Galactose, Natural Sources and Biotech Uses

Nowadays, as the science developed, people are more and more interested in two hot topics, global environment and human health. In the near future, as scientists predict, it's very likely for human to have a new "clean" biofuel coming from carbohydrates and replacing the fossil fuel we are using now, which would be a huge advancement of environmental protection. Also people are learning more about the minute quantity but essential contents in diet, like so-called bifidus factors, which have big affects on health, especially for babies. And interestingly, all of these can be related to the "half milk sugar" (from Chinese) galactose.

In this essay, I will give a broad overview of galactose, including its nature source, some functions, related enzymes and future prospects. As from many aspects, galactose would have an important role in future and more sources would be needed, both natural and artificial. So where to start finding new sources of galactose would be an interesting question. And in this essay, I will try to give some opinions to answer this question.

1. What is galactose?

Galactose, also named D-galactopyranose, is a simple monosaccharide sugar, sharing the same molecular chemical formula $C_6H_{12}O_6$ with glucose and fructose, while they are defined as structure isomers as they have different structures. Galactose has the appearance of white crystal and is less sweet comparing to glucose or fructose. Galactose has an average mass of 180.16 Da. As galactose is consisting of six carbon and one aldehyde group, it is classified as an aldohexose. (see **Fig 1.1**)

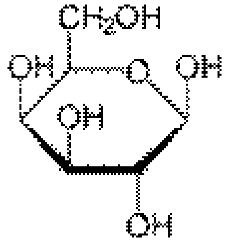


Fig 1.1 Cyclic form structure of galactose

Galactose is an epimer of glucose, only has the different position of the hydroxyl group on carbon-4. [1] Similar with glucose, galactose also has two forms, cyclic form and open-chain form. Four isomers of galactose are cyclic, two of them with a pyranose form, two with a furanose form (see **Fig 1.2**). [2]

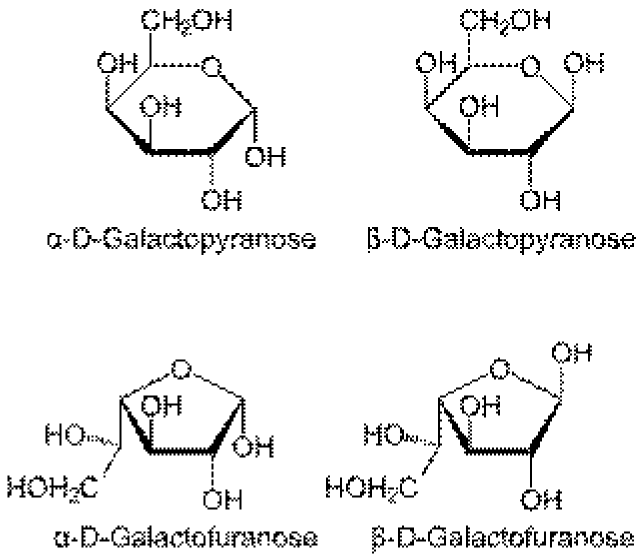


Fig 1.2 Pyranose and furanose forms of D-galactose

There exists two anomers, named α - and β -galactose in the chair form. In the open-chain form, there is a carbonyl at one end. And same as glucose, galactose naturally exist as two enantiomers, D- and L-galactose, while D-galactose (D-Gal) is commonly known as galactose (see **Fig 1.3**). In the following parts, I will focus on D-galactose.

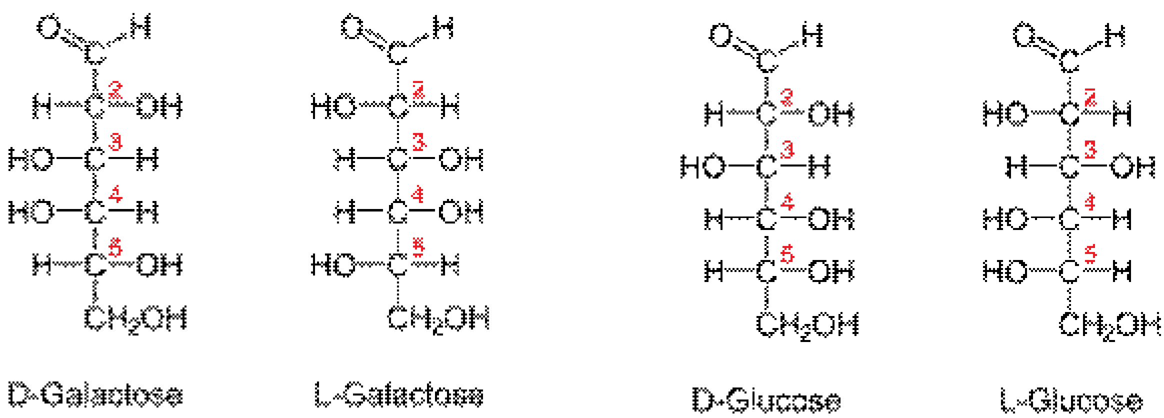


Fig 1.3 Open-chain form structure of galactose and glucose

Galactose exists in both oligosaccharides and polysaccharides naturally. As many hydroxyl groups exist in the sugar molecules, one monosaccharide can be linked to another with glycosidic bonds by the elimination of water molecules. And that's how oligosaccharides are built. Various glycosidic linkages can be formed because a monosaccharide, like galactose, has multiple hydroxyl groups. For example, lactose, the primary disaccharide in milk, consists of glucose and galactose connected by a β-1, 4-glycosidic linkage. While another disaccharide melibiose is formed by an α -1,6-glycosidic linkage between galactose and glucose (see **Fig 1.4**). [3][4]

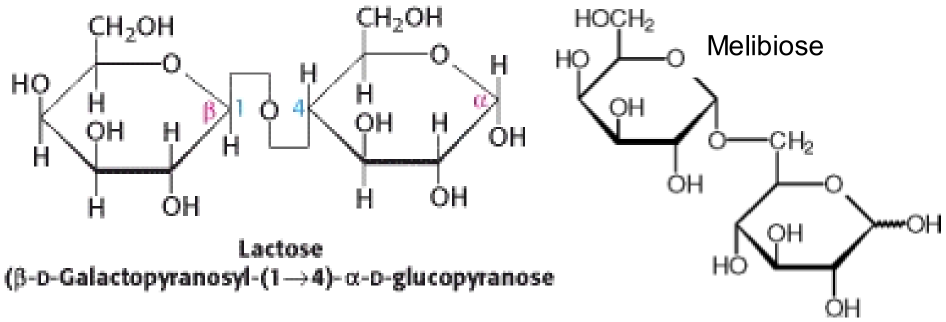
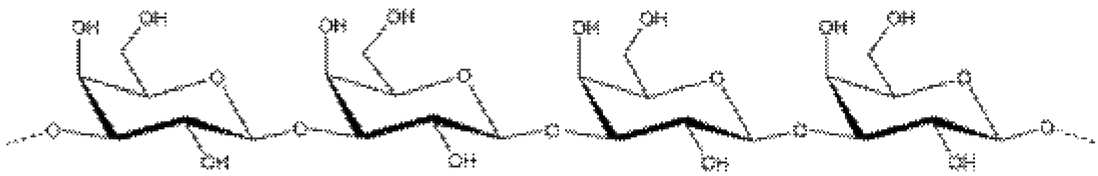
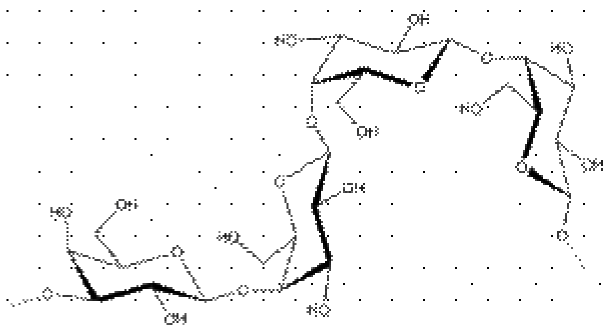


Fig 1.4 Structure of lactose and melibiose

Galactan is a polysaccharide formed by polymerized galactose, and also may have different glycosidic linkages, like β-1,3-galactan, β-1, 4-galactan, (see **Fig 1.5**). And galactose can also be part of a heteropolysaccharide, linked with other sugars. For example, arabinogalactan is consisting of arabinose and galactose, existing naturally in plants and microbes. And the galactan part of microbial arabinogalactan is linked with either β-1,5 or β-1,6 glycosidic linkages. [3][5]



β-1,3-galactan



ß-1,4-galactan

Fig 1.5 Two structures of galactan

2. Natural sources

Galactose has been found in nature existing in many different ways.

In plants, free galactose only exists in very small quantities, like it can be found in the berries of the Ivy League. Galactose often presents as polysaccharide form in a variety of galactan, pectin, various plant gum and so on. For example, K-carrageenan in the red algae is composed of D-galactose and 3, 6 - anhydro-D-galactose. Naturally many plants in common diets, including fruits and vegetables, contain certain amount of galactose (see **Table 2.1**). [6]

Table 2.1 Soluble galactose content (mg/100g fresh weight ± SE) [6]

Fruit/vegetable	**Content**
Apple	8.3 ± 0.7
Bean sprouts, green	4.3 ± 0.2
Beet, red	0.8 ± 0.2
Broccoli	6.8 ± 0.7
Corn	3.7 ± 0.3
Kiwi	9.8 ± 0.4
Papaya	28.6 ± 1.9
Potato, white	1.2 ± 0.3
Potato, sweet	7.7 ± 0.7
Tomato	23.0 ± 2.0

Galactose is also a composition of raffinose, melibiose, and stachyose in plant tissues. And many plants contain galactose existing in the cell wall as a composition of pectin and hemicellulose (see **Fig 2.1**), like the sugar beet pectin (see **Fig 2.2**). Galactose could also consist of galactolipid in chloroplast membranes of green plant tissues. [7][8][9]

Galactose also forms galactans in plants, for instance, (1 → 3) β - and (1 → 6) β -linked gum arabic galactan and (1 → 4) β -linked spruce galactan. [34]

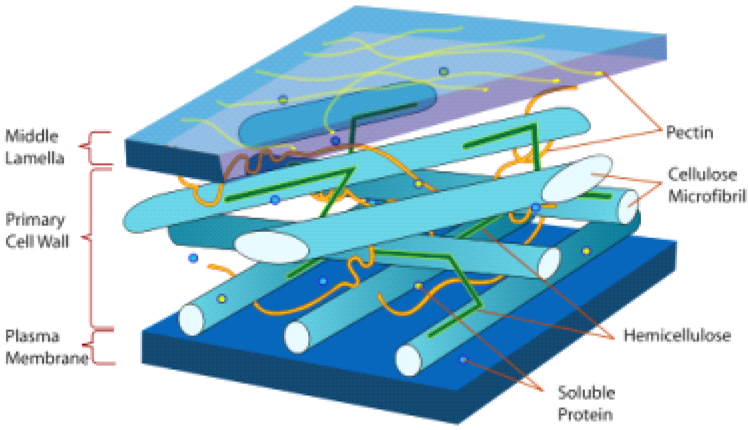


Fig 2.1 Plant cell wall diagram

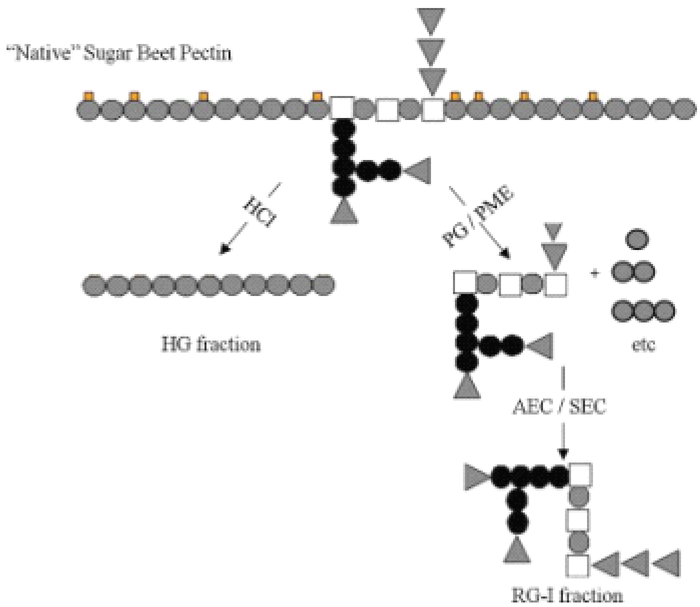


Fig 2.2 Schematic structure of sugar beet pectin: galacturonic acid (●); galactose (●); arabinose (▼); rhamnose (□); and methyl groups (■). PG-endopolygalacturonase I and II from *A. niger*; PME-fungal pectin methyl esterase from *A. aculeatus*; AEC-anion exchange chromatography and SEC-size exclusion chromatography. [7]

In animals, galactose is also present in a variety forms, like lactose, galactogen, polysaccharides, glycolipid, and glycoprotein. Galactose is mostly known as a component of lactose, together with glucose as the other half. Lactose is the major carbohydrate in the milk of most species (see **Table 2.2**). Also low concentrations of free galactose (about 0.2 mM) are found in cow milk and others.

Table 2.2 Composition of Milk from Different Mammalian Species (per 100 g fresh milk) [30]

	Protein (g)	Fat (g)	Lactose (g)	Energy (kcal)
Cow	3.3	3.9	4.6	66
Human	1.3	4.1	7.2	69
Water Buffalo	4.1	9.0	4.8	118
Goat	3.1	3.7	4.4	62
Sheep	5.4	5.8	5.1	93

Galactocerebrosides (or galactosylceramides, see **Fig 2.3**) are important glycosphingolipids existing in the brain and other nervous tissues of most animals, and they are the primary lipid of myelin, which forms the myelin sheath that surrounds the core of a nerve fiber or axon. (see **Fig 2.4**). [10]

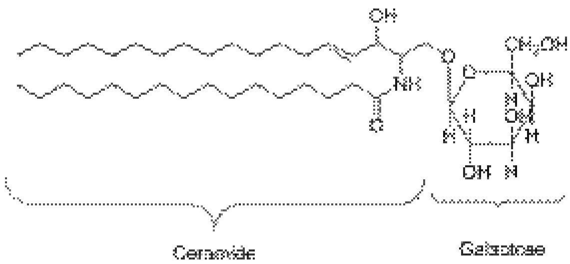


Fig 2.3 A galactocerebroside

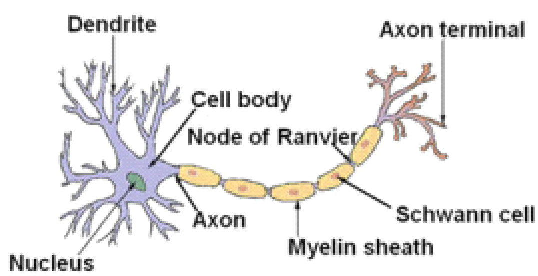


Fig 2.4 Structure of a typical neuron [31]

Galactose is also found in snail and frog eggs and bovine lungs. For instant, the snail eggs contain the galactose homopolymer, galactogen. Research on the galactogen content in the albumen gland of the snail *Bradybaena similaris* showed that the maximum galactogen content was 63.3 mg and the lowest 20.7 mg of galactose per gram of tissue, wet weight. [11]

In microbes, galactose also exists. It is a part of many bacterial polysaccharides and some bacteria are already known that can produce galactan. For example, *Methylobacterium* sp., its exopolysaccharide (EPS) is a 100% galactan, and consists of D-galactopyranose and [4,6-O-(1-carboxyethylidene)]-D-galactopyranose connected by α -1,3-glycosidic linkages. [12]

Based on the sugar composition of EPSs, the *Lactoccocus lactis* strains can be classified into three main groups (see **Table 2.3**). Strains in Group I produce EPS containing galactose, glucose, and rhamnose, for instance, strains SBT 0495 and NIZO B40 produce EPSs with the repeating units consisting of →4)-[α -L-Rha p -(1→2)][α -D-Gal p-1- PO_4-3]- β -D-Gal p -(1→4)- β -D-Glc p -(1→4)- β -D-Glc p -(1→. Group II produce EPS with only galactose, which include strain H414 with an EPS repeating unit →4)-[β -D-Gal p -(1→3)- β -D-Gal p -(1→3)]- α -D-Gal p -(1→4)- β -D-Gal p -(1→3)- β -D-Gal p -(1→ (see **Fig 2.5**). Group III contains EPS consisting of both galactose and glucose. And in addition, there are two strains having a special EPS sugar composition, which are NIZO B39 and NIZO B1137. [33]

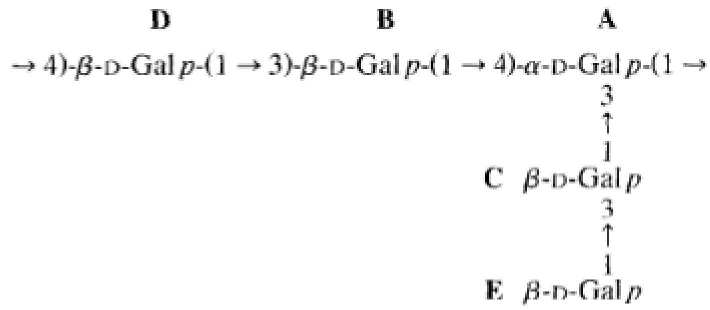


Fig 2.5 Structure of exopolysaccharide from *Lactococcus lactis* subspecies cremoris H414. [13]

Table 2.3 EPS sugar composition of the *Lactoccocus lactis* strains. (Rha, rhamnose; Gal, galactose; Glc, glucose.) [33]

Strain	Molar ratio[b]		
	Gal	Glc	Rha
Group I			
NIZO B40	1.00	1.82	0.88
SBT 0495	1.00	1.70	0.82
NIZO B1136	1.00	1.70	0.82
VI6	1.00	1.46	0.73
VI8	1.00	1.80	0.89
MLT3	1.00	1.46	0.73
Group II			
NIZO B35	1.00		
NIZO B36	1.00		
H414	1.00		
SD8	1.00		
SD11	1.00		
Group III			
NIZO B891	1.00	1.50	
MLT1	1.00	1.46	
MLT2	1.00	1.44	
Unique			
NIZO B39	1.00	0.60	0.55
NIZO B1137	1.00	1.79	

Also the furanose form of galactose is found in nature, namely in bacterial O antigens and in mycobacteria. [2] [9]

In fungi, galactose is produced. Like the genus *Pleurotus* is known as a producer of the polysaccharide galactan. In *Pleurotus pulmonarius*, there is a mannogalactan and it has a main chain of (1 → 6)-linked α -d-galactopyranosyl and 3-*O*-methyl- α -d-galactopyranosyl units, with the main antinociceptive and anti-inflammatory properties. While *P. ostreatoroseus* produces a 5.8 g d.w./l (grams of dry weight per liter of culture medium) amount of crude EPS, contains 4.9% carbohydrate composition of galactose, and a minor water-soluble fraction with a structure of partially 3-*O*-methylated (1 → 4)-linked α -D-galactopyranan. [35][36]

3. Importance in infant nutrition

Galactose has several special roles in infant nutrition. Firstly, breastfeeding infants gain energy from breast milk, which mostly is provided by lactose, together with lipid and protein (see **Table 3.1**). [14][15]

Table 3.1 Human milk volume and composition. (Gross energy density was calculated by summing the values for protein, lactose, and lipid concentrations and multiplying them by 5.65, 3.95, 9.25 kcal/g, respectively.) [14]

	Month of lactation			
	3 mo (n = 58)	6 mo (n = 45)	9 mo (n = 28)	12 mo (n = 21)
Volume consumed by infant (g/d)	811 ± 133	780 ± 185	674 ± 236	514 ± 238
Volume produced (g/d)	895 ± 200	844 ± 237	750 ± 252	516 ± 232
Protein (g/L)	12.1 ± 1.5	11.4 ± 1.5	11.6 ± 1.8	12.4 ± 1.5
Lipid (g/L)	36.2 ± 7.0	37.7 ± 9.6	38.1 ± 8.0	37.2 ± 11.3
Lactose (g/L)	74.4 ± 1.5	74.4 ± 1.9	73.5 ± 2.9	74.0 ± 2.7
Gross energy (kcal/L)	697 ± 67	707 ± 92	709 ± 74	706 ± 110

* $\bar{x}$ ± SD.

Secondly, galactose is essential in the conformation of myelin in brain tissue, and also some glycoprotein in collagen for the newborn infants. Thirdly, galactose is a major component of human milk oligosaccharides (HMOs), which are also known as 1actobacllus bifidus factors, the third most abundant components in milk, and are very important for infants to enhance immune functions and resistance to infections (see **Fig 3.1**). [16] The composition of HMOs is very complex. Beginning with lactose at the reducing end, the molecules are synthesized and the core structure of neural HMOs is [Gal(β 1-3/4)GlcNAc(β 1-]$_{n=0-25}$ 3/6)Gal(β 1-4)Glc. [37]

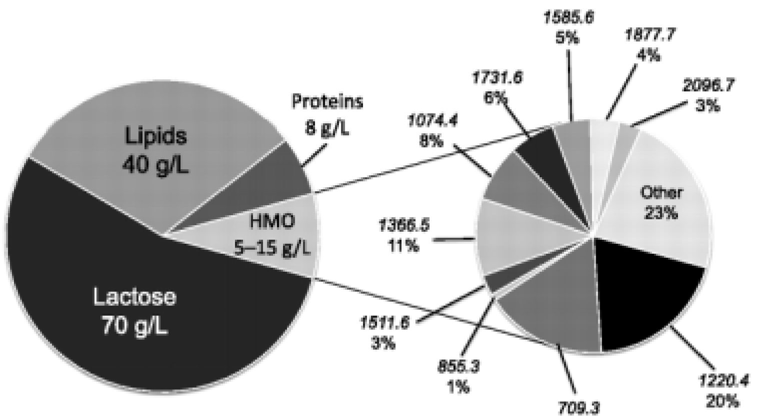


Fig 3.1 Human milk compositions (Left). Pull-out pie chart (Right) showing composition of the most abundant HMOs. [16]

4. Enzymes

As galactose exists in many different forms in living cells, there are a lot of different enzymes involved in its synthesis or metabolism.

4.1 Enzymes related to galactose

Galactose and glucose can be released from lactose by hydrolysis with the help of lactase, one enzyme included in the β-galactosidase family (see **Fig 4.1**).

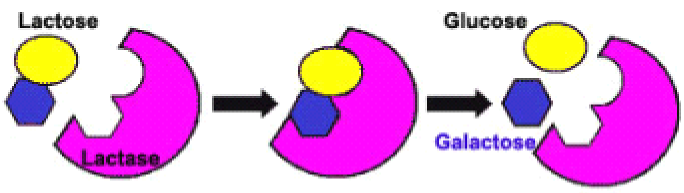


Fig 4.1 Hydrolysis of lactose by lactase

Some people may suffer from the lactose intolerance when consuming dairy products. Lactose intolerance is the state of the human body does not produce lactase to break down lactose. After intake of lactose, the main symptoms would be diarrhea and bloating. This is genetically determined, and not contagious. Some symptoms may be mitigating or aggravating over time. [17] As glucose is the primary metabolic carbohydrate in human body, galactose would convert into glucose highly and rapidly. [18]

The main pathway of galactose metabolism is the Leloir pathway. (see **Fig 4.2**) It will take a three steps process to convert galactose to UDP-glucose, and the enzymes galactokinase, Galactose-1-phosphate uridyltransferase, UDP galactose-4'-epimerase are involved.

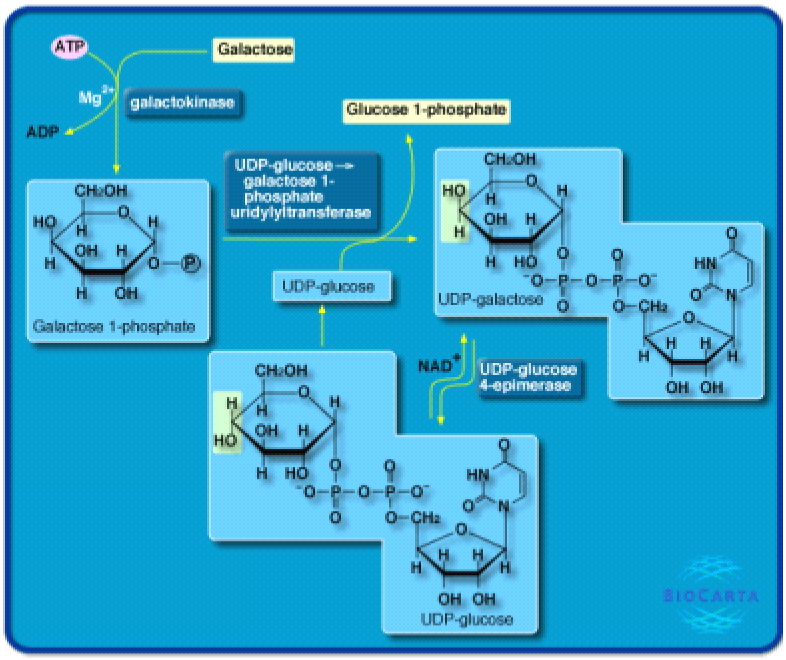


Fig 4.2 The Leloir pathway of galactose metabolism. [32]

In the human body, glucose can be transformed into galactose via hexoneogenesis when necessary, for example, when the mammary glands need to secrete lactose (see **Fig 4.3**).

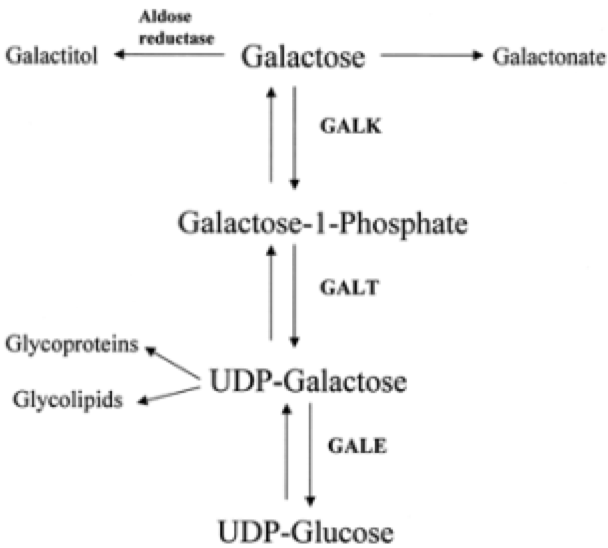


Fig 4.3 A simplified diagram of galactose metabolism. Galactokinase (GALK), galactose-1-phosphate uridyltransferase (GALT), uridine diphosphate galactose 4'-epimerase (GALE). [38]

4.2 Enzymes related to GOS

Galactose oligosaccharides (GOS) belong to the group of prebiotics, which have benefits to the host by positively affecting to the beneficial bacteria in the colon. [19] Currently, the industrial synthesis of GOS is done by some microbial glycoside hydrolases, in this case β-galactosidase, with lactose as substrate. Mechanistically, these glycoside hydrolases are considered to work by a 2-step process, hydrolysis and transgalactosylation (see **Fig 4.4**). Mechanistically, the 1st step is irreversible and formatting a galactosylenzyme intermediate. In the 2nd variant step, the galactosylated enzyme may be intercepted by any sugar in solution, to form transgalactosylation products, which would be GOS.

The existence of β-galactosidase has been found in many microorganisms from archaea, bacteria, and eukaryota. Some are already applied in the GOS industrial production, while there is still interest in finding better microbial enzymes that produce GOS, with a higher activity, a higher yield and/or a more stable reaction. [20]

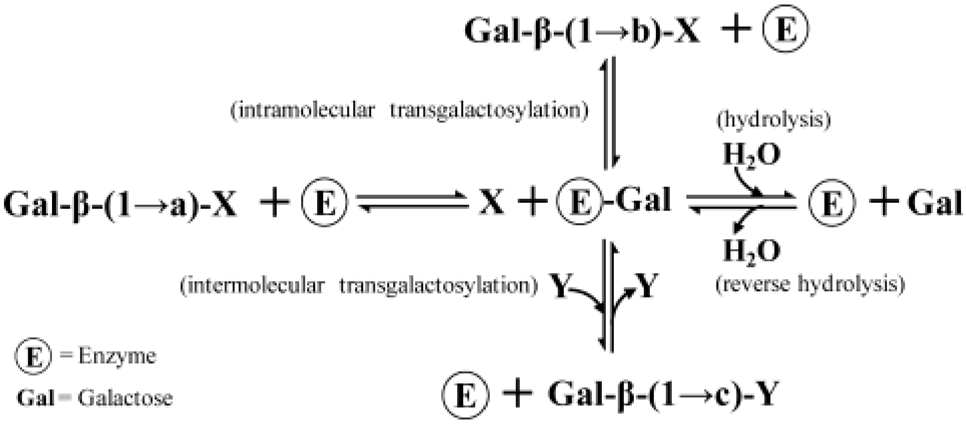


Fig 4.4 General model of GOS synthesis by lactose hydrolysis. (a, b, c: 2, 3, 4, 6, (a≠ b), indicate the glycosidic linkage position. X is galactosyl donor, and Y is galactosyl acceptor. Generally, lactose is the initial substrate (a = 4 and X = Glucose). Y can have one of the following structures: Glucose, Gal, Gal-Gal, or [Gal]**n**-Glc (with $1 \leqslant n \leqslant 6$). [20]

4.3 Enzymes related to EPS

Exopolysaccharides (EPSs) are extracellular homo- or heteropolysaccharides produced by microorganisms. They serve for protection and are secreted into the surrounding environment. [4] Due to the wide diversity in composition, exopolysaccharides have found different functions in microorganisms and various applications in industries. For example, exopolysaccharides from lactic acid bacteria contribute to health properties by imparting functional effects to foods and confer beneficial health effects. Dextran has found application in breads in the bakery industry, which improves softness, crumb texture and loaf volume. Exopolysaccharides are also important in endodontic infections, for instance, dental plaque. EPS have been associated with pathogenicity in mammalian hosts by providing extracellular matrices to form biofilm (see **Table 4.1**). [21][22][23][39]

Components of EPS are mostly monosaccharide, such as pentoses, hexoses (D-Galactose), amino sugars (and D-Galactosamine) or uronic acids (D-Galacturonic acids). For instant galactoglucan is composed of galactose and glucose, also known as EPS II (see **Fig 4.5**).

Table 4.1 EPS-producing bacteria on the outside of oral cavity, constituents of EPS and related diseases. [39]

EPS-producing bacteria	Constituents of EPS	Biofilm infection
Pseudomonas aeruginosa	Alginate, Psl (mannose- and galactose-rich polysaccharide) or Pel (glucose rich polysaccharide)	Cystic fibrosis pneumonia, contact lenses infection, central venous catheter infections
Burkholderia cepacia	Acidic branched heptasaccharide	Cystic fibrosis pneumonia (cepacia syndrome)
Escherichia coli	Cellulose, colonic acid or poly-β-1,6-GlcNAc (PGA)	Intestinal disorders, urinary tract infections, urinary catheter infections
Vibrio cholerae	Glucose- and galactose-rich polysaccharide	Cholera, diarrheal diseases (the EPS protects this organism from environ-mental stress)
Salmonella enterica serovar Typhimurium	Cellulose	Gastroenteritis
Staphylococcus aureus *Staphylococcus epidermidis*	Staphylococcal polysaccharide intercellular adhesion (PIA)	Endocarditis, central venous catheter infections, urinary catheter infections
Bacillus subtilis	Glucose- and mannose-rich polysaccharide	Opportunistic infections, apical periodontitis
Campylobacter jejuni	EPS contains β1-3 and/or β1-3 linkages	Bacterial gastroenteritis

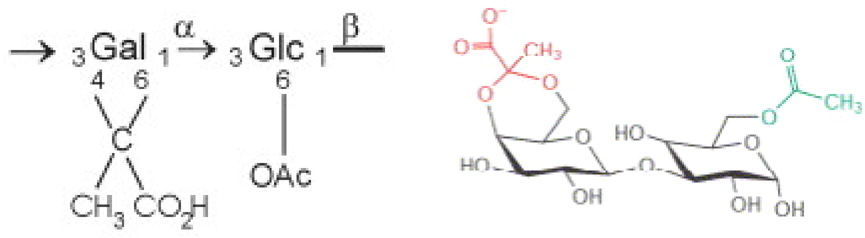


Fig 4.5 *Sinorhizobium meliloti* Galactoglucan (EPS II)

The synthesis of EPS is a multi-step process and depending on the activity of some protein complex. Different enzymes are involved, like glucosyltransferases, galactosyltransferases. [24] Two examples of the metabolic pathways for EPS production are shown here: the first one is *Streptococcus thermophilus*, producing EPS II (see **Fig 4.6**), the other one is *Lactococcus lactis* producing an EPS that is composed of glucose, galactose and rhamnose in a 2:2:1 ratio, (see **Fig 4.7**). [25] [26]

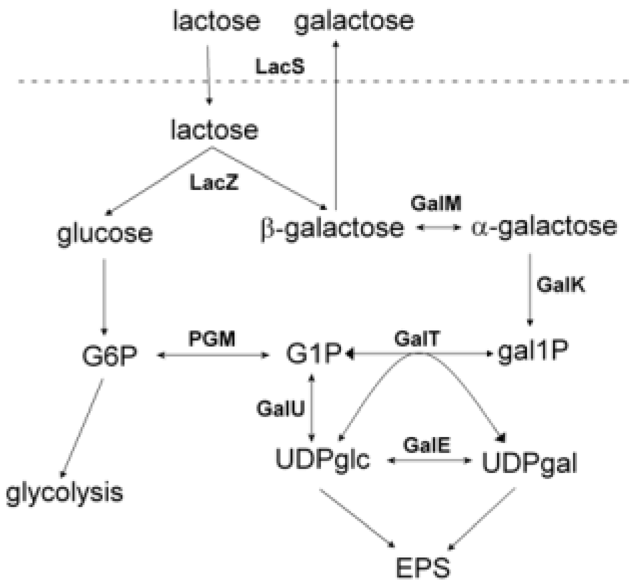


Fig 4.6 EPS biosynthesis in *Streptococcus thermophilus*. (LacS, lactose transporter; LacZ, β-galactosidase; GalM, mutarotase; GalK, galactokinase; PGM, α-phosphoglucomutase; GalT, galactose 1-phosphate udridyltransferase; GalE, UDP glucose 4-epimerase; GalU, UDP glucose pyrophosphorylase; gal1P, galactose 1-phosphate) [25]

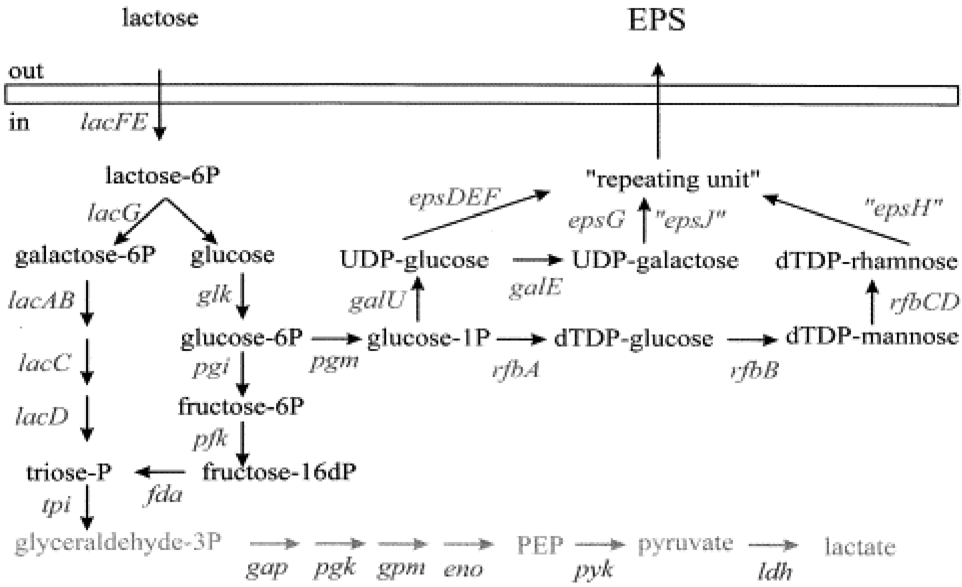


Fig 4.7 EPS biosynthesis in *Lactococcus lactis*. (*epsDEF*, glucosyltransferases; *epsG*, galactosyltransferase; *fda*, fructosediphosphate aldolase; *galE*, UDP-glucose 4-epimerase; *galU*, UDP-glucose synthase; *glk*, glucokinase; *pfk*, phosphofructokinase, *pgi*, phosphoglucoisomerase; *pgm*, phosphoglucomutase; *rfbA*, dTDPglucose pyrophosphorylase; *rfbB*, dTDPglucose dehydratase; *rfbCD*, dTDP-rhamnose synthesising enzyme system) [26]

4.4 Enzymes related to galactan

Galactans are defined as polymers of galactose. They may have different structures and are found in various organisms, for example, several different sulfated galactan in marine red algae (see **Fig 4.8**). [27]

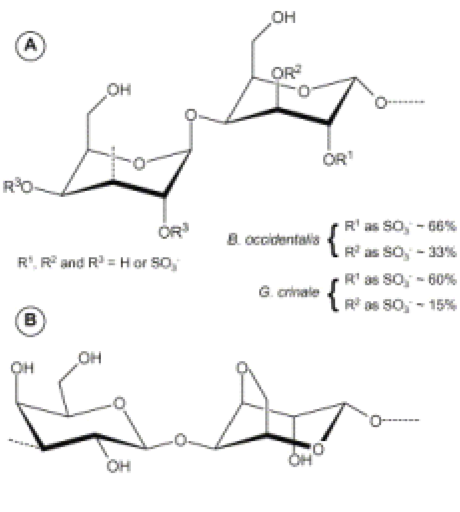


Fig 4.8 Structures of the galactans from various species of marine red algae. [27]

Various enzymes involved in galactan biosynthesis have been characterized. For instant, the biosynthesis of the cell wall galactan including in tuberculosis, *Mycobacterium tuberculosis*, is catalyzed with two galactofuranosyltransferases (see **Fig 4.9**). [28] Another example to get galactan is the reduction of arabinogalactan-proteins by a combination of an α-l-arabinofuranosidase and an endo-β-(1→6)-galactanase in *Neurospora crassa* (see **Fig 4.10**). [29]

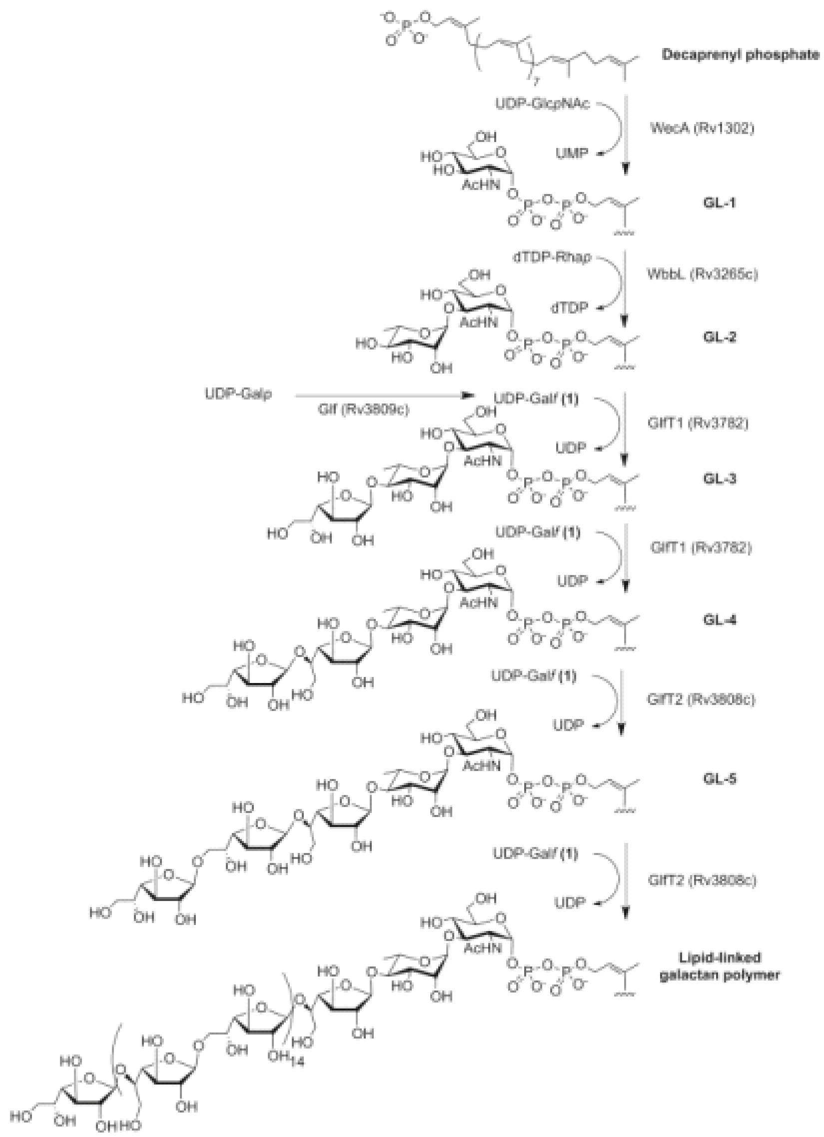


Fig 4.9 Metabolic Pathway for Biosynthesis of Mycobacterial Galactan. (Rv1302: GlcNAc-1-phosphate-transferase, Rv3265c: rhamnosyltransferase, Rv3782: galactofuranosyltransferases GlfT1, Rv3808c: GlfT2) [28]

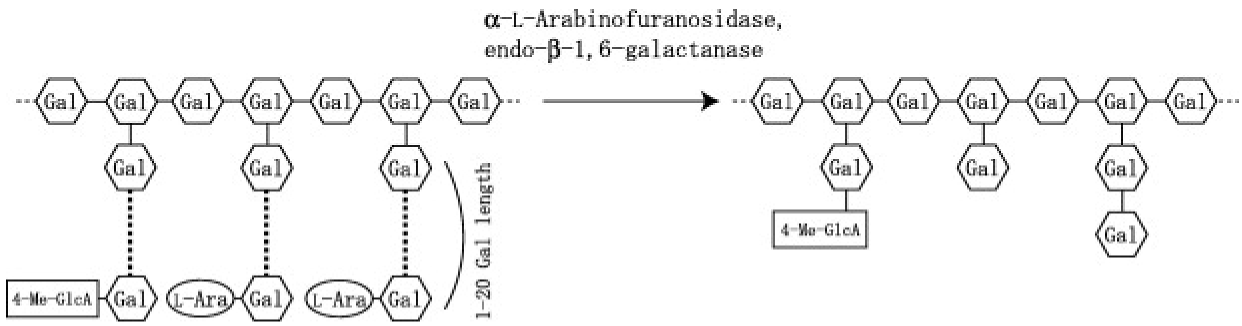


Fig 4.10 Degradation of arabinogalactan-proteins by glycoside hydrolases from *Neurospora crassa* [29]

5. Future prospects

For many years, researchers have been trying to create advanced biofuels synthesized from the sugars in plant cells walls by fermenting microorganisms. These advanced biofuels add no excess carbon to the atmosphere, and also, unlike ethanol, advanced biofuels could replace the fuels we are using now with a gallon-for-gallon standard and no engines modifications are required. While, the primary challenge to the creation is to find a way "to maximize the amount of plant cell wall sugars that can be fermented into fuels," Lawrence Berkeley National Laboratory (Berkeley Lab) researchers note.

Recently, the very good news is, for the first time, an enzyme that is capable of significantly increasing the biosynthesis of galactan in the cell walls of plants has been identified by researchers from the Department of Energy (DOE). This enzyme, found in *Arabidopsis thaliana*, is named GALS1 and is a β-1,4-galactan synthase. The paper is published in the journal *Cell Wall*. [40] Producing more of one of these proteins led to a 50% increase in β-1,4-galactan levels, and importantly the plants remained healthy.

As galactan is readily fermented by yeast into ethanol, this discovery would be a breakthrough for the key challenges to making advanced biofuels cost competitive. And it could really boost the biofuel production. And then, in the future, if the application of advanced biofuel is successfully developed, galactose sources known for now wouldn't be enough. Extra sources and synthesis would be needed.

Also, GOS plays an essential role in food industry. As people are more and more value the food nutrition and the demand of GOS are keep increasing, the production of GOS from lactose in milk now are very likely wouldn't fit the demand in future sufficiently.

Therefore, it will be very interesting and important if there is an alternative source for galactose and/or GOS.

For this aim, the plants containing certain amount of galactan could be an interesting choice. For instance, arabinogalactan is a very rich source for galactose, composed of galactose and arabinose molecules in a 6:1 ratio, together with a small amount of glucuronic acid, which is found in a variety of plants but more abundant in the Larix genus, primarily *Larix occidentalis* (Western Larch). [41][42]

And a novel chemical process for the selective hydrolysis of arabinogalactan into arabinose and galactose over heterogeneous acid catalysts was already successfully made (see **Fig 5.1**). [43] But chemical synthesis will not allow use in infant nutrition, so another synthesis way is still needed.

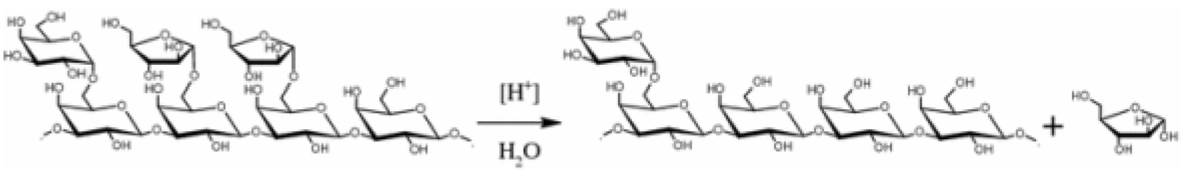


Fig 5.1 Selective hydrolysis of arabinogalactan into arabinose and galactose [43]

Also, galactose could be possibly obtained from glucose in plants or microbes. A proposed pathway for the biosynthesis of L-galactose from glucose is shown in **Fig 5.2**. [44]

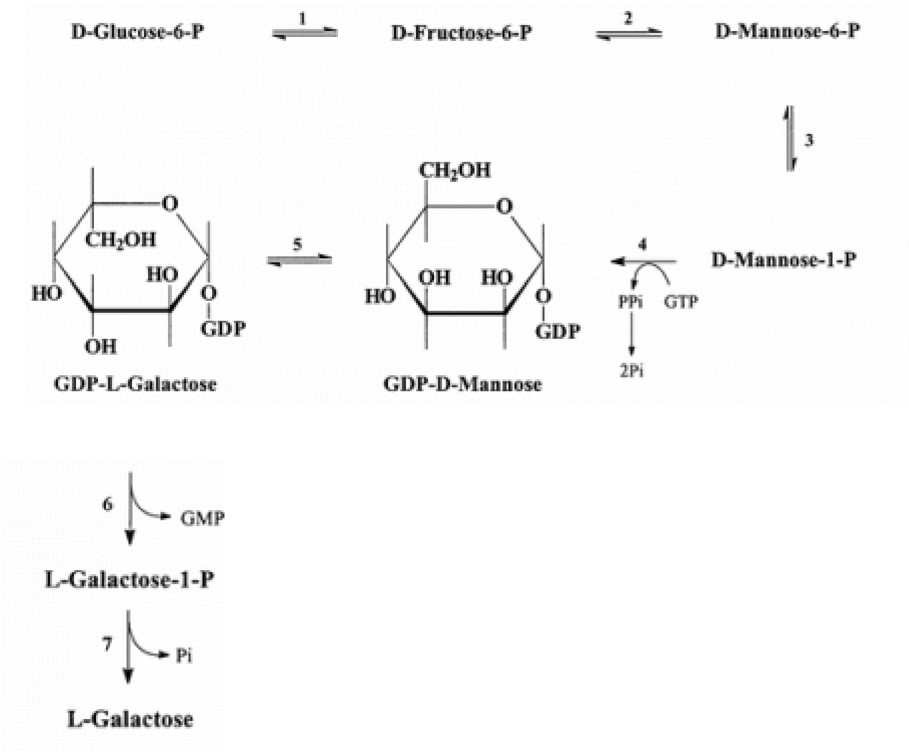


Fig 5.2 A proposed pathway for the biosynthesis of L-galactose. (Enzymes: 1, hexose phosphate isomerase; 2, phosphomannose isomerase; 3, phosphomannose mutase; 4, GDP-D-mannose pyrophosphorylase; 5, GDP-D-mannose-3,5-epimerase.) [44]

Another potential way is to generate a metabolic pathway in living cells, most easily in bacteria, to make full use of the knowledge about galactose relative enzymes and pathways that have already been well studied, by using genetics technologies, like gene cloning, gene recombination, etc.

Certainly, there would be many other possibilities to be found and can be used in the future science world.

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