rate below 93.5ºC, while anhydrous β-form can only be obtained by crystallization at temperatures above 93.5ºC (with a melting point 252.2ºC); the β-anhydride crystals are sweeter and significantly more soluble than the α-hydrate [2]. The hygroscopic amorphous lactose (non-crystalline glass) can be gotten by rapid drying process, during this operation, its viscosity rises up, and consequently crystallization didn't happen. Lactose glass is stable if protected from moisture; however, it rapidly absorbs moisture from the air and becomes sticky [5, 6].

Table1.
Concentration of lactose in milk of some mammals' species

Species	**Lactose (%)**
Sea lion	0.0
Goat	4.1
Camel	4.4
Cow	4.8
Buffalo	4.8
Sheep	4.8
Human	7.0
Donkey	7.4
Green monkey	10.2

Shendurse and Khedkar [6]

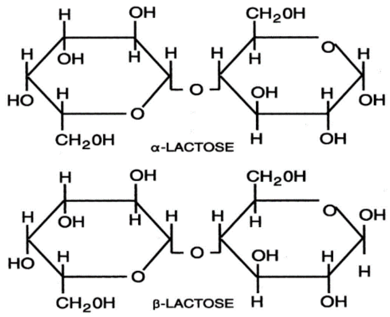

Fig. 1.Molecular and chemical structures of α-lactose and βlactose [8].

2.2 *Mutarotation and equilibrium*

In water solution, lactose is composed of 61.5% β-pyranose and 38.5% α-pyranose, the balance between both forms exhibited by mutarotation; this equilibrium ratio is changed slightly by the differences in temperature, didn't by pH differences [8]. Unlike the ratio, the speed of mutarotation is greatly disturbed by change of temperature and pH; the rate is slow at low temperatures but increases 2.8 times with every 10ºC rise in temperature, becoming almost maximum at about 75ºC; also mutarotation rate is minimum at around pH 5.0 and elevating with divisions on either side of this value [9].

2.3 Solubility and sweetness

In comparison with other disaccharides, lactose has the lowest solubility that is pronouncedly affected by temperature**.** At 15°C, the solubility of the α-form is smaller (7g/100g) than that of the β-form (50g/100g). In the environmental conditions, the solubility of β-lactose is high, but that of α-lactose increases over 93.5ºC. The sweetness of lactose is about 20-30% that of sucrose at ambient conditions (Table 2) which is why lactose is a suitable carbohydrate in infant formulas [10].

Table 2.
Solubility and relative sweetness of lactose

Type of sugar	Relative Sweetness	Solubility (g/100g)	
		10°C	30°C
Sucrose	100	66	69
Lactose	16	13	20
D-glucose	74	48	54
D-galactose	32	28	36

Schaafsma [10]

2.4 Lactose utilization

The advantages of lactose are its use as a food ingredient in infant formula and a compound for the manufacture of pharmaceutical tablets, as well as a raw material for lactose derivatives [11]. Due to its ability to carry flavors and colors, it can use in many food products such as sachet wafers, seasonings, and a range of baked goods. Also, it provides unique properties for bread making as it increases the browning of the crust, depending on the reduction of the nature of lactose. Because of its ability to delay crystallization, it is used widely in confectioneries [12]. Moreover, it acts as substrates in the production of materials (penicillin), as seed material in the manufacture of dairy products (sweetened condensed milk), as a raw material for the production of lactose hydrolyzed products and fermented products [13].

3. Lactose derivatives

Like other sugars, lactose possesses reactive functional groups and can be transformed into many wealthy food-grade derivatives, the most common ones are lactulose, lactitol, β-Galacto-oligosaccharides, lactosucrose, lactobionic acid, tagatose, epilactose. These derivatives are great for industrial applications as they perform positive health benefits. The main basis of their preparation is illustrated in Fig. 2.

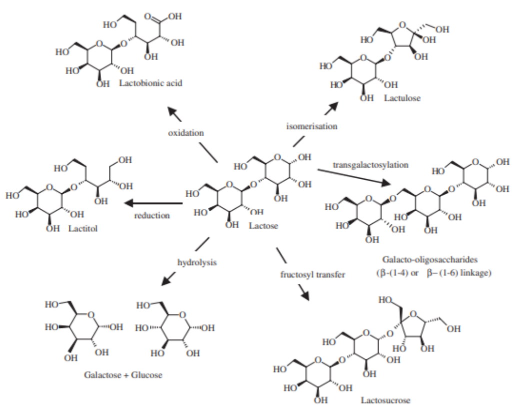

Fig. 2. Main basis of lactose derivatives preparations [2]

3.1 Lactulose

3.1.1 Properties

Lactulose is available in two formulations: Crystals (powder to be dissolved in water) and liquid syrup (solution). Carbohydrate impurities are found up to 3% in the crystalline and approximately 30% in the liquid form [14]. Dry lactulose is a white, odorless crystal, with a melting point of 168.5–170.0ºC. It is soluble in water, giving yellowish and odorless with a sweet taste solution, while poorly soluble in methyl alcohol and insoluble in ether. The solubility of lactulose in water is 76.4% (w/w) at 30ºC, which increases to 86% at 90ºC. Its sweetness is 0.48–0.62 of sucrose and 1.5 of lactose [6]. Its acidic hydrolysis gives galactose and fructose. Unlike lactose, lactulose isn't hydrolyzed by human intestinal enzymes, but it can be fermented by some colon bacteria and act as a prebiotic. Lactulose is stable and slightly decomposed when heated to 130ºC for 10 min at low pH, which makes it a suitable ingredient for food processing [6].

3.1.2 Preparation

Lactulose (4-O-β-D-galactopyranosyl-D-fructose, $C_{12}H_{22}O_{11}$) is a synthetic sugar, which doesn't find naturally and can be obtained by isomerization in basic media using various catalysts[15]. Chemically, around30% of lactulose was obtained after heating of lactose solution in an alkaline medium (calcium hydroxide) at 35°C for 36 hr. Later, carbonates (K & Na), hydroxides (k, Na &Ca), magnesium oxide, sodium aluminates, tertiary amines and borates have been used as alkali catalysts for synthesis of lactulose [16]. At presents of these catalysts at 70-100°C, Schuster-Wolff-Bühring et al. [17] obtained approximate 20–33% of lactulose through a few hrs, after that the level of lactulose decreased markedly because it's breakdown into galactose and other unfavorable secondary resultants as formic and iso-saccharinicacids, which reduced the pH of the isomerization media. Lactulose was also produced enzymatically using β-galactosidases from different sources with great technological interests depending on their low commercial values [18]. The lactose is hydrolyzed to the galactose and glucose by the effect of the β-galactosidase enzyme giving a galactosyl-β-galactosidase complex associated with a transfer the galactosyl moiety to acceptor (fructose) and producing lactulose (Fig. 3) [19]. Lactulose isn't detectable in raw milk but it exists in milk and its products post heating, therefore it can differentiate between both raw and heated milk [20]. The salt system of milk (chlorides, citrates, carbonates, phosphates, and bicarbonates of K, Ca, Na and Mg) is a favorable buffer for the formation of lactulose from lactose during heat treatment of milk [21].

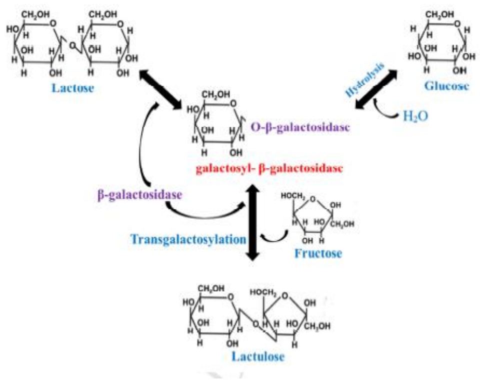

Fig. 3. Enzymatic trans-galactosylation mechanism in lactulose synthesis [19]

3.1.3 Food applications

Lactulose was incorporated into some food products (cake, cookies, chocolate, confectionary, chewing gum, yoghurt, and ice cream) to improve their sensory, browning and sweetness features [22]. The incorporation effect of lactulose increases probiotic counts, acidifying rate and consequently milk acidity. At the end of cold storage, pH value was lowered in lactulose including samples [23]. Also, lactulose exhibits a protecting effect on the *Lactobacillus* strains against bile acids severe conditions in gastrointestinal tract, as well as during products refrigeration period [24]. Depending on the ability of lactulose to improve texturizing, color (browning), flavor, solubility, stabilizing behaviors and viscosity close to the sucrose solution and sweetness close to 0.62 of sucrose, it can be used as a sucrose replacement in confectionary products [25]. Concerning infant formula, addition of 0.5% lactulose is sufficient to improve *bifidobacteria* flora up to the level noticed observed in babies with lactating babies [26].

3.1.4 Pharmaceutical Applications

3.1.4.1 Anti-constipation and anti-encephalopathy

Lactulose belongs to valuable compounds with therapeutic potentials [17]**.** In humans, lactulose has been used in curing chronic constipation and prevention of portal systemic encephalopathy; brain toxicity resulting from liver failure to change ammonia into urea [27]**.**Beynen et al. [28]illustrated that lactulose stimulates bacterial growth in the colon which in turn enhances faecal nitrogen excretion and lowers the entry of colonic ammonia into the bloodstream, leading to a lesser workload for the liver and less urinary nitrogen excretion. Due to its indigestible property, as a prebiotic, lactulose can pass through the upper area of the digestive tract without degradation (existence of non-hydrolysable β-glycosidic bond) to the colon where it is metabolized by bacteria producing carbon dioxide gas, acetic, lactic, and formic acids that lead to stool softening, as well as, increasing peristalsis. Therefore, it can be applied as a laxative agent [18]. Recently, lactulose may decrease the risk of *Clostridium* related diarrhea in hospitalized adult patients having antibiotics, as lactulose might involve the influences on bacterial colonization, toxin production, and/or toxin activity [29]**.**

3.1.4.2 Anti-gallstone and anti-tumor activity

A marked decrease in lithogenic marker was performed by lactulose, which consequently minimized the risk of gallstones development**.** The major cause for the anti-colorectal carcinogenesis of lactulose can be mechanized via shifting the bacterial composition and their metabolisms resulting in a minimal amount of bile acids factor (7-α-dehydroxylase) [25]**.** Lactulose decreases effectively toxic bacterial enzymes and other carcinogens. It possesses DNA-protecting efficiency and can regulate the immunologic mechanism, consequently exhibits tumor-preventing potential [30]**.** More lactulose can provide useful tools for managing metastatic prostate cancer from spreading to the skeletal bones through β-galactosidase-mediated interactions [31]**.**

3.1.4.3 Anti-tooth decay

Like all non-digestible and fermentable carbohydrates, lactulose enhances the intestinal absorption of calcium and magnesium, therefore, they didn't cause tooth decay [3]**.** Beynen et al. [28] reported that lactulose consumption was also found to produce a dose-dependent increase in the apparent absorption of calcium and magnesium, but not phosphorus. Indigestible disaccharides (e.g., maltitol and fructose anhydride and lactulose) directly increase the intestinal permeability of Ca in the absence of fermentation by activating the paracellular transport pathway through tight junctions [32]. The intestinal bacteria ferment indigestible oligosaccharides in the large intestine and thereby produce organic acids including short-chain fatty acids, lactic acid, and succinic acid). The acidification of the large intestine makes the Ca and Mg salts soluble, and the resulting increase in the ion concentrations of these minerals increases their absorption in the large intestine.

3.2 Lactobionic Acid

3.2.1 Properties

Lactobionic acid (LDA) is a white powder, high dissolve in water and poorly dissolve in organic solvents (glacial acetic acid, ethyl alcohol and methyl alcohol) [33]**,** with a molecular weight of 358.3 Da and melting point of 128-130ºC [34]**.** It has a sweet taste and pH-lowering efficiency. It has strong mineral-complexing characteristics. LBA is indigestible and fermented by the intestinal flora, probably exerting prebiotic effects. Thus its energy value is estimated at 2 kcal/g [3]**.** It can be subjected to dehydration and given lactone. LDA is hygroscopic in nature (gives a gel with 14% moisture from the air) so, it is valuable for cosmetics industry [35]**.** Its mineral salts are commercially prepared for medical, industrial and research purposes [36]**.**

3.2.2 Preparation

LBA (4-O-β-galactopyranosyl-D-gluconic acid) is built of galactose linked with gluconic acid by ether-like linkage; where several hydroxyls are evidenced and responsible for the intermolecular forces; the transformation of lactose to LBA comes through oxidation of the free aldehyde group of its glucose to the carboxylic group (Fig. 4). Classically, LBA was obtained by a chemical electrolysis of lactose. Further, new methods became targets of next studies [32], as several methods such as electrochemical process, biotechnological process (biocatalytic–microbial and enzymatic method), catalytic hydrogenation and heterogeneous catalytic oxidation were included [37, 38]**.**

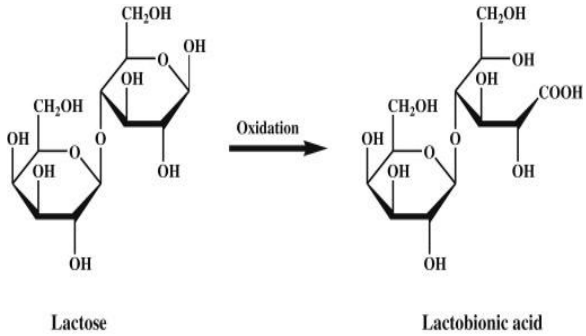

Fig 4. Preparation of LBA from lactose through oxidation

3.2.2.1 The electrolytic method

LBA has been also prepared by electrolytic oxidation processes. Isbell [39] produced calcium lactobionate by electrochemical oxidation of lactose in the presence of bromine and calcium carbonate, using graphite electrodes. In the 90s, platinum and gold electrodes were used, and gave higher LBA yields (90-100%) [40, 41]; gold electrodes were the best catalyst for the oxidation process [32]. This electrolytic method is expensive, requires a large amount of energy and is environmentally harmful [42].

3.2.2.2 Biotechnological method

Biotechnological processes (microbial enzymatic routes) are conducted to obtain LBA; these processes are greatly promising ways regarding the costs and benefits. However, these methods still need to be improved [42]. The bio-catalytic production of LBA was first tested with species of *Pseudomonas*, more precisely, *Pseudomonas taetrolens* that obtained 75% of yield [43]. However, other microorganisms have also been included. The production yield of LBA with filamentous fungi is close to 50% post 120 hr; this evidences the existence of residues of lactose oxidase activity [44]. Oxidizability of lactose was also found in red algae at an optimum pH of 5 [45]. *Acetobacterorientalis* was found able to give 97-99% at rest-cell conditions in nutrient rich media [46]; acetic acid bacteria (*Gluconobactercerinus*) performed the highest lactose oxidizing capacity among microorganisms [47]. The enzymatic oxidation method of transforming lactose to LBA needs oxygen, and gives hydrogen peroxide (by-product) which is changed spontaneously into oxygen [48]. The enzymes used in production of LBA are lactose-oxidases (oxidase, cellobiose-dehydrogenase and glucose/fructose-dehydrogenase) [32]; next a mix of enzymes (LactoYIELDTM) was produced [49], to use whey (rich in lactose) as substrate for LBA production. The enzymatic bio-catalytic process gives higher yields in compare to the microbial process [50]. The enzyme within this method can be inactivated by the liberation of hydrogen peroxide, and can be inversed by the addition of catalase [36**].**

3.2.2.3 Catalytic hydrogenation and oxidation

This method is uncommon compared to other methods of LBA production because LBA is the main product. For this concern, the reaction must be done at atmospheric pressure, pH 8.0-9.0 and temperature (50-70°C), utilizing air or oxygen eco-friendly oxidizing agents [51]. Hydrogenation and oxidation of the lactose to LBA, as well as other by-products, may be attained in a reactor, batch wise, using high pressures (20-70 bar) and temperatures (110-130°C). Few quantities of noble metal catalysts are required in this process [38].

3.2.3 Food Applications

LBA presents potential of supplementation in food products [52]. As a food additive, LBA can act as stabilizer or gelling agent and an antioxidant (dessert products) [53], an acidifier agent (fermented milk products) [54] and an aging inhibitor (bread) [55]. As a technological feed additive, LBA has been reported to improve egg shell qualities through rising calcium absorption [56]. For providing a valuable approach for calcium supplementation, non-dairy and milk-based beverages, and cheese containing Ca-lactobionate have been processed [57, 58]. García et al. [59] investigate the role of dairy whey permeate to obtain LBA by *L. taetrolens*and the subsequent fermentation of the acid by *Lactobacillus casei* to convert lactose into a prebiotic LBA. Also, they stated that *L. casei*was capable to consider LBA as a secondary source of carbon, and LBA concentration also diminished and lactic acid production increased in the media; so the end product composed LBA (prebiotic) and *L. casei*strain (probiotic) as a symbiotic product. LBA was incorporated in the preparation of 14 different cheese formulations via the replacement of milk fat (~ 25%) by LBA; this leads to a slight rise in firmness and slightly minimizes melting [60]. In the case of cheese and yogurt manufacture, LBA performs a crucial role indecrement souring time and preservation of aroma [61]. LBA is also known as a chelating agent, in which the antimicrobial properties of some compounds (nisin mixture + thymol mixture) can be improved by adding chelating agents like LBA [62]. In meat products, LBA acts as a water holding capacity agent, giving higher yields and water content after treatment of meat products [58]. Furthermore, LBA has been suggested to be an effective water-retaining agent in meat-based industries [63], as samples containing LBA showed the lowest drip loss. Additionally, LBA inhibited structural damage (delete of the secondary structure of the protein due to freeze-thaw operation), minimizing the tendency of water loss in meat and its derivatives post-heat changes; so, LBA can be considered as an alternate for frozen cured meat and its products. LBA can also be used in bread formulations. LBA to flour values (0.005% to 3% LBA) were proved as inhibitor aging of bread, being added randomly in a bread production process [64]. In cooking products, LBA provides functional properties and sensory attributes via the decrease of unfavorable Maillard browning [65]. Also, it is used to improve the flavor of beverages and foods [66]. LBA was stated to a crucial role in retarding lipid oxidation in food products reflecting antioxidant property [67].

3.2.4 Pharmaceutical applications

A previous study on 18 healthy men reported that ingestion of LBA 24g/day resulted in occurrence of fermentation in the human colon and signs of flatulence. Receiving high doses caused lactose intolerance-similar symptoms; however, correct doses assist in the intestinal functions and flow [68]. Unfavorably, crude LBA may irritate to the mucous membranes however none studies investigated its toxicology as its use was established for research only [69]. LBA is approved as an antioxidant chelator because of its capability to prevent the production of hydroxyl radicals by formation of metal complexes with Cu^{+2}, $Fe^{+3}$and Fe^{+2} [70]. It is a potent pharmacological compound because of its high affinity with endocytotic receptor in human hepatic malignancy; recently it is suggested against tissue rejection in fields of medicine [71, 72]. In an experimental study, Mukherjee and Yun [73] suggested the anti-obesity efficiency of LBA (oral or ip) as it significantly reduced the lipogenic capacity, also it is recorded for managing of the body weight and improving metabolism; this property is due to indigestibility of LBA by digestive enzymes. Otherwise, LBA take a part in the digestion of lactose, possibly due to a competition for binding with the β-galactosidase released in the intestine [3].

3.3 Lactitol

3.3.1 Properties

Lactitol is non-hygroscopic white, sweet, odorless, crystalline solid disaccharide with 30-40% sucrose sweetness. It can exist in different crystalline forms with varies melting points: XRD and IR-spectra declared three hydrate forms (mono-, di-, and tri-hydrate), two anhydrate (A & B), and one amorphous form. Monohydrate is the most common form**.** Depending on the grinding and drying, monohydrate form melts within the range of 93-100°C [74]**.** It is very soluble in water**,** isstable under humid and heat conditions, and does not take part in the Maillard reaction. At low pH, it slowly hydrolyzes to sorbitol and galactose. It is very resistant to microbiological breakdown and fermentation [75]**.**

3.3.2 Preparation

Lactitol [4-*O*-β-D-Galactopyranosyl-D-glucitol] monohydrate is a disaccharide analog of lactulose or another valuable derivate from lactose. Lactitol is not found in nature; industrially and it was reported to be obtained by the catalytic (Ni, Pd, or Ru) hydrogenation of the carbonyl group of lactose (Fig. 5). The products are highly dependent on the catalyst type, reaction temperature (110-150°C), and pressure of hydrogen (20-70 bars) [76]**.** The primary product is lactitol with a yield of over 90%, besides 1.7-1.9% lactulitol. Lactitol probably hydrolyzed then hydrogenated and produced galactitol and sorbitol[77]**.**

3.3.3 Food applications

Lactitol is alcoholic sugar that is used as a sweetener. It is approved (the American FDA) as a food additive. Lactitol can be utilized not only as a low caloric sweetener but also as a bulking agent (assist food formulation), dryo-protectant, humectant, and prebiotic source. It has been used for the synthesis of emulsifiers, surfactants, polymers, and hydrogels. Large numbers of patents were stated in varied applications (low-calorie confectionery and chocolate, sugar-free chewing gum, surfactant, cleaning products, and animal feed [77]**.** Lactitol also has prebiotic capacity in dairy products (yoghurts, ice cream, etc.), as it stimulates the growth of probiotic microorganisms (several genera of lactic acid bacteria) [78, 79]**.**Lactitol gives a glassy matrix that immobilizes the protein system and inhibits unfolding. It is also able to form hydrogen links with the protein structure, therefore assisting in keeping the enzyme's activity. Favorably, pathways are possibly accepted for drying protein preparations. Santana et al. [80] concluded that adding (5%) of lactitol not only inhibited protein denaturation through freeze-drying, but also showed a dryo-protectant effect when compared with other agents (sorbitol and maltodextrin) concerning physiochemical measurements (whiteness, gel formation, and foaming). Lactitol was used as a sugar replacer in cake formulations; this gave a batter of comparable flow index and temperature of starch gelatinization; moreover, the sensory evaluation didn’t differ from the batter formulated with sugar [81]**.** The effect of lactitol, as a sucrose replacer, on the texture profile of cookie dough was investigated; the results suggested that lactitol gave medium values of hardness and consistency, and relatively great values of cohesiveness and adhesiveness; these texture attributes are parallel to those of obtained from sucrose-formulated cookie dough [82]. Gurditta et al**.** [83] reported that application of lactitol, as replacing sugar, in Chhana-murki (dairy dessert from India) yielded a desirable color, appearance, sweetness, and overall acceptance. A 50% decrease in the caloric content was gotten by a combination of Splenda and lactitol; however, the viscosity and the capability to incorporate air were negatively influenced [84]**.** Clearly stated, an addition of lactitol 5% led to prolonged stability of the isoenzyme glutathione transferase activity [85]**.** With respect to the stabilizer agent of lactitol, Klewicki [86] reported that only 3% of the oligosaccharides were subjected to hydrolysis by the existence of lactitol. Also, lactitol showed a protective effect on α-amylase activity during heating (87).

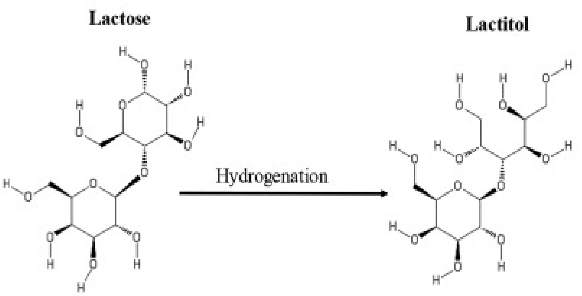

Fig. 5. Hydrogenation of the carbonyl group of lactose to produce lactitol

3.3.4 Pharmaceutical applications

Lactitol has been used spreadly in the treatment of hepatic encephalopathy and constipation as it is a potent laxative. In humans, its metabolism doesn't dependent on insulin. Lactitol is applied as a non-caloric sweetener in calorie-reduced and diabetic foods; also, lactitol did not disturb glucose or lactate homeostasis as it is weakly absorbed in the gastrointestinal tract in healthy subjects and cirrhotic-patients [88]. As lactulose alternate lactitol is used in the improvement of hepatic encephalopathy [89]. Lactitol behaves as a prebiotic; it can regulate the amount of the beneficial bacteria and downregulate the number of putrefactive bacteria, drop the pH of the small intestine, and reduce the formation and absorption of ammonia. Lactitol markedly elevates *Bifidobacterium* and *Lactobacillus* [90].
Animal studies did not record any embryo-toxic or teratogenic effects of lactitol [91] as it is minimally absorbed and gives a hypoglycemic response. As it is catabolized into energy with a negligible amount of insulin as it contains 2 kcal/g calories with a sweetness of 30-40% sucrose [92].

3.4 Galactooligosaccharides

3.4.1 Properties

Galactooligosaccharides (GOS) are human milk constituents and different foods (banana, onions, garlic, chicory, and soybeans); however, their amount in these foods is not enough to display any potential influence. Therefore, their best route could be via supplementation of diets or inclusion in foods. The GOS is highly soluble and has a relative sweetness (35% of sucrose). Their viscosity is higher than that of corn syrups with a high-fructose concentration; they reduce the water activity and freezing point and show valuable moisture retention abilities. Their energy value is close to 1.0-2.0 kcal/g [93]. Their chemical formula is (galactose) n - glucose, where "n" ranges between 1 and 4. The galactose-galactose bonding is a β-(1-3), β-(1-4), β-(1-6), with the β-(1-4) being predominant, while the galactose-glucose bonding is essentially β-(1-4). Some disaccharides are also found in GOS such as galactobiose and allolactose [94].

3.4.2 Preparation

GOS are belonging to the non-digestible oligosaccharides group, mainly produced by the trans-galactosylation reaction of lactose with β-galactosidase enzymes, as illustrated in Fig. 6[95]. Commercially, GOS is obtained by using fungal β-galactosidases; in this reaction, β-galactosidases hydrolyze lactose to glucose and galactose and catalyze lactose trans-galactosylation to GOS [96]. Based on the source of the enzymes, the produced oligosaccharides are β(1-4) and/or β(1-6). β-galactosidase of *K. lactis* produces β-(1-6) oligosaccharides, β-galactosidase of *S. elviae* produces 4-galactosyl-lactose, β-galactosidase of *B. circulans* produces β-(1-2), β-(1-3), β-(1-4) or β-(1-6) linkages, consequently giving a large variety of oligosaccharides [97]. Similarly, mannose, glucose, fructose, galactose, N-acetylneuraminic acid, maltodextrins, glucuronic acid, and a number of aromatic compounds were displayed to act as galactose acceptors for β-galactosidases, giving practically infinite forms of oligosaccharides [98, 99]. The use of lactic acid bacteria as sources of β-galactosidases offers actual potential for the formation of GOS. Their trans-galactosylation is enhanced at high lactose concentration and low water content; the process is greatly influenced by β-galactosidase-source and the reaction conditions (time, temperature, pH, and enzyme-substrate ratio) [100]. Whey protein (WP) is considered a promising source for Galacto-oligosaccharides production; it is an inexpensive by-product from cheese production, comprising mainly lactose and salts[101].

3.4.3 Food Applications

It has been extensively reported that GOS-food applications are well known [102,103]. Galacto-oligosaccharides are beneficial ingredients to be applied in a large scale of food products due to their stability against pH and temperature, high acceptable taste, relatively low sweetness and caloric index; they were common used as food ingredients in some countries many years ago [95]. Because of their acid and temperature stability, high solubility, small glycemic index, and negligible carcinogenic effects, they are suitable for the confection industry (with reduced sugar), hard-candies (with reduced-calorie) [104]. GOS are mainly used in fermented yoghurt and milk, nutrition bars, health drinks, beverages, breakfast cereals, bakery products, meat products, mineral supplements, weight loss products, green foods, soups and sauces, pet food, and infant food. Their prebiotic characteristics made them suitable for nutritional and functional usage; they were used for texture modification, fat replacement, and moisture retention [102,105]; that is why their participation in a large scale of foods (chewing gum, confectionery, yoghurt, ice cream, and bakery infant formulas) is in a progressive increase. GOS has versatile pharmacological applications. Because of their resemblance to human milk oligosaccharides, they are used in growing-up milk and infant formula (2.4 g/L) to activate the growth of bifidobacteria and lactobacilli in the intestine of the infant. They are used in the development of specialized foods for the elderly and hospitalized people [103].

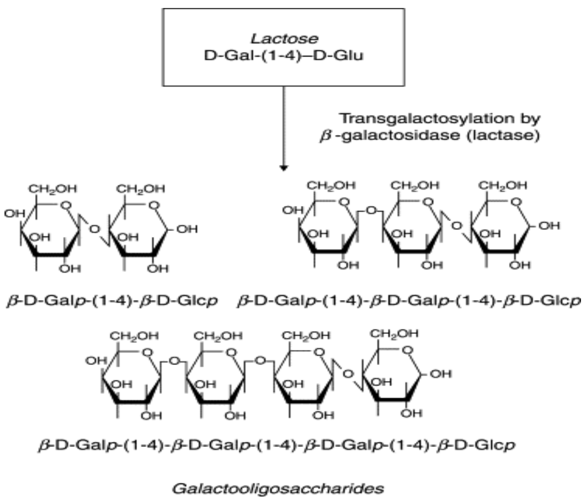

Fig. 6.Production of GOS by trans-galactosylation reaction of lactose [94]

3.4.4 Pharmaceutical Applications

Because of the prebiotic characteristics of oligosaccharides towards bacteria of skin, some cosmetic formulation for this objective has been investigated [106]. GOS have evidenced great health benefits such as activities against pathogen, treating capability for gastrointestinal disturbances, valuable effects on absorption of mineral and enhancement of immune system [107,108]. Depending on the osmotic effects (carry water into the large bowel) of oligosaccharides and their high fermentation rate & production of gases, the consumption of excessive doses of GOS may led to unfavorable symptoms such as intestinal discomfort, flatulence or even diarrhea [109].

3.5 D-tagatose

3.5.1 Properties

The D-tagatose or tagatose (white crystal or powder) is a keto-hexose isomer of galactose a stereoisomer of fructose with a molecular weight of 180.16 Da and a melting point of 133–135ºC [110]. D-tagatose, a unique rare sugar, has been used as a novel functional sweetener in the nutritional supplement market. It was classified as a generally recognized as safe (GRAS) substance due to its remarkable health benefits. It provides a slightly less sweet sucrose-like taste (90–92%) and < 50% of its calories (1.5 kcal/g). It is more soluble and stable at pH 2–7 [111]. It has physical and sensory properties that resemble sugar and is recommended as a replacer for it [112].

3.5.2 Preparation

Basically, tagatose was prepared from whey, lactose or galactose by alkaline isomerization, but nowadays it is manufactured by an enzymatic route from lactose. Schematic diagram of the industrial D-tagatose production process by chemical and biological methods, selectively using lactose or whey as the starting material, as shown in Fig 7 [113].

3.5.2.1 Chemical process

Utilizing calcium catalyst and strong acid, the mass-production of D-tagatose was first applied into practical application through chemical catalysis**,** but this method has disadvantages like by-products formation, hard purification steps and chemical waste residues [113]. To avoid these disadvantages,biological production using several biocatalyst sources have been included greatly next[114].

3.5.2.2 Biological process

In 1984, bacterial tagatose was first produced using several microorganisms by oxidation of galactitol. Another way to transfer D-galactose to D-tagatose is recommended using lactic acid bacteria [115]. *Enterobacteragglomerans* also manufactures D-tagatose from D-galactose when grown on an L-arabinose pre-induced medium [116]. L-arabinose isomerase (AI) was found to be the most efficient enzyme for isomerizing D-galactose into D-tagatose [6]. AIs from various prokaryotic microbes have been identified, including those from mesophilic, thermophilic, and hyperthermophilic bacteria [113]. Particularly, the thermo-AIs which exhibited optimum temperatures at 60–70°C were approved to be extremely suitable for industrialization of D-tagatose. Under this circumstance, the highest yield of Dtagatose was reported to be 370 g/l with a conversion rate of 74% (w/w) from Dgalactose by isomerization of a purified thermo-AI. However, purified enzymes have certain limitations that need to be taken into account when it comes to industrial production, such as complicated purification steps and poor stability in operation [117].

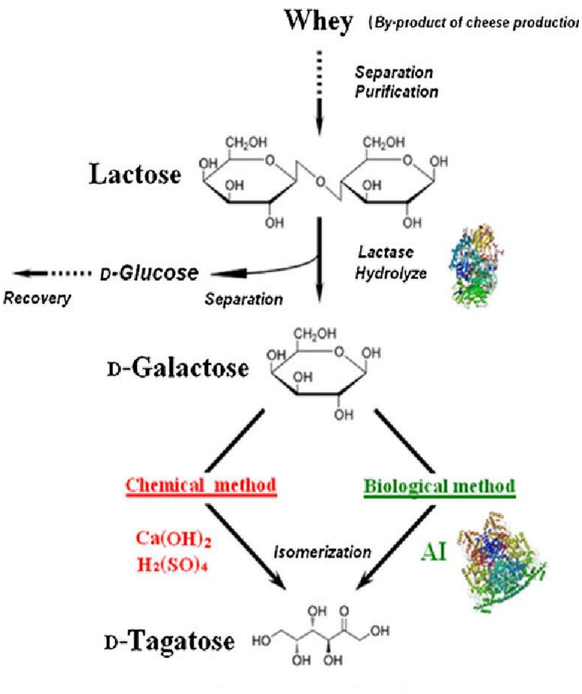

Fig. 7. Chemical and biological methods of tagatose production [113]

3.5.3 Food applications

Due to its low-calorie sweetener, D-tagatose can be used in various beverages, foods, health products, and dietary supplements. Also, it can be used in the manufacture of low carbohydrate diets, cereals, bakery, health bars, confectionery, candy, chocolate, chewing gum, yoghurt, milk-based drink, and soft drink [118]. In 2005, Europe approved tagatose as a food ingredient; as it is indigestible and fermented in the colon, it exerts prebiotic effects [119]. Torrico et al. [120] recommended that strawberry yogurts with tagatose (80%) instead of sucrose were highly acceptable. Because tagatose elicits sweetness without any unwanted quality trait in aqueous solutions, Fujimaru et al. [121] declared that the technological and sensory activities of tagatose on yogurt products are still weakly investigated. Indeed, FDA in the United States approved tagatose for use in food products [122].

3.5.4 Pharmaceutical applications

As a low-calorie sweetener, tagatose was approved for non-chronic drugs, toothpaste, and mouth wash. Because of its ameliorating efficiencies against diabetes, obesity, blood metabolite disturbance, anti-aging, anti-oxidant, and prebiotic, tagatose attracts attention [118]. Moreover, tagatose possesses numerous health benefits like promotion of weight loss [123], anti-plaque, non-cariogenic, anti-halitosis, prebiotic, and anti-biofilm properties [124], organ transplantation [125], enhancement of pregnancy, fetal development, anemia, and hemophilia [126]. It is also important during the synthesis of other physically active compounds, and as an additional in detergent and cosmetics [127]. D-Tagatose can restore cell damages caused by free radicals. Despite its weak iron-chelating potential, tagatose inhibits the iron-induced cytotoxicity via reducing the leakage of iron-induced free radicals from membrane lipid peroxidation and protein carbonyl production [125]; also, tagatose gives protection against the hepatic damage resulting from pro-oxidant drugs, evidencing its antioxidant property [126]. Due to its flavor-enhancing properties, it is a perfect and probable agent for the mask the unpleasant taste of medicines [118].

3.6 Lactosucrose

3.6.1 *Properties*

Lactosucrose (O-β-D-galactopyranosyl-(1,4)-O-α-Dglucopyranosyl-(1,2)-β-D-fructofuranoside) is a functional trisaccharide obtained from sucrose and lactose under the catalysis of β-fructofuranosidase (β-D-fructofuranosidefructohydrolase, EC 3.2.1.26) [127]. It is a very hygroscopic white solid with bland taste with a molecular weight of 504.44Da; its melting point is around 181°C [128]. Its solubility in water is higher than that of lactose. Relative to sucrose, lactosucrose sweetness is 0.3; its powder form is stable for one hour 120ºC and pH 4.5; it has high moisture-retaining capacity [35].

3.6.2 Preparation

First lactosucrose production was reported in 1957 by enzymatic synthesis, where β-fructofuranosidase catalyzes the transfer of fructosyl residue from sucrose to lactose. Three different enzymes can be used as biocatalysts in the enzymatic synthesis; Levansucrase and β -fructofuranosidase are the highest studied, while β-galactosidase has also been reported later [129]. Lactosucrose production by levansucrase of different sources was reported using lactose as acceptor and sucrose as fructosyl donor as fructosyl residue transfers from sucrose to the C-l location of the glucose in the lactose [130]. Lactosucrose is industrially produced by means of another fructosyltransferase derived from *Arthrobacter*. Chen et al. [131] proved a thermostable enzyme (β-fructofuranosidase) from *Arthrobacter* sp., which was closely correlate with the industrial requirements; the maximal trend of lactosucrose was 109 g/L post-incubation of the pure enzyme (40 µg/mL) with 150 g/L sucrose and lactose for 10 min (50°C, pH 6.0). Generally, this study supplies a better enzyme candidate for the synthesis of lactosucrose at higher temperature; the performance of the biocatalyst may be improved by enzyme engineering in the future (Fig 8). Lactosucrose can be produced form lactose post enzymatic hydrolysis with existence of sucrose catalyzed by the enzyme β-galactosidase; the liberated galactosyl-chain can be joined to the C_4 of the glucose-moiety of sucrose, leading to generation of lactosucrose [132]; however, the amount was less than that obtained via transfructosylation of lactose [129].

3.6.3 Food applications

Lactosucrose has been used, on a large scale, in the manufacture of functional foods; it was reported as a sweetener for beverages, confectionaries, desserts, sweets, bakery products, and yogurts [34]. For the food processing industry, due to its ability of lactosucrose to raise water-holding capacity, it can decrease syneresis or serum separation along with product storage; due to this property, lactosucrose can be used as a fat replacer to decrease syneresis and enhance some particular characters such as consistency and texture [133]. Due to its low-digestive and low-cariogenic sweetener, lactosucrose was included in bakery products [134], yogurts [135], ice creams, infant formula, snacks, cookies, desserts, candies, chocolates, chewing gum, instant juice, instant soup, and mineral water [136]. Furthermore, lactosucrose was added to fish feed to increase nutrient absorption and decrease self-contamination [137].

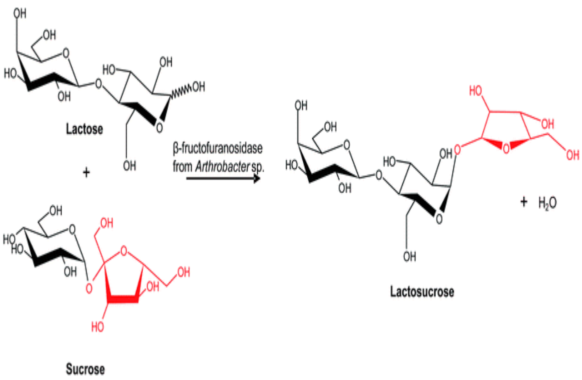

Fig 8. The biosynthesis of lactosucrose using the β-fructofuranosidase from *Arthrobacter* sp. [131]

3.6.4 Pharmaceutical applications

The bifidogenic action of lactosucrose has been known since it is fermented by bifidobacteria in the colon [138]. Ingestion of large amounts of lactosucrose, may lead to an elevation in the osmotic pressure of the stomach and intestine and induce diarrhea. However, its consumption inhibits the growth of colonic clostridia [139]. In women, Teramoto *et al* [140] determined that lactosucrose ingestion reduces fecal pH, ammonia, and putrefactive compounds. The assays suggested that lactosucrose performs some protective activities on indomethacin-induced enteropathy; this activity is attributed to the maintenance of intestinal microbiota[141]. It possesses anti-obesity properties as long-term ingestion of 5% lactosucrose for 8 weeks succeeded to reduce abdominal adipose tissue weight [142]. Also, it improved calcium and phosphorous absorption in rats [140]. Lactosucrose exhibits a higher laxative potential than other lactose-based prebiotics, therefore it has anti-diarrhea against prebiotic intake [143]. Lactosucrose performs a water-holding capacity, which fasts the bowel peristalsis movement and facilitates fecal formation and excretion [144]. Itsconsumption inhibited 2-mono-oleoyl-glycerol absorption that resulted in decrement of plasma triacylglycerol levels [145]. Lactosucrose was suggested as an anti-inflammatory agent for bowel disease [146], enhancer of immunoglobulin-A level [147], and preventive agent against IgE-mediated allergic diseases [148]. Its consumption has no effect on serum glucose or insulin [149]. It wassuggested in pharmaceutical and cosmetic products as it acts as excipient [150], nutritive support and microflora regulator [151], or as a preventive agent against some skin diseases [152].

3.7 Epilactose

3.7.1 Properties

Epilactose is non-digestible bioactive lactose derivative that has a molecular weight 342.3 g/mol and molecular formula of $C_{12}H_{22}O_{11}$as in Fig 9 [153]. It is found in extremely little amounts in heat-treated bovine milk, and it can't be synthesized chemically [154]

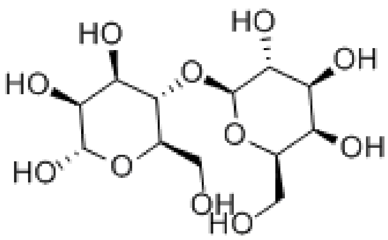

Fig.9. Molecular configuration of epilactose [153]

3.7.2 Preparation

Another disaccharide isomer of lactose is epilactose (4-*o*-β-D-galactosyl-D-mannose) which is produced in little quantities through lactose catalyzed-isomerization, but it can be synthesized in large quantities by enzymatic epimerization of lactose using different microbial cellobiose 2-epimerase [153] which catalyzes a hydroxyl stereoisomerism at the C-2 site of the glucose moiety of lactose. In a 5-step process and using cellobiose 2-epimerase of *R. albus*, Epilactose was obtained (91.1% pure and 11.3% yield): 1) epimerization, 2) crystallization recovery, 3) enzymatic-hydrolysis, 4) eliminating monosaccharides via yeast, and 5) purification using column chromatography [155].

3.7.3 Pharmaceutical applications

Similar to various oligosaccharides, epilactose performs a prebiotic behavior [156] and enhances mineral absorption [157]. It enhances post-gastrectomy osteopenia and anemia through increasing Ca and Fe absorption [158]. It has prebiotic properties as it is a non-digestible disaccharide that could induce proliferation of the beneficial microorganisms in the intestine [153, 156]. It had potential preventive ability against colon cancer as it did not elevate blood glucose and could prevent the transformation of primary bile acids to secondary ones [156]. In addition, epilactose has anti-arteriosclerosis as it was found able to increase blood short-chain fatty acids and other organic acids levels, and decrease blood total- and low-density lipoprotein-cholesterols levels; also it increased the weight of cecum-wall [157].

3.8 Uncommon derivatives

Ultimately, other uncommon types of lactose derivatives were found such as lactosides, lactosylhalides, anhydro derivatives, cyclic acetal derivatives, halogenated, esters derivatives, nitrogen-containing derivatives, deoxy derivatives and unsaturated derivatives. [159-161].

4. Conclusion

Lactose is a unique abundant disaccharide, with low nutritional value, present in exists in milk, being synthesized from galactose and glucose in the mammary gland. It exists in three anomeric forms: monohydrate α-lactose, anhydrous β-lactose, and amorphous lactose. Recently, lactose is widely accepted that lactose intolerance in lactase deficient individuals should not be a cause to discourage milk consumption. In moderate doses, and distributed over meals, lactose may even act as a prebiotic in these populations; it is used as the main source for many lactose-derivatives like lactulose, lactitol, galacto-oligosaccharides, and lactobionic acid, lactosucrose, epilactose, D-tagatose….etc. Lactose-derivatives can be obtained through different processes including isomerization, oxidation, electrochemical, and biotechnological (biocatalytic–microbial and enzymatic) processes. Lactose derivatives can be used in a wide range of dairy and non-dairy applications such as stabilizers, gelling agents, antioxidants, aging inhibitors, and emulsifiers... etc. Due to their promising variable characteristics, lactose derivatives have been incorporated in many nutria-pharmaceutical applications for managing many health disorders such as hepatic encephalopathy and malignancy, constipation, diabetes, and obesity.

4. References

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