Applied Microbiology and Biotechnology (2019) 103:8753–8761
https://doi.org/10.1007/s00253-019-10151-3

MINI-REVIEW

Recent studies on the biological production of D-mannose

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Received: 9 August 2019 / Revised: 18 September 2019 / Accepted: 22 September 2019 / Published online: 22 October 2019

Abstract

D-Mannose is an epimer of glucose at the C-2 position and exists in nature as a component of mannan. It has 60 and 86% sweetness than that of sucrose and D-glucose, respectively. Because of its low-calorie and nontoxic features, D-mannose is used widely in food, medicine, cosmetic, and food-additive industries. Besides, it exhibits many physiologic benefits on health: immune system, diabetes mellitus, intestinal diseases, and urinary tract infections. It is used as a starting material to synthesize immunostimulatory agents, anti-tumor agents, vitamins, and D-mannitol. However, D-mannose production using chemical synthesis and plant extraction cannot meet the requirements of the industry. This article presents recent research on the biological production of D-mannose. The physiologic benefits and applications of D-mannose are summarized. Besides, different D-mannose-producing enzymes from various sources are discussed in detail with regard to their biochemical characteristics, catalytic efficiency, and reaction kinetics for D-mannose production. Furthermore, attempts to use enzymatic conversion to produce D-mannose are reviewed.

Keywords D-Mannose · Physiologic benefits · Biological production · Isomerase · Epimerase

Introduction

Recently, the incidence of several chronic diseases, such as diabetes mellitus, hyperlipidemia, and hypertension, has increased rapidly worldwide. The occurrence of these diseases is closely related to the overconsumption of high-sugar and high-fat foods (Zhang et al. 2017b). Therefore, it is necessary to pay close attention to the effects of diet on human health.

Functional sugars have received considerable attention due to their excellent physiologic properties, such as low calories and low sweetness, and they have broad applications in the food, medicinal, and beverage industries (Huang et al. 2018a). For example, D-tagatose has numerous health benefits, including few calories, anti-biofilm effects, promotion of weight loss, and no glycemic effect (Oh 2007). D-Tagatose is widely used as a low-calorie functional sweetener. D-Allose possesses anti-tumor, anti-inflammatory, and anti-hypertensive properties (Chen et al. 2018b). D-Mannose shows several health benefits, too, such as being a prebiotic (Korneeva et al. 2012), promoting insulin secretion (Machicao et al. 1990), and aiding treatment for a deficiency in phosphomannose isomerase (Lonlay and Seta 2009). This monosaccharide can also be used as a starting material for the production of vitamins (Chen et al. 2007), anti-tumor agents (El-Nakkady et al. 2012), and immunostimulatory agents (Etchison and Freeze 1997). Because of its valuable properties and wide applications, D-mannose has gained much attention and interest.

D-Mannose is mostly found in nature as a component of mannan, hemicellulose, and cellulose in dietary fiber (Hu et al. 2016a). The structure of D-mannose is extremely similar to that of D-glucose and D-fructose. In detail, D-mannose is an epimer of D-glucose at the C-2 position and the aldose isomer of D-fructose. The content of D-mannose varies in different plants. It has been reported that the contents of D-mannose were 0.04 to 0.08% and 0 to 0.03% in the fresh apple flesh (Gheyas et al. 1997) and mango (Yashoda et al. 2007), respectively. The content of D-mannose reaches up to 21.2% in spent coffee grounds (Mussatto et al. 2011). Therefore, these D-mannose-containing plants are important raw materials for the preparation of D-mannose. The current top-selling brands of D-mannose including NOW Foods, Source Naturals, and

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Vibrant Health are derived from plant sources and most of them are made into capsules or powdered form (Hu et al. 2016a). The extraction of D-mannose from plants is mainly carried out by extraction. In addition, D-mannose could also be synthesized by chemical methods. Due to the poor specificity of the inorganic catalyst on substrate, the chemical reactions are often accompanied by the formation of many byproducts, which are not suitable for industrial production of D-mannose. With the development of microbiotechnology, the enzymatic production of D-mannose has gradually attracted considerable interest. At present, four types of microbial enzymes are reported to have the potential applications for the production of D-mannose, including D-lyxose isomerase (LIase, EC 5.3.1.15), D-mannose isomerase (MIase, EC 5.3.1.7), cellobiose 2-epimerase (CEase, EC 5.1.3.11), and D-mannose 2-epimerase (MEase, EC 5.1.3.-). The four enzymes could produce D-mannose directly based on D-glucose or D-fructose as substrate through the isomerization or epimerization reactions.

Here, we have summarized recent studies on the biological production of D-mannose. The physiologic benefits and applications of D-mannose have also been discussed in detail. Besides, different D-mannose-producing enzymes, such as MEase, LIase, CEase, and MEase, from various sources, are compared with regard to their biochemical characteristics, catalytic efficiency, and reaction kinetics for D-mannose production. Furthermore, some attempts to use enzymatic conversion to produce D-mannose have been reviewed.

Beneficial effects and applications of D-mannose

D-Mannose is a white crystal or crystalline powder. It has sweetness of 60 and 86% compared with that of sucrose and D-glucose, respectively (Hu et al. 2016a). It is easy to dissolve in water but slightly soluble in ethanol; at 17 °C, 248 g of D-mannose can be dissolved in 100 g water to give a 71-wt% solution (Hu et al. 2016a). Upon heating of D-mannose, the Maillard reaction occurs (Yaylayan and Forage 1992). The caloric value of D-mannose is 3.75 kcal/g, which is lower than that of many types of sugars (Pohl et al. 2012). D-Mannose is transported and absorbed in the human body through free diffusion, and its transportation rate is one tenth to that of glucose in the small intestine. D-Mannose in the human body is not converted readily into glycogen, and 95 to 98% of it is catalyzed to D-fructose-6-phosphate by phosphomannose isomerase, and only ~2% of D-mannose is used for N-glycosylation (Sharma et al. 2014).

As an important hexose, scientists are interested in the function of D-mannose. Several studies have found that D-mannose has many functions in the human body. Iwasaki and Medzhitov (2015) showed that D-mannose plays an important part in the human immune system. D-Mannose-binding lectin is an important component of the innate immune system. It can recognize D-mannose on the surface of pathogens and is the first line of defense in human immunity (Turner 2003). Deletion or genetic mutation of D-mannose-binding lectin leads to the susceptibility and severity of diseases (Müller et al. 2010; Sharma et al. 2012). In addition, D-mannose receptors can recognize the specific molecules or pathogens on the surface of hepatocytes and maintain the internal environment by participating in receptor-mediated endocytosis and phagocytosis (Ohnishi et al. 2012).

D-Mannose can be used as a raw material to synthesize high-value products, such as immunostimulants (Ranta et al. 2012), vitamins (Chen et al. 2007), anti-tumor-related drugs (Kamel et al. 2010), anti-human immunodeficiency-related drugs (Botos et al. 2002), and D-mannitol (Mishra and Hwang 2013). These products can be used in disease treatment and nutrient metabolism. For example, D-mannitol is widely used in food and pharmaceutical products because of its low-caloric and cariogenic properties (Dai et al. 2017). Besides, it is chemically inert and is used commonly in the pharmaceutical formulation of chewable tablets and granulated powders (Saha and Racine 2011).

Also, D-mannose has been used widely in food, medicine, cosmetic, and food-additive industries. As mentioned above, D-mannose is a low-calorie monosaccharide and has 60% of the sweetness of sucrose, making it a potential alternative sweetener for use in food processing. The general public is paying increasing attention to health issues, and the demand for low-calorie and low-sweet sugars is increasing (Zhang et al. 2017b). The biochemical property of D-mannose as a food component is very stable (Montero et al. 2004). D-Mannose is added to ice cream as a stabilizer (Sutton and Wilcox 2010). Besides, the combination of a certain ratio of D-galactose and D-mannose exhibits recrystallization behavior to locust bean gum. As a reducing monosaccharide, D-mannose can take part in the Maillard reaction, which can increase the melting point and improve the color, flavor, and taste of food (Yaylayan and Forage 1992). Elghaouth et al. (1995) declared that D-mannose can slow down the decay rate of apples and peaches.

Many antibiotics are added to the fodder used for the growth of livestock and poultry, but excessive use of antibiotics can cause environmental pollution and/or drug resistance (van Immerseel et al. 2002). Therefore, finding an alternative method to replace antibiotics has become very important. Researchers have demonstrated that D-mannose can inhibit the infection by *Salmonella typhi* in chickens and that D-mannose has no side effects, indicating the potential of replacing the antibiotics used against *S. typhi* (van Immerseel et al. 2002). In addition, D-mannose has been found to inhibit the colonization and abscission of pathogens in the intestinal tract (Berge and Wierup 2012).

Aloe vera plays an important part in the chemical industry as a moisturizer, whitening agent, and skin sunscreen (Chen and Dong 2008). Its physiologic functions are closely related to the presence of *Aloe* polysaccharides, which are rich in mannan and glucomannan (Eshun and He 2004). D-Mannose can make the skin more moisturized, softer, and smoother after washing (Schmidt et al. 1991). Wivell and Deckner (1995) invented a skincare product containing D-glucose, D-mannose, and D-glucuronic acid, which can cleanse and moisturize the skin. In addition to the aforementioned physiologic benefits, D-mannose can be used as an antibiotic screening agent in research on transgenic plants (Joersbo 2001). D-Mannose can also provide energy for transgenic maize plants from protoplasts (Wang et al. 2000).

D-Mannose production

Plant extraction

D-Mannose is extracted mainly from fruits, herbs, and palm (Hu et al. 2016a). Currently, the main extraction methods included acid hydrolysis, thermal hydrolysis, and enzymatic hydrolysis. Zhang et al. (2009) presented a route for the purification of D-mannose from palm kernel. First, the palm kernel was hydrolyzed by sulfuric acid at the temperature of 100 °C and then the hydrolysis solution was further treated by endo-β-mannanase. Subsequently, the solution was filtered through a silica gel column and subjected to desalting treatment with an ion exchange resin. Finally, the D-mannose crystals were obtained after purified by ethanol with a yield of 48.4% (Zhang et al. 2009). Fan et al. (2014) used microwave-assisted coupled with sulfuric acid treatment method to extract D-mannose from deproteinized palm kernels. After optimizing the extraction condition by response surface methodology, D-mannose yield of 92.11% was achieved at 148 °C for 10 min 31 s at a substrate-to-solvent ratio (w/v) of 1:49.69. However, this method requires the consumption of a large amount of organic reagents, e.g., sulfuric acid, and is not friendly to the environment.

Chemical synthesis

D-Mannose can also be produced from D-glucose by chemical methods, which are catalyzed mostly through molybdate catalysts (Hu et al. 2016a). Using ammonium molybdate as a catalyst, 32.6% yield of D-mannose was obtained after reaction about 150 min at 98 °C, pH 2.0, and 55% glucose concentration (Zhang et al. 2017a). Using a mixed catalyst of ammonium molybdate and calcium oxide, 44.8% yield of D-mannose was achieved after reaction for 80 min at 150 ° C, pH 3.0 (Xu et al. 2014). However, this method also has disadvantages. For example, the chemical reaction must be carried out at a high-temperature and low-acid environment, which increases the production costs. Furthermore, many byproducts produced in the reaction system are difficult to isolate in subsequent downstream processes.

Biological production using microbial enzymes

As a dietary supplement, D-mannose has many physiologic functions and is used widely in food, pharmaceutical, and cosmetic industries. However, the content of free D-mannose in nature is low and far below the demands of industrial applications. The synthesis of D-mannose by a chemical method requires strict control of temperature, pH, time, and pressure in the reaction process. Moreover, due to the weak specificity of the inorganic catalyst used in the reaction, many byproducts or toxic products are usually produced, which is unacceptable for consumers. An extraction method using acid hydrolysis from D-mannose-containing plants also has disadvantages. Due to the high crystallinity of plant cell walls, the hydrolysis of D-mannan requires a high temperature and high concentrations of acid/alkali/organic reagents, which are also not acceptable. Therefore, the biological production of D-mannose using microbial enzymes has attracted attention considerably because of the mild reaction conditions and few byproducts. As mentioned above, LIase, MIase, CEase, and MEase demonstrate the potential for the production of D-mannose on a large scale. According to the Izumori strategy, D-mannose can be converted from other hexoses by biological enzymes (Izumori 2002; Mu et al. 2015). The enzyme production of D-mannose is based mainly on D-fructose or D-glucose as the raw material, which is realized by isomerization or epimerization of monosaccharide (Fig. 1).

MIase

MIase (EC 5.3.1.7) is another important isomerase for D-mannose production. MIase reversibly catalyzes the isomerization of D-fructose and D-mannose. This enzyme has been isolated and characterized from *Pseudomonas saccharophila* (Palleroni and Doudoroff 1956), *Xanthomonas rubrilineans* S-48 (Takasaki and Takano 1964), *Streptomyces aerocolorigenes* (Takasaki 1967), *Mycobacterium smegmatis* (Hey-Ferguson and Elbein 1970), *Pseudomonas cepacia* (Allenza et al. 1990), *Agrobacterium radiobacter* M-1 (Hirose et al. 2001), *Thermobifida fusca* MBL10003 (Kasumi et al. 2014), and *Marinomonas mediterranea* (Saburi et al. 2018) and is also found in *Escherichia coli* and *Salmonella enterica* (Itoh et al. 2008).

The biochemical characteristics of these enzymes have also been investigated. Temperature and pH affect enzyme activity greatly. The optimal temperature and pH for the isomerase

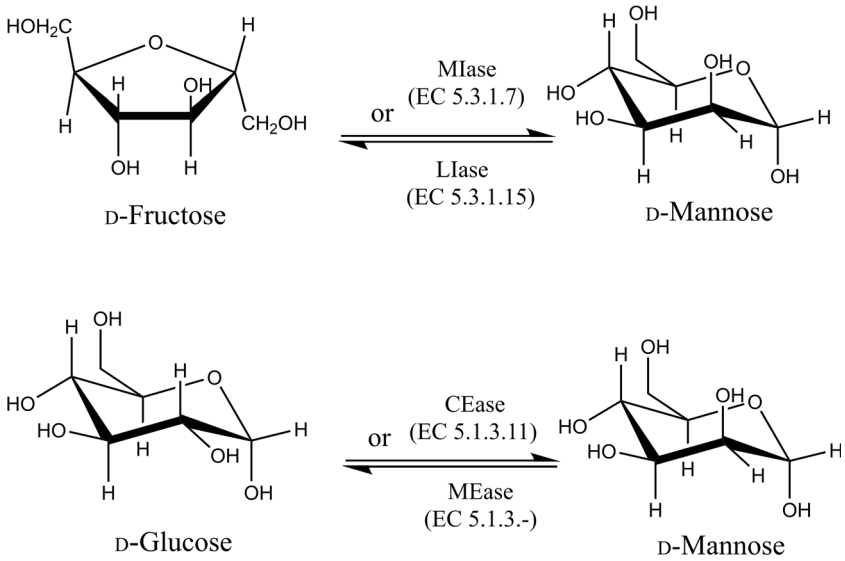

Fig. 1 Production of D-mannose from D-fructose and D-glucose using different enzymes. MIase, D-mannose isomerase; LIase, D-lyxose isomerase; CEase, cellobiose 2-epimerase; ME, D-mannose 2-epimerase

activity of these MIases ranged from 30 to 60 °C and 6.4 to 8.0, respectively (Table 1). Interestingly, maintenance of isomerization activity does not require the participation of metal ions in MIases. On the contrary, the addition of divalent metal ions, such as Cu^{2+}, Cd^{2+}, or Ca^{2+}, can inhibit their activity significantly (Kasumi et al. 2014). If the isomerization is started by MIase using D-mannose as a substrate, the concentration ratio of D-fructose:D-mannose is 75:25 to 65:35 at reaction equilibrium (Hey-Ferguson and Elbein 1970; Hirose et al. 2001; Kasumi et al. 2014; Takasaki 1967). These results suggest a higher conversion rate from D-mannose to D-fructose. However, the low conversion ratio of D-mannose based on D-fructose leads to a shortage for D-mannose production by MIase on a large scale.

Hu et al. (2016b) reported that a recombinant MIase can also achieve the same conversion rate and productivity under the same concentration of substrate at pH 7.0 and 45 °C, in contrast to LIase from *P. stuartii* (Table 2). Hirose and colleagues tried to immobilize *A. radiobacter* cells containing MIase to produce D-mannose from D-fructose (Hirose et al. 2003). They prepared the cells by adsorption on chitosan or glutaraldehyde crosslinking in the presence of albumin. Finally, 9 g D-mannose accumulated in the effluent (180 mL) at pH 8.0 and 55 °C for 14 days.

Reports focusing on the crystal structure of MIases have been limited to MIase from *M. mediterranea* (PDB: 5X32) and a hypothetical protein YihS (later characterized as MIase) from *S. enterica* (PDB: 2AFA) (Itoh et al. 2008). MIase (PDB: 5X32) from *M. mediterranea* is formed by an $(\alpha/\alpha)_6$-barrel, which is a typical characteristic structure in enzymes from the N-acylglucosamine 2-epimerase (AGE) superfamily (Saburi et al. 2018). Research has revealed that the residue amino acids responsible for catalysis and substrate binding are similar to those enzymes from the AGE superfamily, such as CEase and aldose–ketose isomerase. In the catalytic domain of MIase (PDB: 5X32), α7/α8 and α11/α12

Table 1 Comparison of the properties of MIase and kinetic parameters toward D-mannose substrate

Enzyme source	Optimal temperature (°C)	Optimal pH	K_m (mM)	K_{cat} (s^{-1})	K_{cat}/K_m (mM^{-1} s^{-1})	Equilibrium ratio mannose/fructose	Reference
P. saccharophila	30	7.5	NR	NR	NR	NR	Palleroni and Doudoroff (1956)
X. rubrilineans	35	7.8	0.12	NR	NR	NR	Takasaki and Takano (1964)
S. aerocolorigenes	NR	NR	1.4	NR	NR	25:75	Takasaki (1967)
M. smegmatis	37	7.5	7	NR	NR	35:65	Hey-Ferguson and Elbein (1970)
E. coli K12	NR	NR	80	NR	NR	NR	Stevens et al. (1981)
P. cepacia	50	6.4	NR	NR	NR	NR	Allenza et al. (1990)
A. radiobacter M-1	60	8.0	20	NR	NR	25:75	Hirose et al. (2001)
T. fusca MBL10003	60	8.0	115 ± 15	788 ± 40	6850 ± 200	25:75	Kasumi et al. (2014)
M. mediterranea	30	7.3	16.7 ± 1.8	329 ± 2.2	19.7	30.2:69.8	Saburi et al. (2018)

NR, not reported

loops play an important part in the opening of the substrate-binding site (Saburi et al. 2018). Elucidation of the crystal structure of MIase provides molecular insights into understanding the reaction mechanism of enzymes and substrates. However, insufficient information of the crystal structure of MIase has seriously restricted development studies on molecular modification of MIase and hampered attempts to increase its catalytic efficiency on D-fructose through site-directed mutagenesis.

LIase

LIase (EC 5.3.1.15) is an aldose–ketose isomerase that could be used to produce D-mannose (Cho et al. 2007). It can catalyze isomerization with various substrates. For example, it can catalyze isomerization at the C-2 position of D-lyxose, D-fructose, and L-ribose, thereby producing D-xylulose, D-mannose, and L-ribulose as products, respectively (Huang et al. 2018a). Isomerization of LIase has a critical role in microbial metabolism because these ketopentoses (D-xylulose, L-ribulose) can be phosphorylated further to form intermediates (D-xylulose-5-phosphate, L-ribulose-5-phosphate) through the action of kinases (Cho et al. 2007). These compounds are the common intermediates of the pentose phosphate pathway. Because of its broad spectrum of substrate specificity, LIase has been applied for the production of many functional sugars (Huang et al. 2018a). Several LIases have been produced by different microorganisms, including *Cohnella laevoribosii* RI-39 (Cho et al. 2007), *Providencia stuartii* (Kwon et al. 2010), *Serratia proteamaculans* (Park et al. 2010b), *E. coli* O157:H7 (van Staalduinen et al. 2010), *Bacillus licheniformis* (Patel et al. 2011), *Dictyoglomus turgidum* (Choi et al. 2012), and *Thermosediminibacter oceani* (Yu et al. 2016).

Recently, Yu et al. (2016) characterized a LIase from a hyperthermophile strain of *T. oceani*. The LIase exhibited potential for D-mannose production. The authors showed that 101.6 g L^{-1} of D-mannose could be obtained from 400 g L^{-1} of D-fructose in 9 h, with a conversion rate of 25.4% and productivity of 11.28 g L^{-1} h^{-1} at pH 6.5 and 60 °C. By using *P. stuartii* free LIase, 150 g L^{-1} of D-mannose could be produced from 600 g L^{-1} of D-fructose in 2 h, at pH 7.5 and 35 °C, with a conversion rate of 25% and productivity of 75 g L^{-1} h^{-1} (Park et al. 2010a). By immobilization of LIase from *P. stuartii* using Duolite resin A568, 75 g L^{-1} of D-mannose is obtained from 300 g L^{-1} of D-fructose with a conversion rate of 25% and a productivity of 75 g L^{-1} h^{-1} after 23 cycles (Park et al. 2010a). Additionally, to produce D-mannose from D-glucose directly, a one-pot enzyme process of D-mannose production from D-glucose has been constructed by co-expression of the D-glucose isomerase (GIase, EC 5.3.1.5) from *Acidothermus cellulolyticus* and LIase from *T. oceani* in *E. coli* BL21(DE3) cells (Huang et al. 2018b). Using this co-expression system, 60 g L^{-1} of D-mannose is obtained from 400 g L^{-1} of D-glucose in 8 h at pH 6.5 and 65 °C, suggesting the potential for industrial production of D-mannose.

In general, a high temperature is beneficial for the industrial production of functional sugars. A high temperature can accelerate the conversion rate of enzymatic reactions, reduce the risk of microbial contamination, and increase the solubility of products and substrates (Huang et al. 2018a). However, if the reaction temperature is high, the Maillard reaction occurs and some unexpected byproducts are produced because of nonenzymatic browning effect (Chen et al. 2018b). Hence, temperature control is very important in sugar processing. Besides, if the effect of nonenzymatic browning is to be reduced, control of the system pH in weak-acidic conditions is an effective

Table 2 Comparison of different sources of the microbial enzymes used for production of D-mannose

Source	Immobilization/ free enzyme	Substrate (g L^{-1})	Reaction condition	D-Mannose (g L^{-1})	Conversion rate (%)	Productivity (g L^{-1} h^{-1})	Reference
T. oceani	Free LIase	Fructose, 400	pH 6.5, 60 °C, 9 h	101.6	25.4	11.28	Yu et al. (2016)
P. stuartii	Free LIase	Fructose, 600	pH 7.5, 35 °C, 2 h	150	25	75	Park et al. (2010a)
T. dichotomicum	Free LIase	Fructose, 500	pH 7.5, 60 °C, 6 h	110.5	22.1	18.42	Zhang et al. (2019)
P. stuartii	Immobilization LIase	Fructose, 300	pH 7.5, 35 °C, 1 h	75	25	75	Park et al. (2010a)
C. saccharolyticus	Free CEase	Glucose, 500	pH 7.5, 75 °C, 3 h	75	15	25	Park et al. (2011)
A. radiobacter	Immobilization cells (MIase)	Fructose, 200	pH 8.0, 55 °C, 14 days	50 (9 g/180 mL)	25	0.15	Hirose et al. (2003)
E. coli	Free MIase	Fructose, 600	pH 7.0, 45 °C, 2 h	150	25	75	Hu et al. (2016b)
R. slithyformis	Free MEase	Glucose, 500	pH 8.0, 50 °C, 48 h	122	24.4	2.54	Saburi et al. (2019)
D. fermentans				114	22.8	2.38	

Table 3 Comparison of the properties of LIase and kinetic parameters toward D-mannose substrate

Enzyme source	Optimal temperature (°C)	Optimal pH	Metal ion	V_{max} (U mg^{-1})	K_m (mM)	K_{cat} (s^{-1})	K_{cat}/K_m (mM^{-1} s^{-1})	Specific activity (U mg^{-1})	Reference
C. laevoribosii	70	6.5	Mn^{2+}	131.8 ± 7.4	34 ± 1.1	46.1 ± 2.6	1.4 ± 0.1	13.4	Cho et al. (2007)
P. stuartii	45	7.5	Mn^{2+}	NR	22 ± 0.1	2640 ± 41	116 ± 1.9	523 ± 9.8	Kwon et al. (2010)
S. proteamaculans	40	7.5	Mn^{2+}	NR	32.2 ± 0.22	16,170 ± 148	502 ± 1.2	5.42 ± 0.075	Park et al. (2010b)
E. coli	50	7.5	Mn^{2+}	13.1 ± 0.02	19.8 ± 0.24	12.7 ± 0.02	640 ± 8.73	4.73 ± 0.05	van Staalduinen et al. (2010)
B. licheniformis	40–45	7.5–8.5	Mn^{2+}	390 ± 1.2	26 ± 0.8	43 ± 0.1	1.6	41 ± 1.3	Patel et al. (2011)
D. turgidum	75	7.5	Co^{2+}	NR	13 ± 1	178 ± 3	14 ± 1	1668 ± 63	Choi et al. (2012)
T. oceani	65	6.5	Mn^{2+}	NR	32.8 ± 1.8	5686 ± 39	173 ± 5	5.3 ± 0.1	Yu et al. (2016)
T. dichotomicum	60	7.5	Mn^{2+}	NR	80.8 ± 2.5	3141.6 ± 36.3	38.9 ± 1.3	7.6 ± 0.3	Zhang et al. (2019)

NR not reported

strategy because the byproducts produced in the carbonyl ammonia reaction are hydrolyzed readily under acidic conditions (Shen and Wu 2004). These LIases show different biochemical properties with regard to temperature, pH, and kinetic parameters (K_m, K_{cat}, K_{cat}/K_m). Table 1 shows that the optimal temperature and pH range are from 40 to 75 °C and 6.5 to 8.5, respectively. Except for the LIase from *C. laevoribosii* (Cho et al. 2007) and *T. oceani* (Yu et al. 2016), the optimal pH of the other LIases have weak-alkaline characteristics. Therefore, for the industrial production of D-mannose, LIases with weak-acidic properties are needed, and the realization of this goal is dependent upon the molecular modification of LIase based on crystal structure or screening novel LIase-producing strains from nature. Different from MIase, LIase is a metal ion-dependent isomerase. For most LIases, Mn^{2+} is the optimal metal ion for the isomerase activity of LIase from *C. laevoribosii* (Cho et al. 2007), *P. stuartii* (Kwon et al. 2010), and *S. proteamaculans* (Park et al. 2010b), whereas Co^{2+} is the optimal metal ion for LIase from *D. turgidum* (Choi et al. 2012) (Table 3). With D-mannose as the substrate, *D. turgidum* shows the highest specific activity of 1668 ± 63 U/mg, whereas *E. coli* exhibits the lowest specific activity of 4.73 ± 0.05 U/mg.

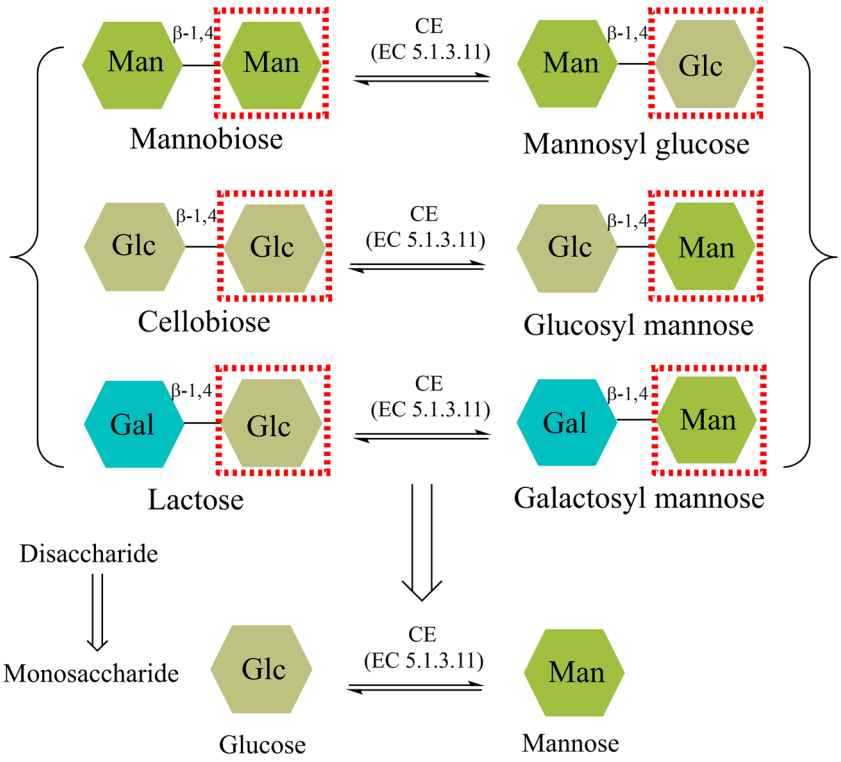

Fig. 2 Reaction of cellobiose 2-epimerase (CEase) with mannobiose, cellobiose, and lactose as substrate, and the production of D-mannose from D-glucose using CEase (schematic)

CEase

CEase (EC 5.1.3.11) was isolated and identified first from the culture broth of *Ruminococcus albus*, in which CEase was found to catalyze cellobiose into glucosyl mannose through epimerization (Fig. 2) (Tyler and Leatherwood 1967). Subsequently, some studies revealed that CEase can convert other β-1,4-linked disaccharides, such as mannobiose and lactose, through epimerization at the C-2 position (Fig. 2). Disaccharides, such as mannobiose, cellobiose, and lactose, can be converted into mannosyl glucose, glucosyl mannose, and galactosyl mannose using CEase, respectively. Besides, CEase can catalyze the isomerization between keto-disaccharides and aldo-disaccharides (Chen et al. 2018a). To investigate the possibility of catalyzing monosaccharide substrates through epimerization, Park et al. (2011) studied the epimerization of CEase on different monosaccharides: D-glucose, D-mannose, D-xylose, D-lyxose, L-allose, L-gulose, L-arabinose, D-fructose, D-xylulose, L-psicose, L-sorbose, and L-ribulose. Their experimental results provided the first evidence that CEase from *C. saccharolyticus* can catalyze D-glucose, D-mannose, D-xylose, D-lyxose, and D-fructose through epimerization at the C-2 position. In particular, with D-glucose as a substrate, the value of K_{cat}/K_m is ~ 25% that of D-mannose (Park et al. 2011). At 75 °C and pH 7.5, 75 g L^{-1} of D-mannose and 47.5 g L^{-1} of D-fructose are produced from 500 g L^{-1} of D-glucose after reaction for > 3 h by CEase. However, the reaction formed D-fructose as a byproduct at equilibrium because CEase can carry out isomerization and epimerization simultaneously.

MEase

Recently, Saburi et al. (2019) reported two novel MEases, named Runse_4512 and Dfer_5652, from *Runella slithyformis* and *Dyadobacter fermentans*, respectively, and showed that they are new members of the AGE superfamily. Similar to CEase, MEase also can convert D-glucose to D-mannose directly (Fig. 1). Upon reaction for 48 h at 50 °C and pH 8.0 with 500 g L^{-1} of D-glucose as substrate, 122 and 114 g L^{-1} of D-mannose are produced in the system using Runse_4512 and Dfer_5652 with a conversion rate of 24.4 and 22.8%, respectively (Saburi et al. 2019).

Future perspectives

D-Mannose exhibits many physiologic benefits for human health and is used widely in food, medicine, cosmetic, and food-additive industries. However, the detailed research about the action mechanism on human health is relatively scarce. Many studies should be performed to increase people's understanding for this functional sugar. In addition, among the aforementioned four enzymes that were used for the production of D-mannose, most of them display properties with weakly alkaline optimal pH, and this property is not preferable for industrial production. To meet the requirements of the industry, required research is needed to improve the properties of such enzymes through protein-engineering techniques, such as site-directed mutagenesis or directed evolution. Besides, more MEases and CEases should be screened from nature because the two enzymes are capable of converting D-glucose to D-mannose directly. Furthermore, considering safety issues, a food-grade host, such as *Bacillus subtilis*, should be constructed for the expression of these enzymes in the future.

Funding information This work was supported by the National Natural Science Foundation of China (No. 31801583); the Natural Science Foundation of Jiangsu Province (No. BK20180607); the Research Program of State Key Laboratory of Food Science and Technology, Jiangnan University (SKLF-ZZA-201901); and the Postgraduate Research and Practice Innovation Program of Jiangsu Province (No. KYCX19_1817).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain studies with human participants or animals carried out by any of the authors.

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